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(54) **COMPOSITIONS AND METHODS FOR TREATING HERPES VIRUSES**

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(73) Assignee: **PRESIDENT AND FELLOWS OF HARVARD COLLEGE**, Cambridge, MA (US)

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(60) Provisional application No. 61/511,016, filed on Jul. 22, 2011.

Publication Classification

(51) **Int. Cl.**

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A61K 31/4985	(2006.01)
A61K 31/4375	(2006.01)
A61K 31/437	(2006.01)
A61K 31/47	(2006.01)
A61K 31/4035	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/513*** (2013.01); ***A61K 31/47*** (2013.01); ***A61K 31/195*** (2013.01); ***A61K 31/4035*** (2013.01); ***A61K 31/4375*** (2013.01); ***A61K 31/437*** (2013.01); ***A61K 31/4985*** (2013.01)

USPC **514/250**; 514/269; 514/312; 544/319; 546/156; 514/567; 562/451; 514/417; 548/473; 514/416; 548/472; 514/292; 546/86; 514/300; 546/113; 544/346; 546/123; 435/184; 435/235.1

(57) **ABSTRACT**

Compositions and methods that are useful for the treatment of herpesvirus infection (including herpes simplex virii) are disclosed. Methods for identifying compounds useful for the treatment of herpesvirus infection are also disclosed.

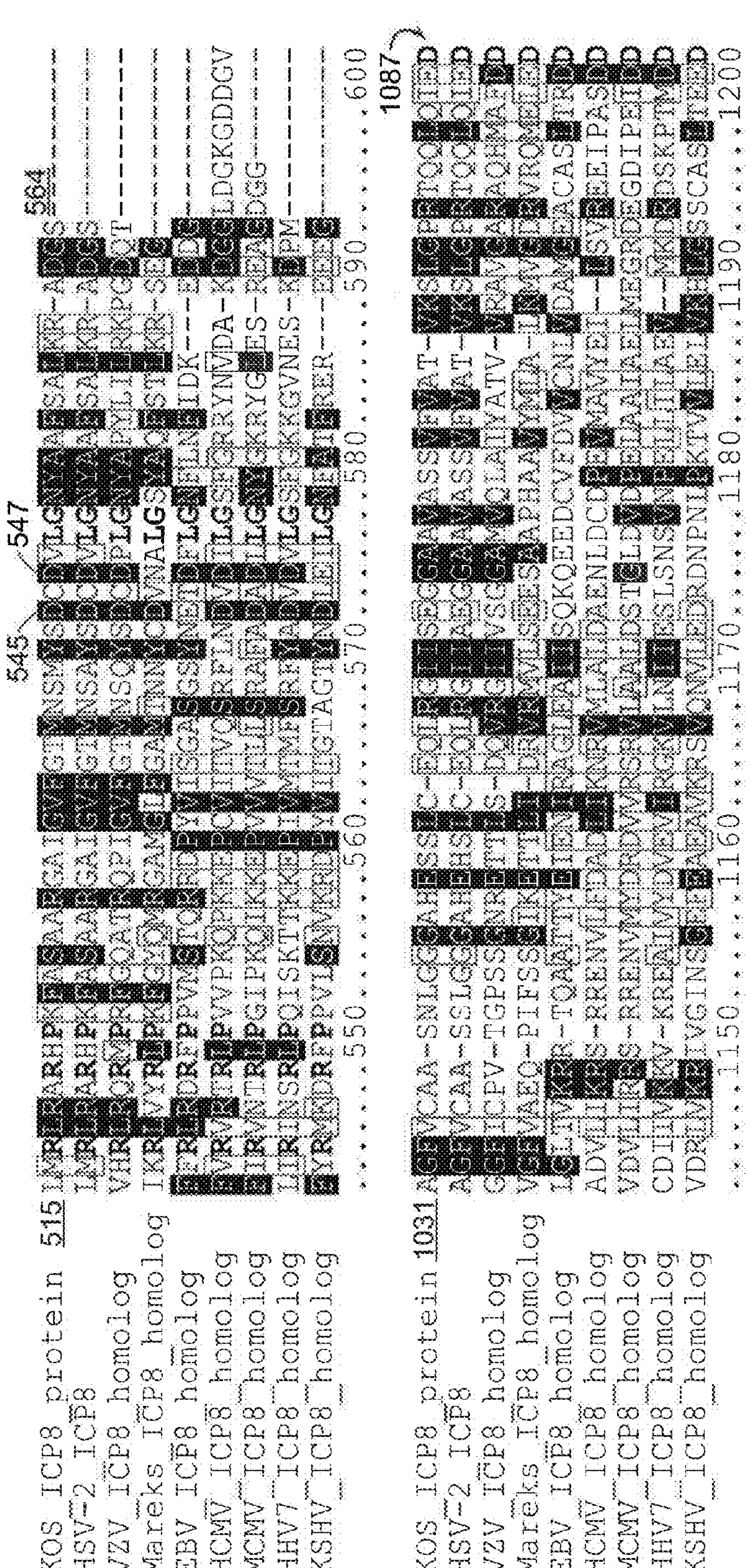

FIG. 1A

FIG. 1B

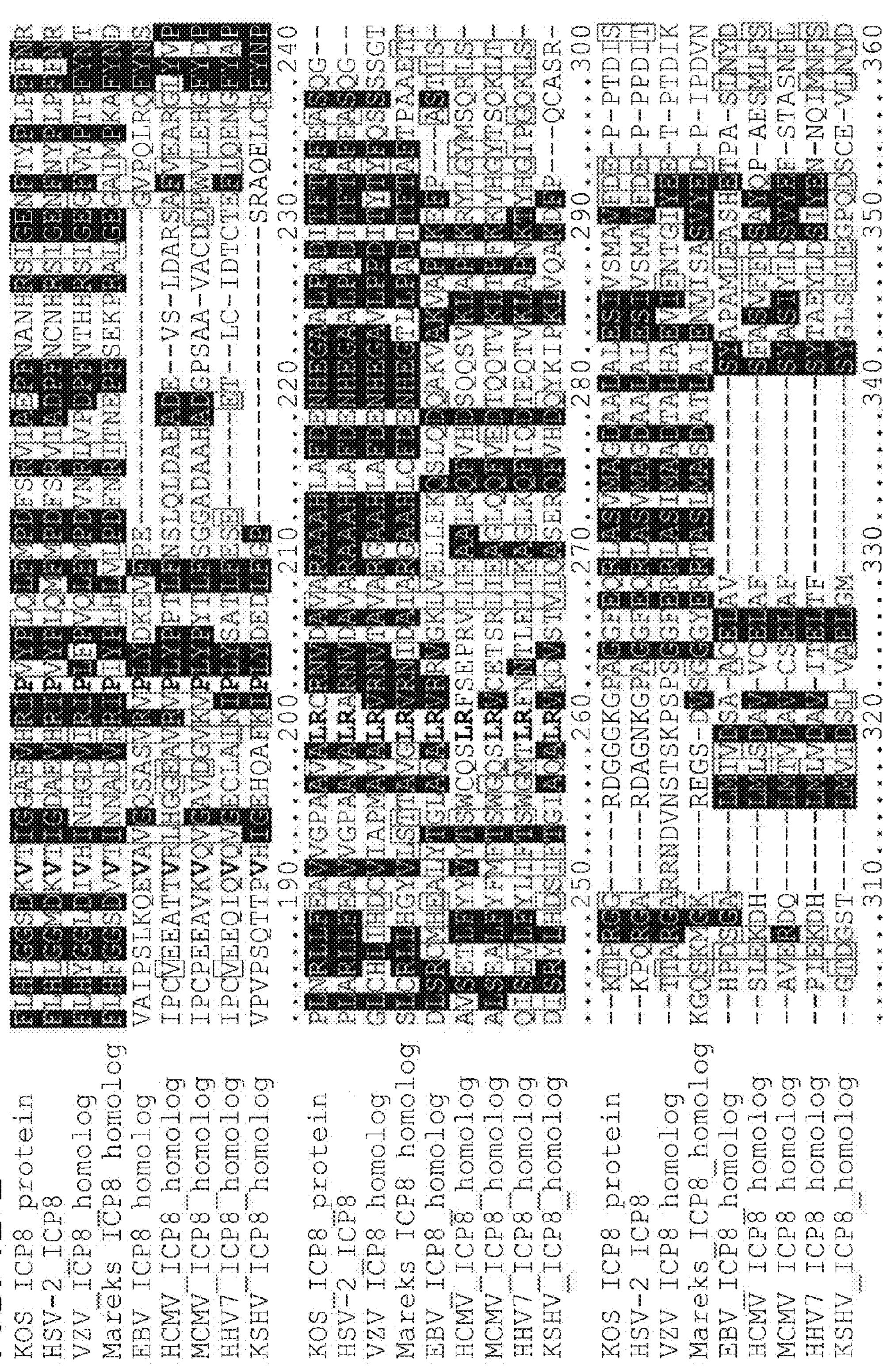

FIG. 1B-2

FIG. 1B-3

KOS_ICP8_protein
HSV-2_ICP8
VZV_ICP8_homolog
Mareks_ICP8_homolog
EBV_ICP8_homolog
HCMV_ICP8_homolog
MCMV_ICP8_homolog
HHV7_ICP8_homolog
KSHV_ICP8_homolog

370 380 390 400 410 420

KOS_ICP8_protein
HSV-2_ICP8
VZV_ICP8_homolog
Mareks_ICP8_homolog
EBV_ICP8_homolog
HCMV_ICP8_homolog
MCMV_ICP8_homolog
HHV7_ICP8_homolog
KSHV_ICP8_homolog

430 440 450 460 470 480

KOS_ICP8_protein
HSV-2_ICP8
VZV_ICP8_homolog
Mareks_ICP8_homolog
EBV_ICP8_homolog
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HHV7_ICP8_homolog
KSHV_ICP8_homolog

490 500 510 520 530 540

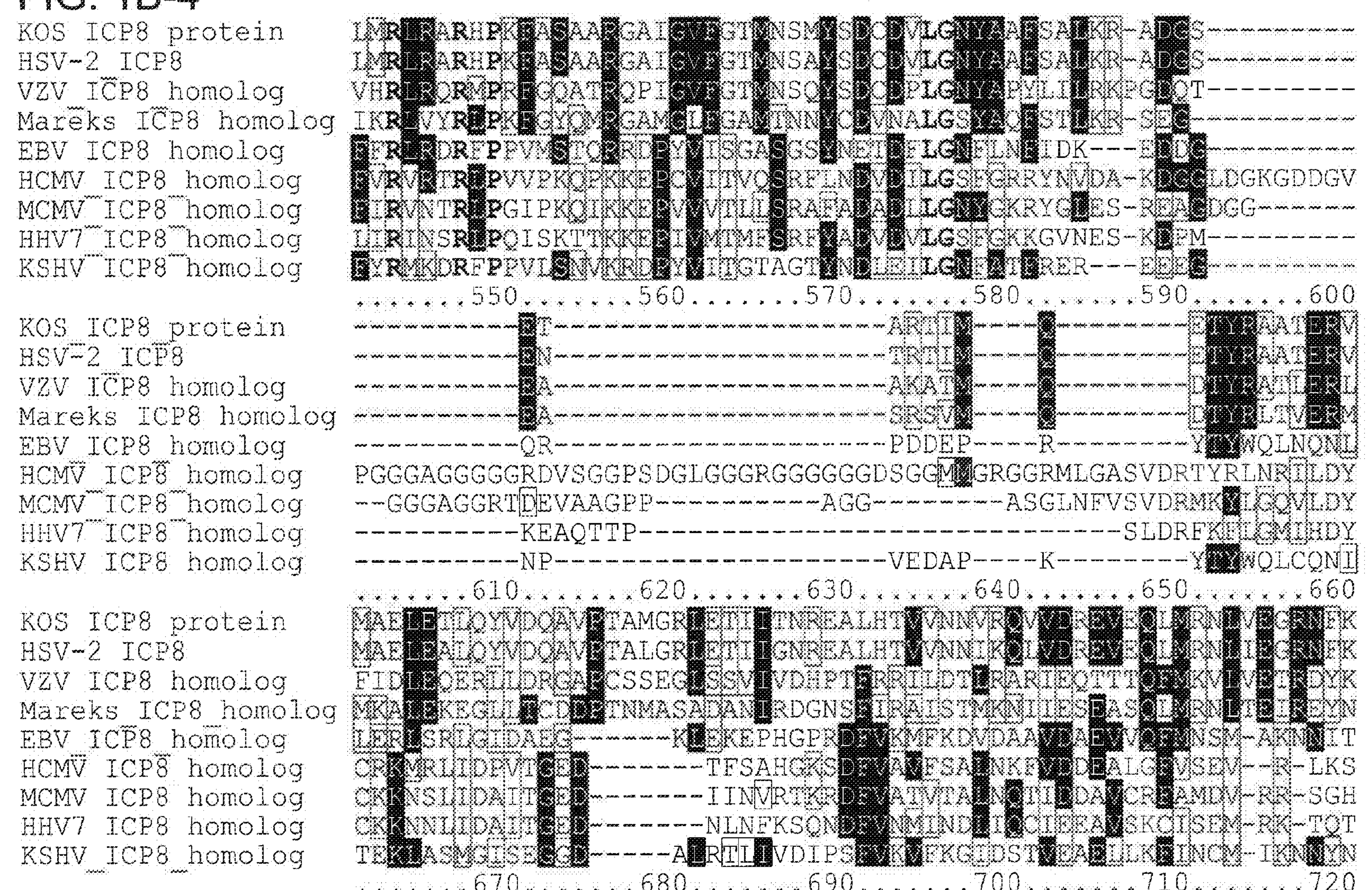

FIG. 1B-4

FIG. 1B-5

```
KOS_ICP8_protein      FRDGLGEANHAMSLTLDPYACGPCPLLQLLGRRSNLAVYQDLALSQCHGVFAGQSVEGRN
HSV-2_ICP8            FRDGLAEANHAMSLSLDPYTCGPCPLLQLLARRSNLAVYQDLALSQCHGVFAGQSVEGRN
VZV_ICP8_homolog      IREGLSEATHSMALTFDPYSGAFCPITNFLVKRTHLAVVQDLALSQCHCVFYGQQVEGRN
Mareks_ICP8_homolog   IREGLGDANHTLSLAVEPYASGICPVLAELSRTIILAVVQDMALSQCSIVMQGQQVEARN
EBV_ICP8_homolog      YKDLVKSCYEVMQYSCNPEAQPACPIFTQLFYRSLLTILQDISLPIGMCYENDNEGLCQS
HCMV_ICP8_homolog     SRDEVAGETQAFNLDINPYAVAFQPLLAYAYFRSVFYVIQNVALITATSFIVDNPLTTNL
MCMV_ICP8_homolog     GRREISGSTQSFNLDLSPYATAFSPVLSFQYYRIMFSIIQNLALINAASYVVDNPLTTAQ
HHV7_ICP8_homolog     SREQIENCLQSFNIDTTPLSLAFSPFFVELYYKVIFIVLQNLALIIGTGYVMERECTENL
KSHV_ICP8_homolog     FRENIKSVHETLQFACNVYWQAPCPVFLTLYYKSLLTVIQDICLTSCMMYEQDNPAVCIV
                      .......730.......740.......750.......760.......770.......780

KOS_ICP8_protein      ----FRNQEQPVLRRRVMDMFNNGFLSAKTLTVALSEGAAICAPSLTA-G-QTAPAESSF
HSV-2_ICP8            ----FRNQEQPVLRRRVMDLFNNGFLSAKTLTVALSEGAAICAPSLTA-G-QTAPAESSF
VZV_ICP8_homolog      ----FRNQEQPVLRRRFVDLFNGGFISTRSITVTLSEG-PVSAPNPTL-G-QDAPAGRTF
Mareks_ICP8_homolog   ----FRTQEQAVLKRRVLELQNAGFITSKTITVTLFDQ-QICVPTPSK-S-QYDSVISNM
EBV_ICP8_homolog      PPEMLKGHYQTLLCTNERSLAIDSGVLTAKEAKVVHGEP-TCDLPDLDRAL-QGRVYGRRL
HCMV_ICP8_homolog     VSKMMIQHEQSIHGAESTTSSRKGFLFTKQIKSSKNSD-HDRLLEFRLYA-QGIYAVVEM
MCMV_ICP8_homolog     ISKEVTLHEQSICGAEGTTPLKKGFLNVKDTKNLKSVE-FERIMEFRSFQETERYRKIST
HHV7_ICP8_homolog     ISKELMQQYQSLYGAFYNSHEKKGFLNMKTVKIASNVD-MEQYIEFNLFK-SGKYAKISI
KSHV_ICP8_homolog     FSELLKMHEQIMWTNEKGACEDKGAIITGGELKIVHQSM-FCDLFETDAAI-GGMFAPARM
                      .......790.......800.......810.......820.......830.......840

KOS_ICP8_protein      EGDVARVTLGFPKELRVKSRVLFAGASAN-ASEAAKARVASLQSAYQKP-D-KRVDILLG
HSV-2_ICP8            EGDVARVTLGFPKELRVKSRVLFAGASAN-ASEAAKARVASLQSAYQKP-D-KRVDILLG
VZV_ICP8_homolog      DGDLARVSVEVIRDIRVKNRVVFSGNCTN-LSEAARARLVGLASAYQRQ-E-KRVDMLHG
Mareks_ICP8_homolog   EGDLVKVIVEIFRELKVKNKVLFGGGIRGAASEATKSRLAGMVEAYQRP-T-KTMHVLNG
EBV_ICP8_homolog      PVRMSKVLMLCPRNIKIKNRVVFTGENCA-------------LQNSFIKSTTRRENYLING
HCMV_ICP8_homolog     EIKLSRLSVPTLIMVRVKNRPIYRAGKGN-------------AGSVIFRRDHVPRRNPAKG
MCMV_ICP8_homolog     EIKSCKMSVQSLKSCRIKNRPISKTPQ---------------SSVIFRKGALQRKNPIKG
HHV7_ICP8_homolog     QANLQRLSMQCLLDFRVKNRPFNKPNKNT-------------QNNPIFKKV-KQKKNEISG
KSHV_ICP8_homolog     QVRLAPAMLMVEKTIKIKNRIIFSNSTGA-E-----------SIQAGFMKEASQRDSYTVGG
                      .......850.......860.......870.......880.......890.......900
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FIG. 1B-6

```
KOS ICP8 protein      PLGFLLKQFHAAIFPNGKPPGSNQPNPQWFWTALQRNQ----LPARLL----SREDIETIAF
HSV-2 ICP8            PLGFLLKQFHAVIFPNGKPPGSNQPNPQWFWTALQRNQ----LPARLL----SREDIETIAF
VZV ICP8 homolog      ALGFLLKQFHGLIFPRGMPPNSKSPNPQWFWTLLQRNQ----MPADKL----THEEITTIAA
Mareks ICP8 homolog   PLGFAVKRYHTLIFPDVKMPNGATPNALNFWTILLRNQ----LPAGIL----SKEEEDKSLF
EBV ICP8 homolog      PYMKFLNTYHKTLFPDTKLSSLYLAH------NFSRRRSVPVLSGAS---AEEYSDLAIF
HCMV ICP8 homolog     CLGFLIYRHHERLFPECGLPCLQFWQ------KVCSNA---LPKNVPIGDMGEFNAFVKF
MCMV ICP8 homolog     CLSFLIFRCHEKLFPRCGLSCLEFWQ------RVLQQS---LERSVNVGKVEDFDNIVRF
HHV7 ICP8 homolog     CLSFLIFKYHERLFPNLKISCLEFWQ------RILIRN---MEKTIDIGNVEDMRSFIKE
KSHV ICP8 homolog     PYMKFLNALHKTLFPSTKTSALYLAH------KIGQTTKNPILPGVS---GEHLTELCNY
                      ........910.......920.......930.......940.......950.......960

KOS ICP8 protein      IKKFSLDYGAINFINLAPNNVSELAMYYMANQILLRYCDHSTYFINTLTAIIAGSRRPPSV
HSV-2 ICP8            IRKFSLDYGAINFINLAPNNVSELAMYYMANQILLRYCDHSTYFINTLTAVIAGSRRPPSV
VZV ICP8 homolog      VKRFTTEEYAAINFINLPPTLIGELAQFYMANLILKYCDHSQYLINTLTSIITGARRPRDP
Mareks ICP8 homolog   IKKFTKSYADMNYINISPTQFGDIAQFYIANTILKYCSHKHFFINTLISALVAVSRRPRDP
EBV ICP8 homolog      VDGGSRAHEESNVIDVVPGNLVTYAKQRLNNAILKACGQTQFYISLIQGLVPRTQSVPAR
HCMV ICP8 homolog     LVAVTADYQEHDLLDVAPDCVLSYVESRFHNKFLCYYGFKDY-IGSLHGLTTRLTTQNHA
MCMV ICP8 homolog     LLTVTDSKLESDVVDIQPDCLLSYVENRFHNKFLYMFGFRDY-MSSIQGMSTRLTPQNHS
HHV7 ICP8 homolog     TFRVINSYDELDLLDIQPECLLSFIEYYFHNKLLSVLCYRDY-LTSIHAYTSKLVPQNPM
KSHV ICP8 homolog     VMASSQAFEEINVLDIVPDTLTSYAKIKLNSSILRACGQTQFYATTLSCLSPVTQLVEAE
                      ........970.......980.......990......1000......1010......1020

KOS ICP8 protein      QAAAAWSAQG----GAGLEAGARALMDAVDAHPGAWTSMFASCNLLRPVMAARPMVVLGL
HSV-2 ICP8            QAAAAWAPQG----GAGLEAGARALMDSLDAHPGAWTSMFASCNLLRPVMAARPMVVLGL
VZV ICP8 homolog      SSVLHWIRKD-VTSAADIETQAKALLEKTENLPELWTTAFTSTHLVRAAMNQRPMVVLGI
Mareks ICP8 homolog   AIVLPWIERE-ITKGQDVAPAAQQLIASMSDHKDIWCATFSSSTNLVCSIMTTKPFVVLGI
EBV ICP8 homolog      DYPHVLGTRA-VESAAAAAEAATSSL--T------ATGVVCAATDCLSQVCKARPVVTLPV
HCMV ICP8 homolog     QFPHVLGASPRFSSSPAEEALHVKGL--KTAGVEAPMATTVARESLVRSVFEHRSLVTVPV
MCMV ICP8 homolog     QFPCLLKDASKFASILAEVVLHFKKM--KLDGVKAPQVATITREPVLKKLFDQRSLASVSF
HHV7 ICP8 homolog     LFPVFLKEHETFSSVQEYVMHVKKL--VGNGLKEPMTASLTKEPNFGSIFTQRSITTFGI
KSHV ICP8 homolog     EYPHVLGPVG-LSSPDEYRAKVAGR--S-------VTIVQSTLKQAVSTNGRLRPIITVPL
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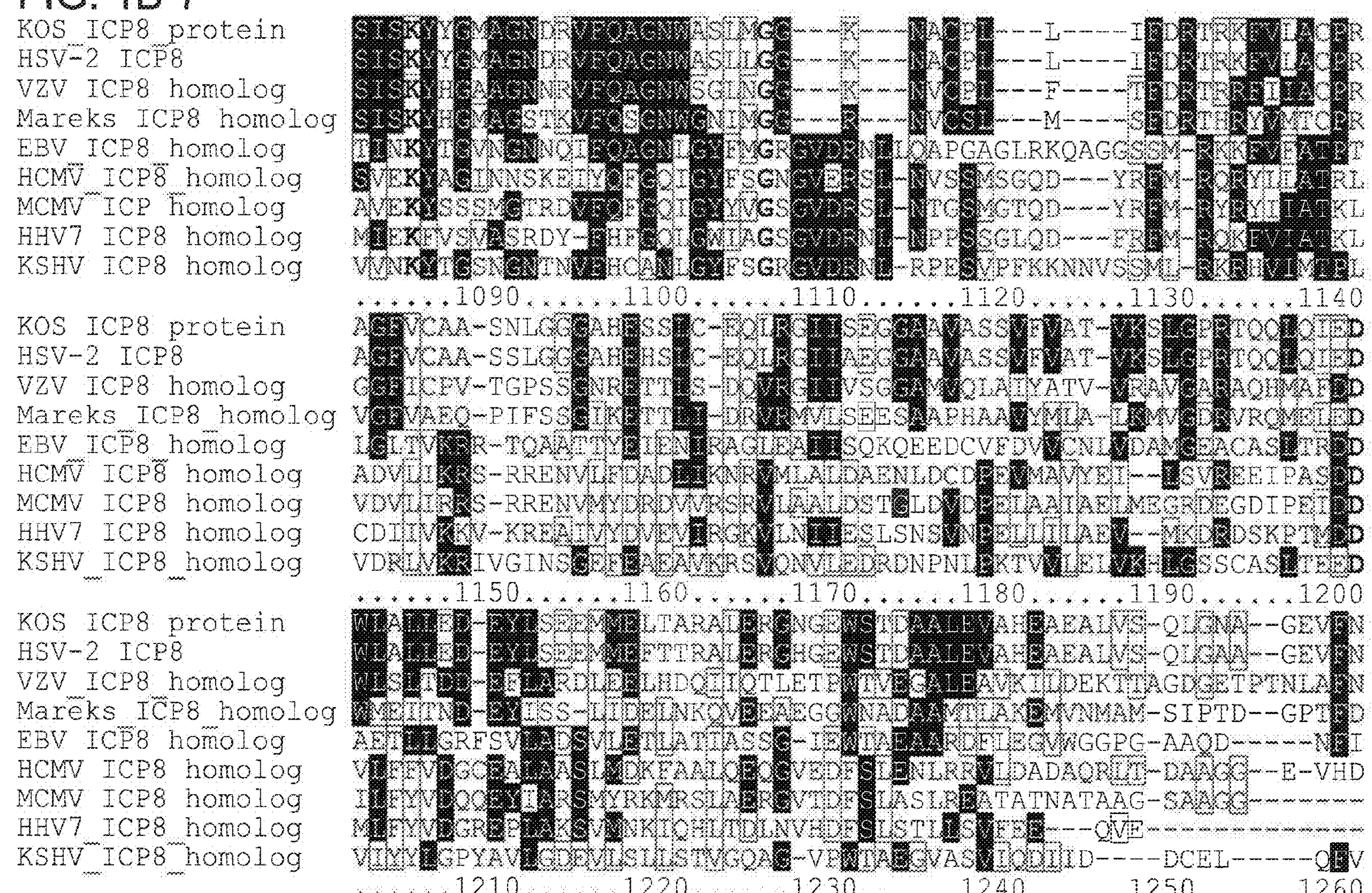
FIG. 1B-7
KOS_ICP8_protein
HSV-2 ICP8
VZV ICP8 homolog
Mareks ICP8 homolog
EBV ICP8 homolog
HCMV ICP8 homolog
MCMV ICP homolog
HHV7 ICP8 homolog
KSHV ICP8 homolog
1090
1100
1110
1120
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1240
1250
1260

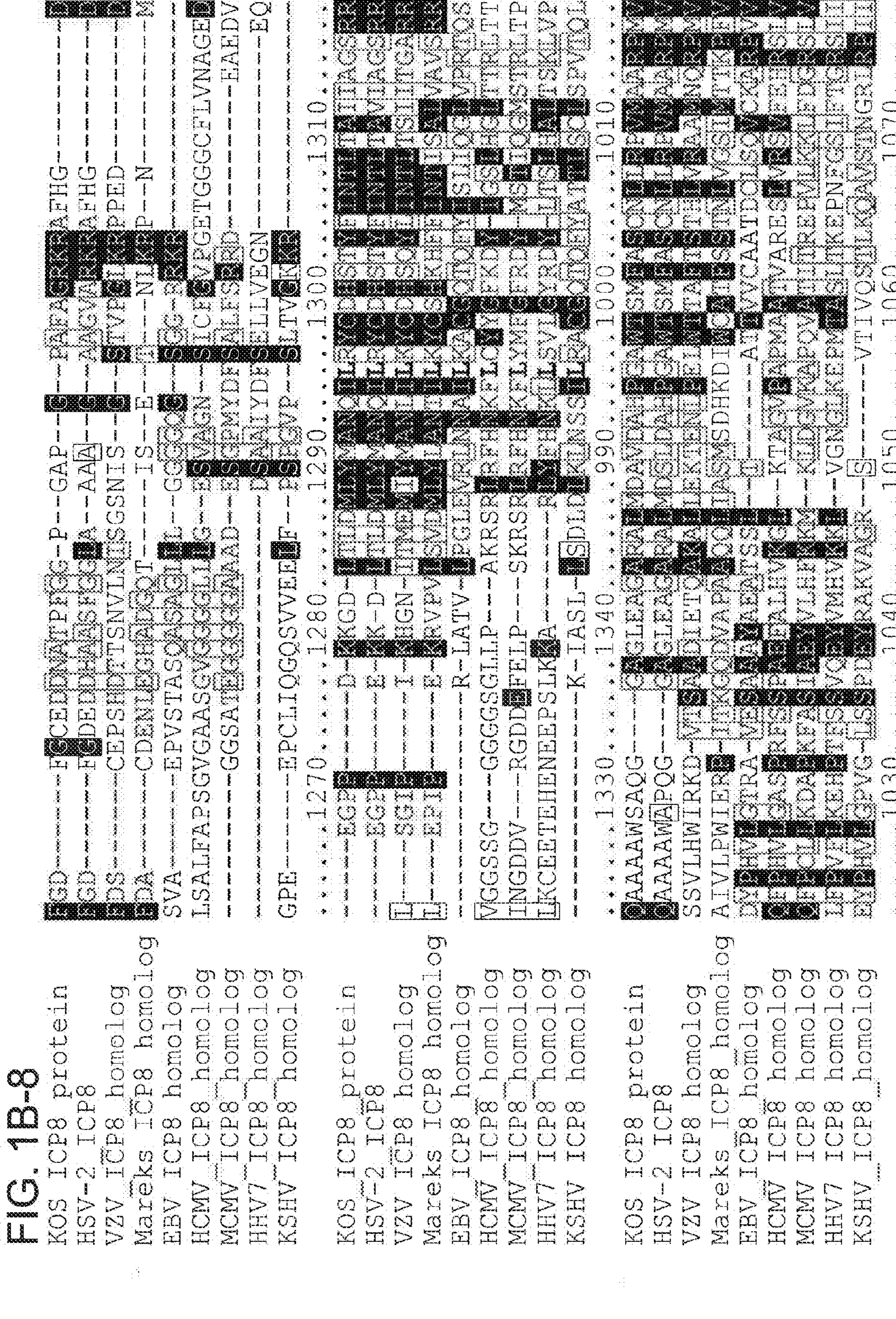

FIG. 1B-8

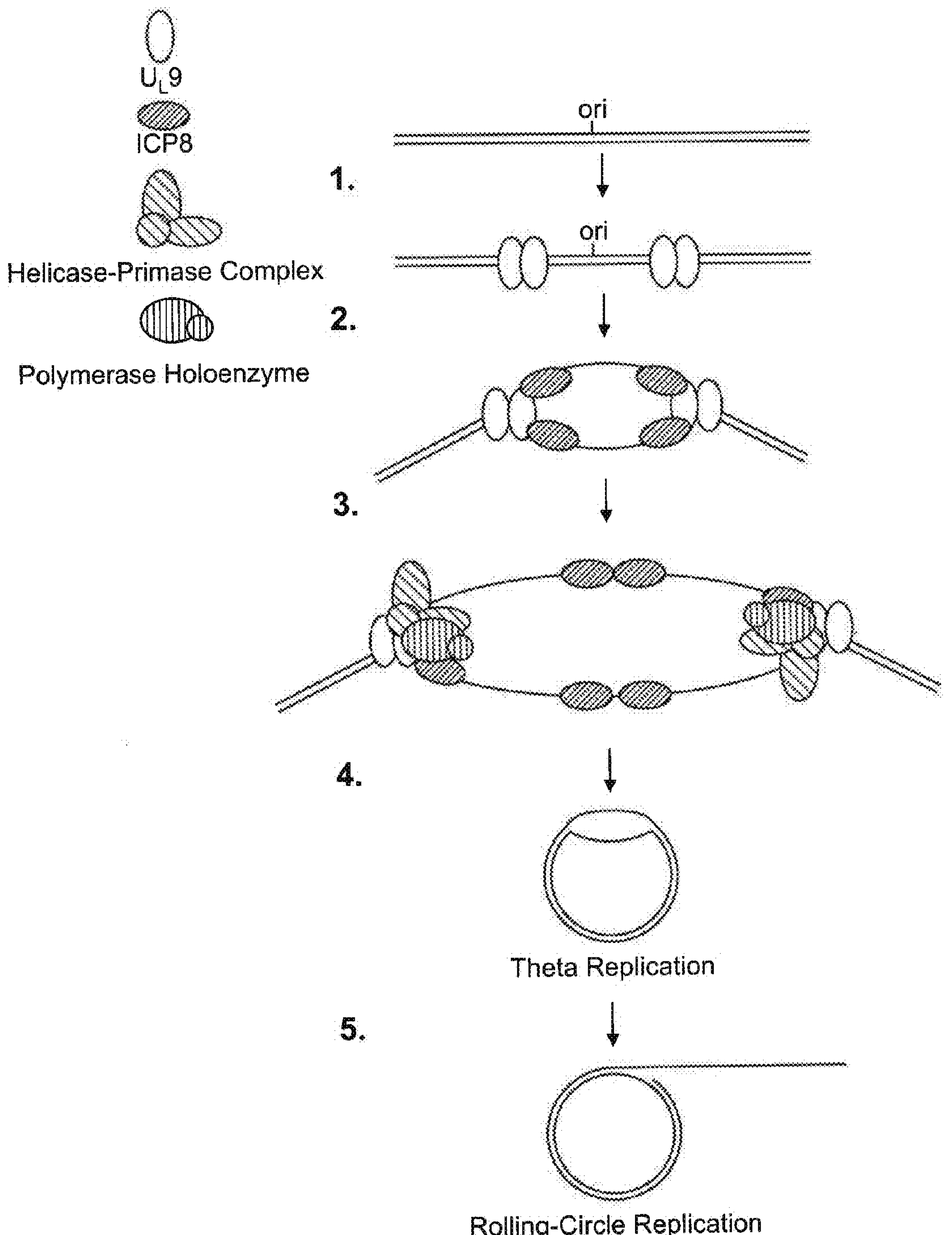

FIG. 2

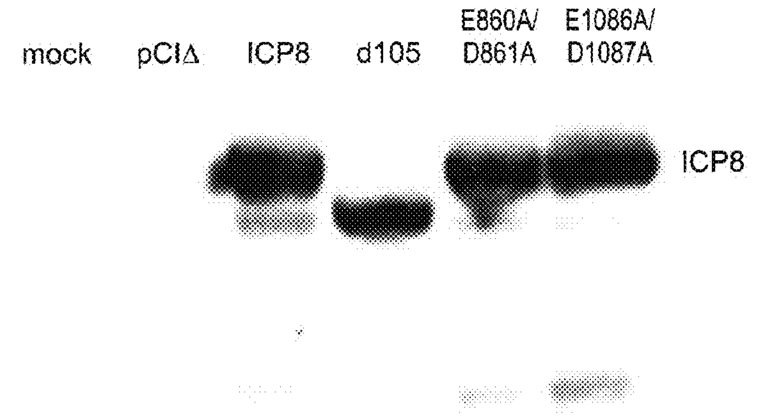

FIG. 3A

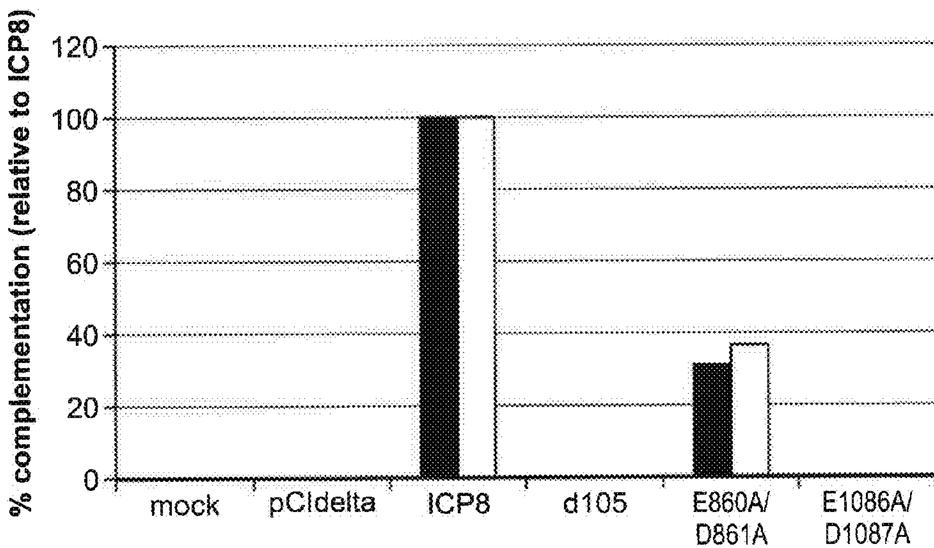

FIG. 3B

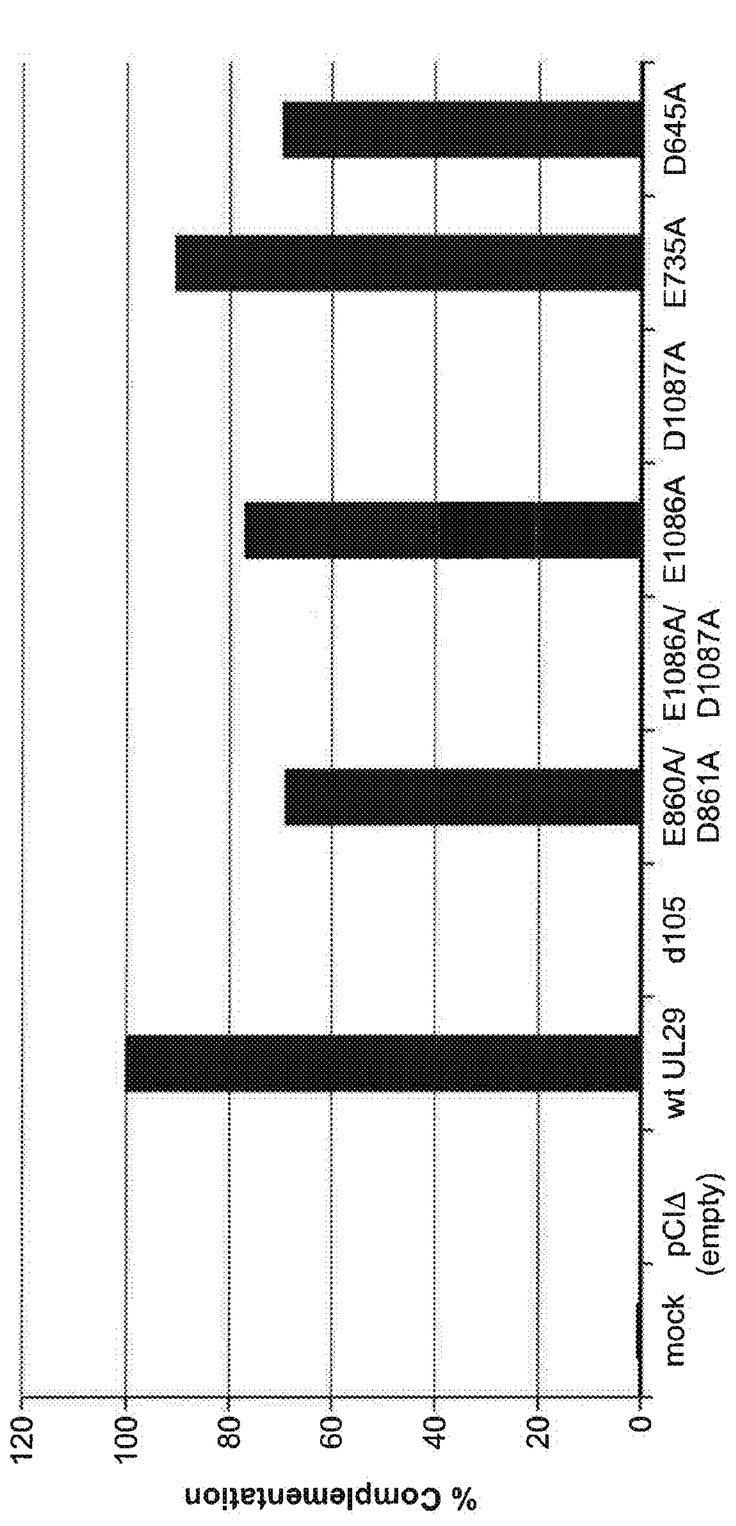

FIG. 3C

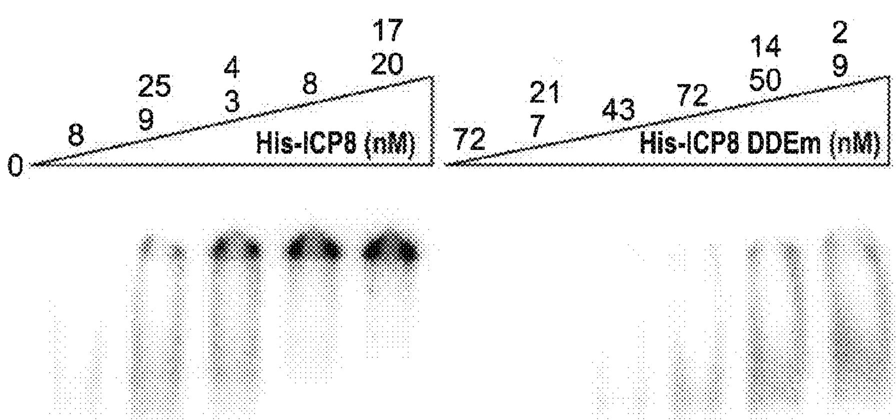

FIG. 3D

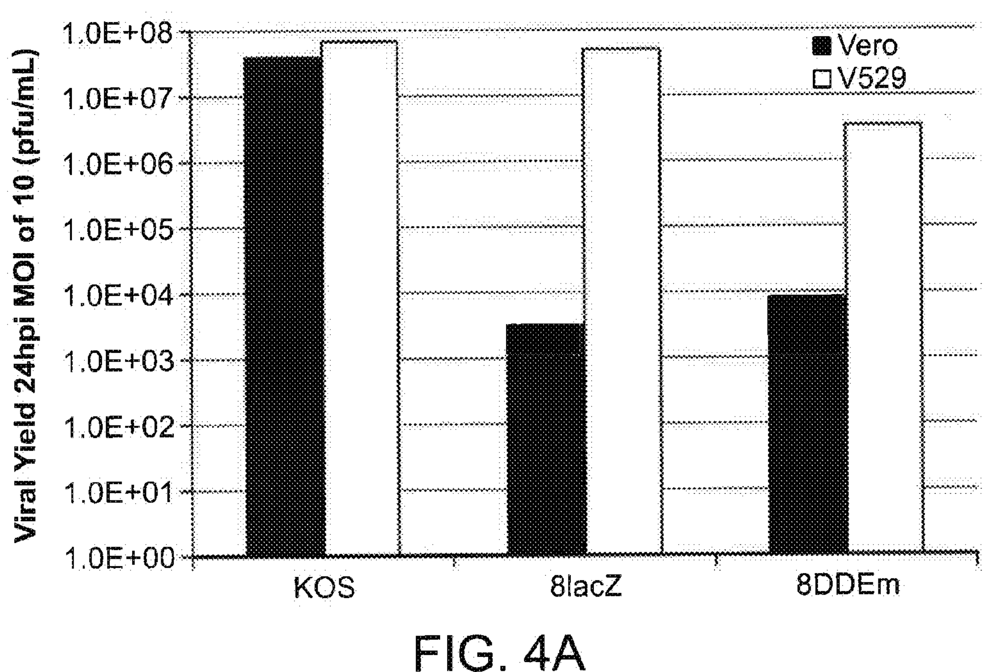

FIG. 4A

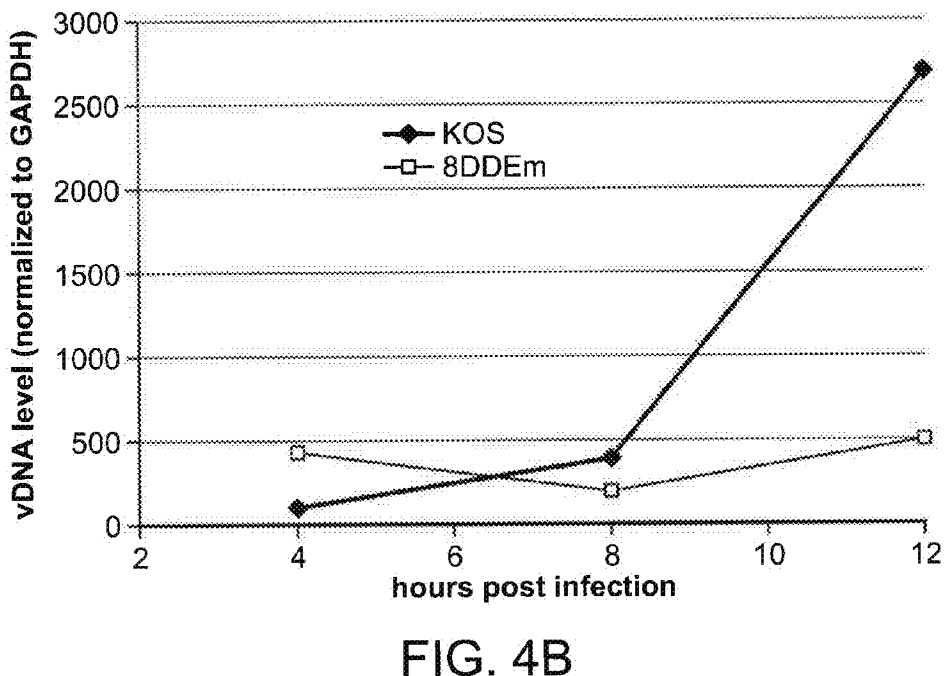

FIG. 4B

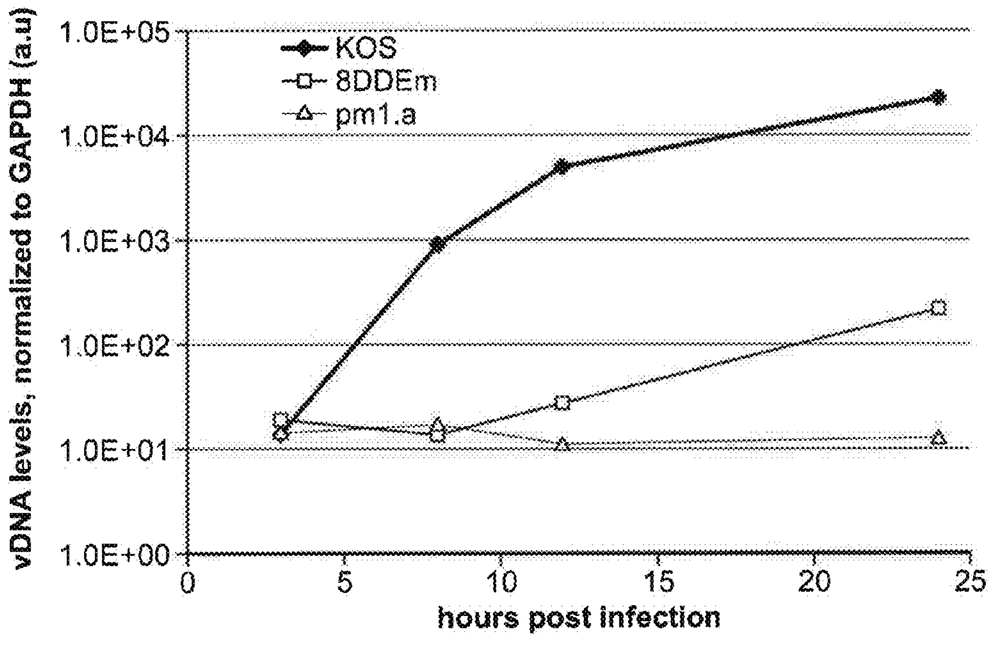

FIG. 4C

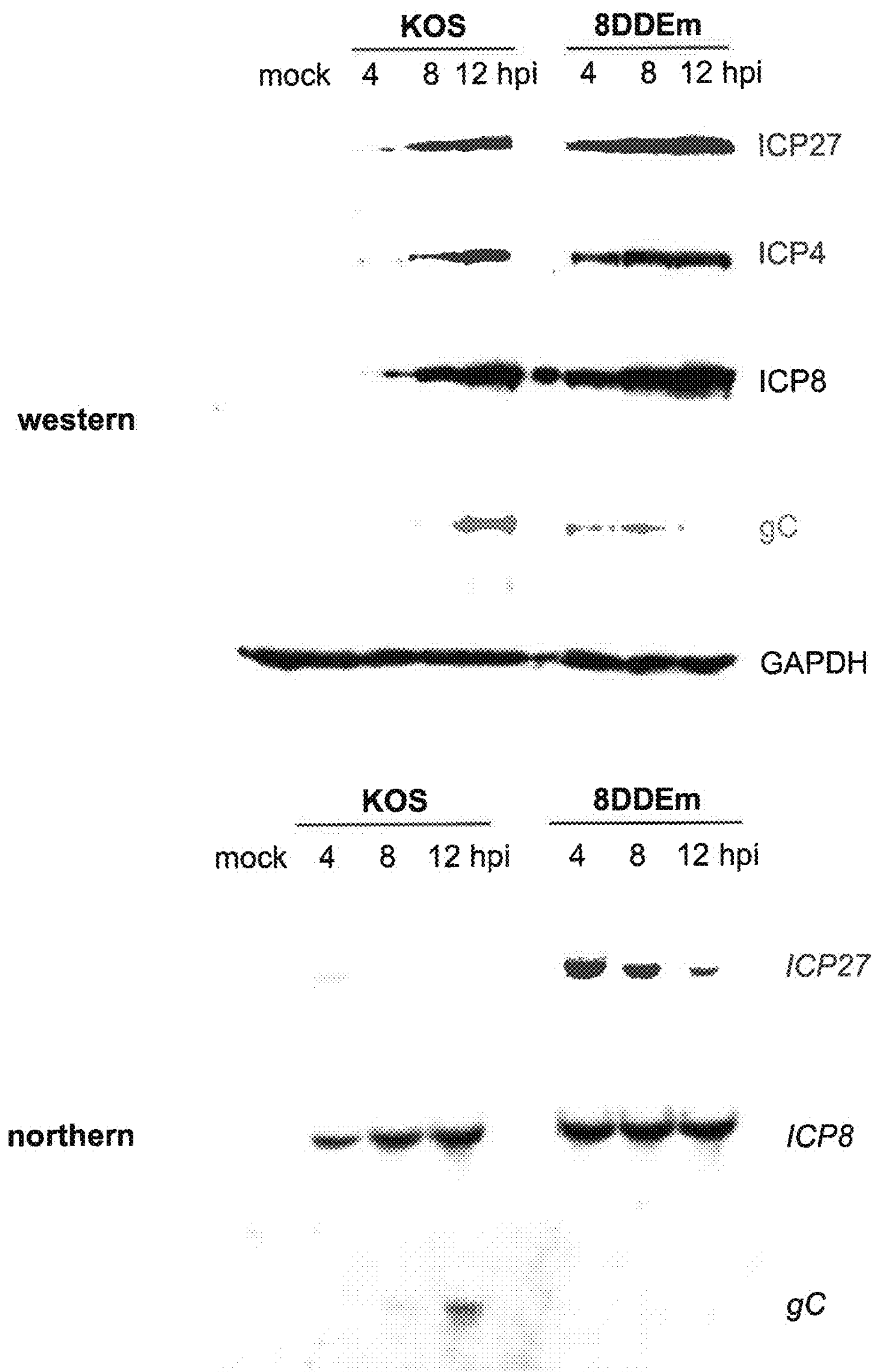

FIG. 5

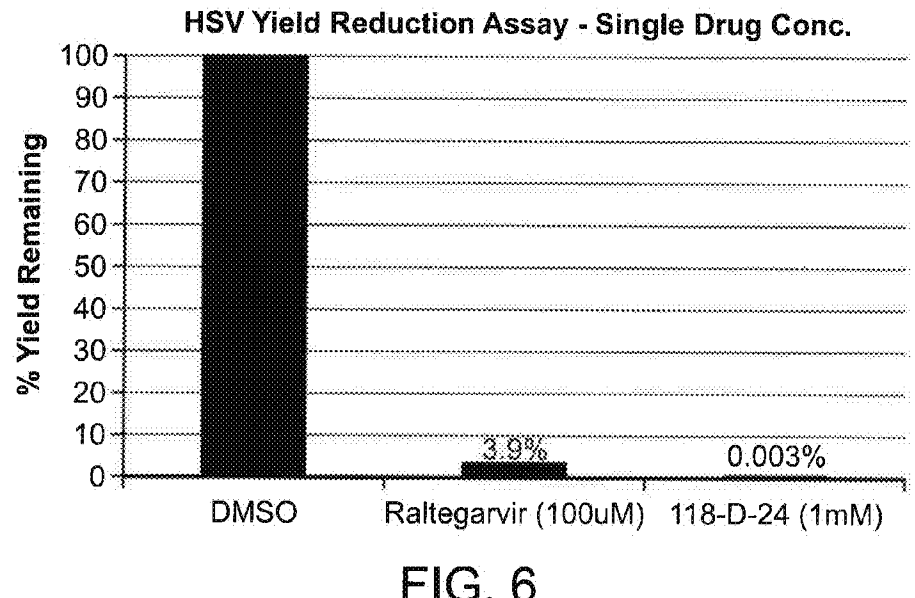

FIG. 6

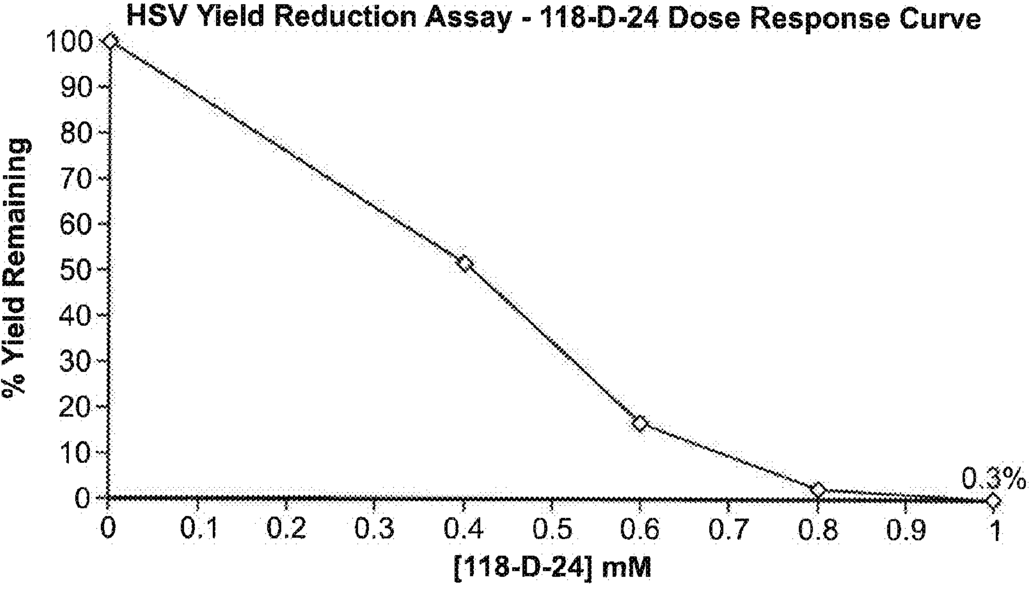

FIG. 7

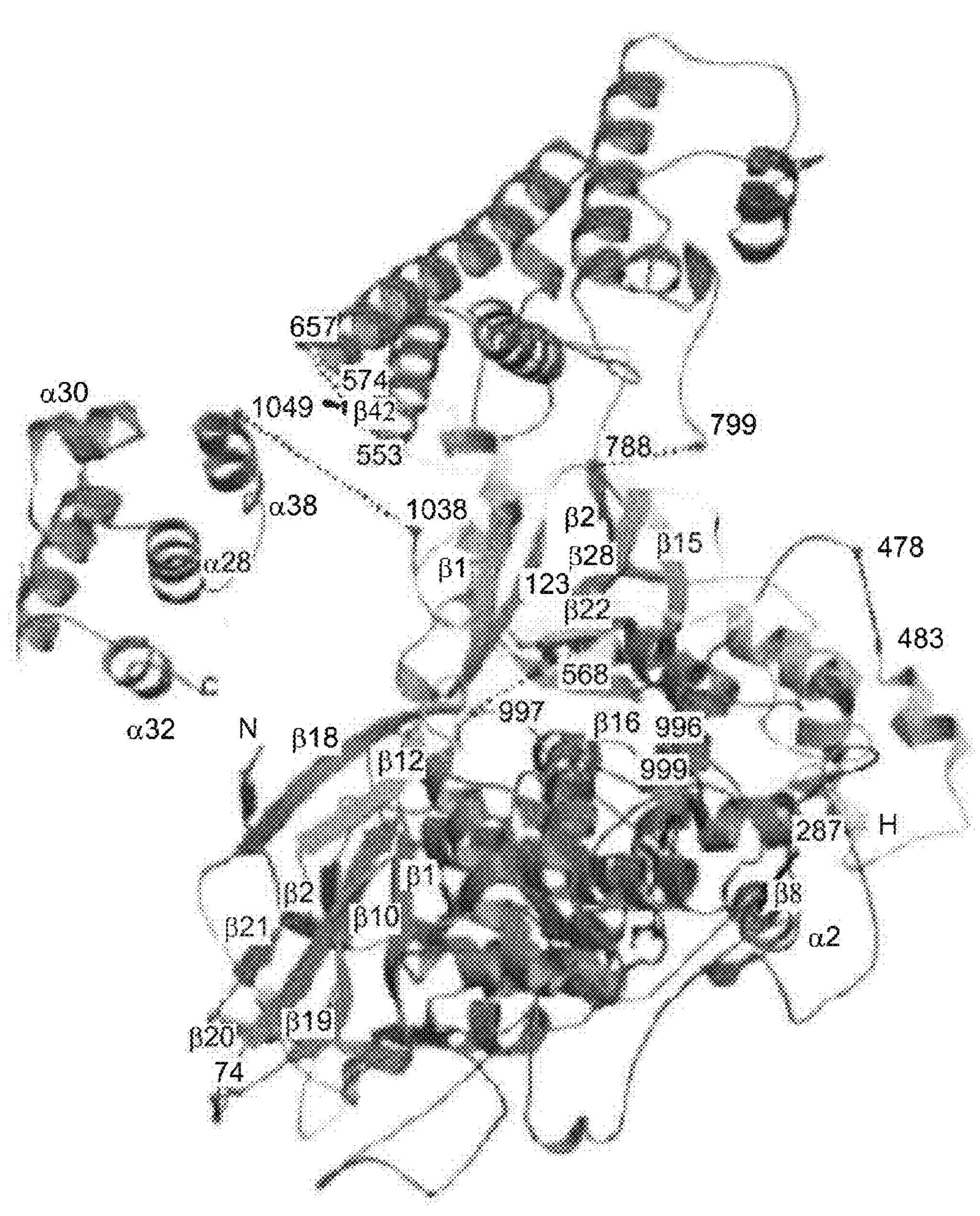

FIG. 8

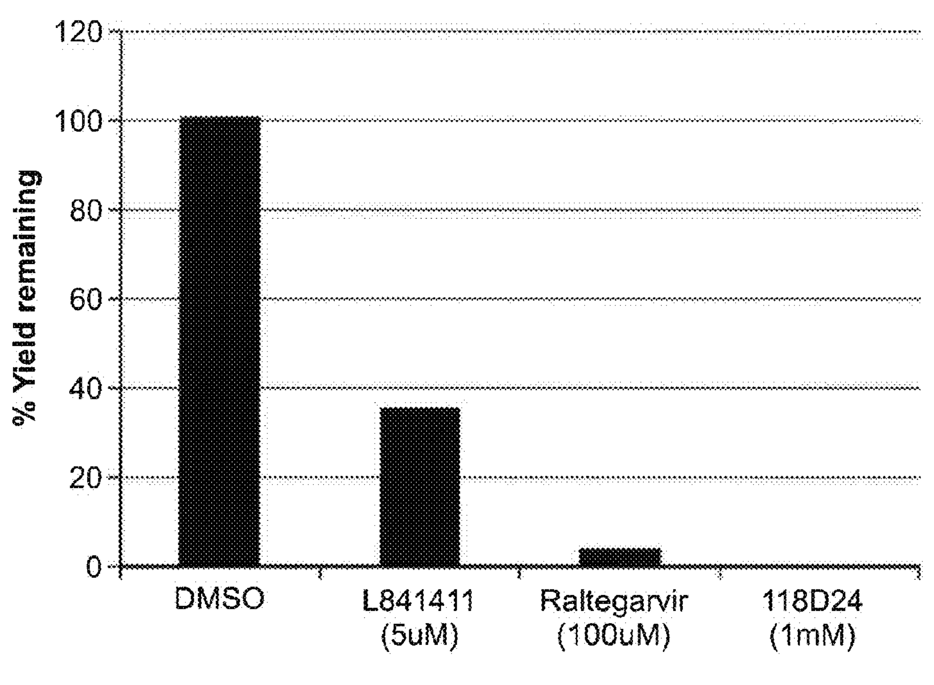

FIG. 9

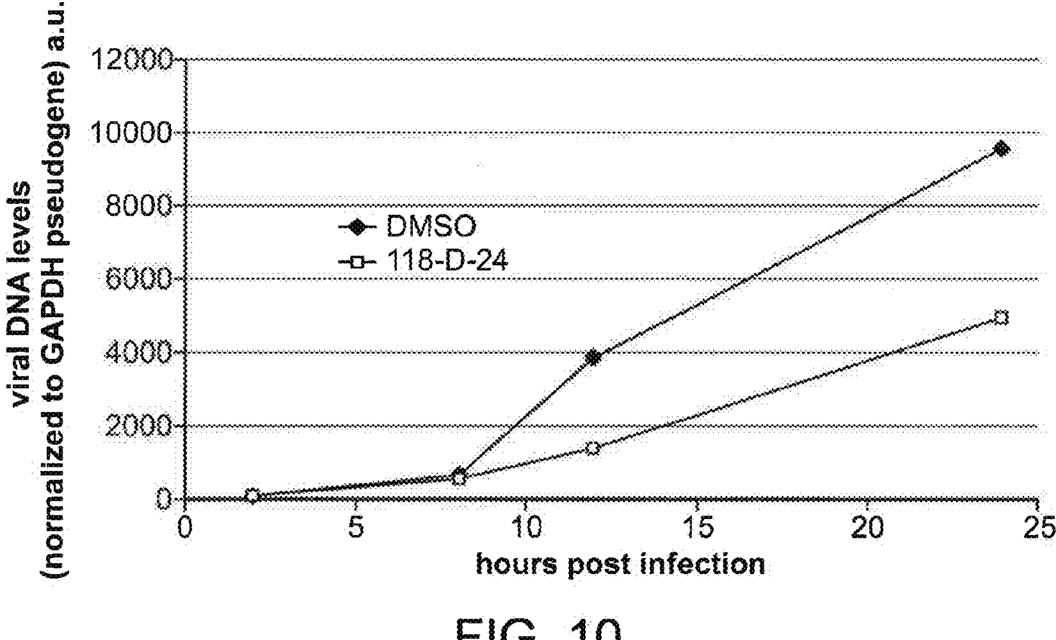

FIG. 10

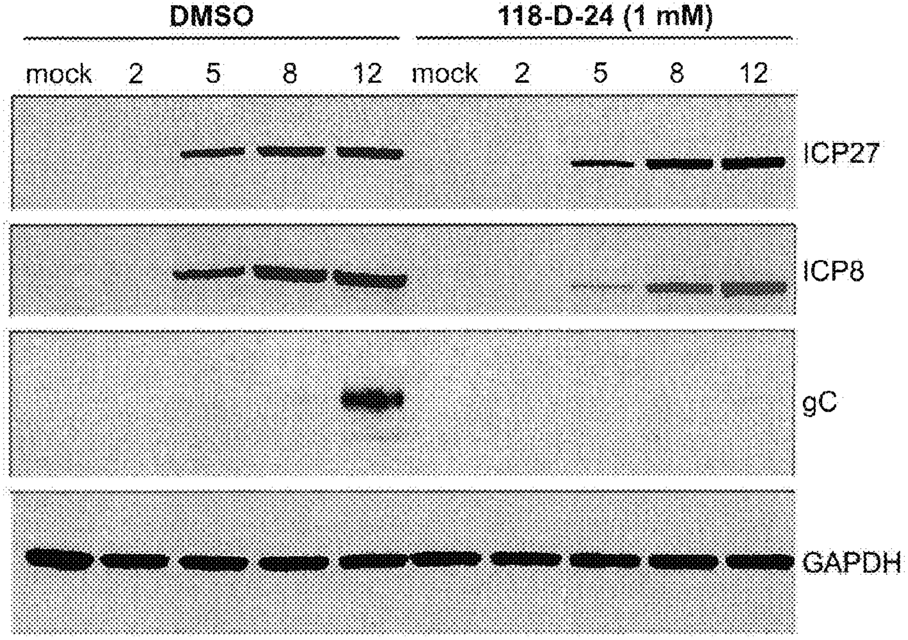

FIG. 11

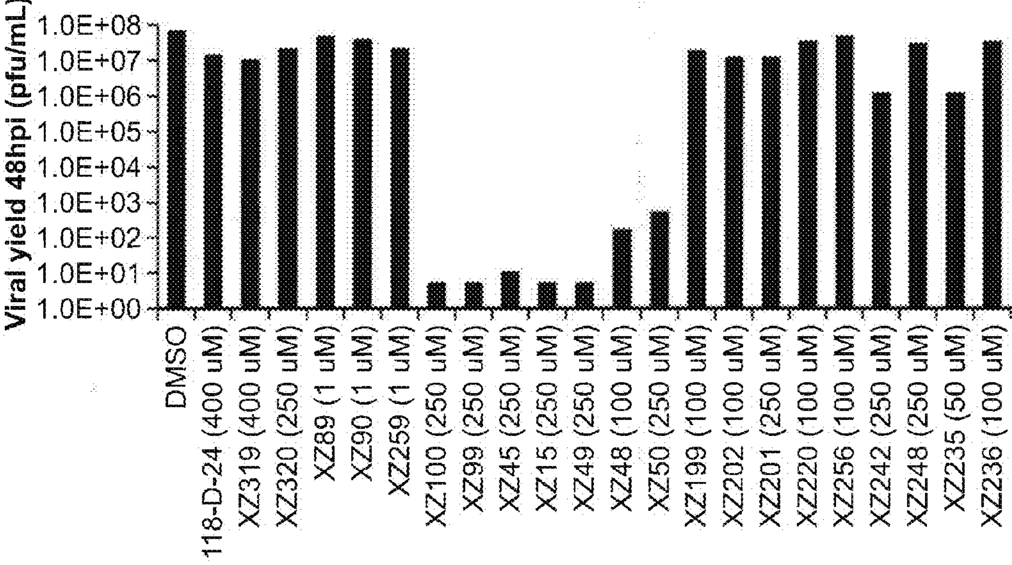

FIG. 12

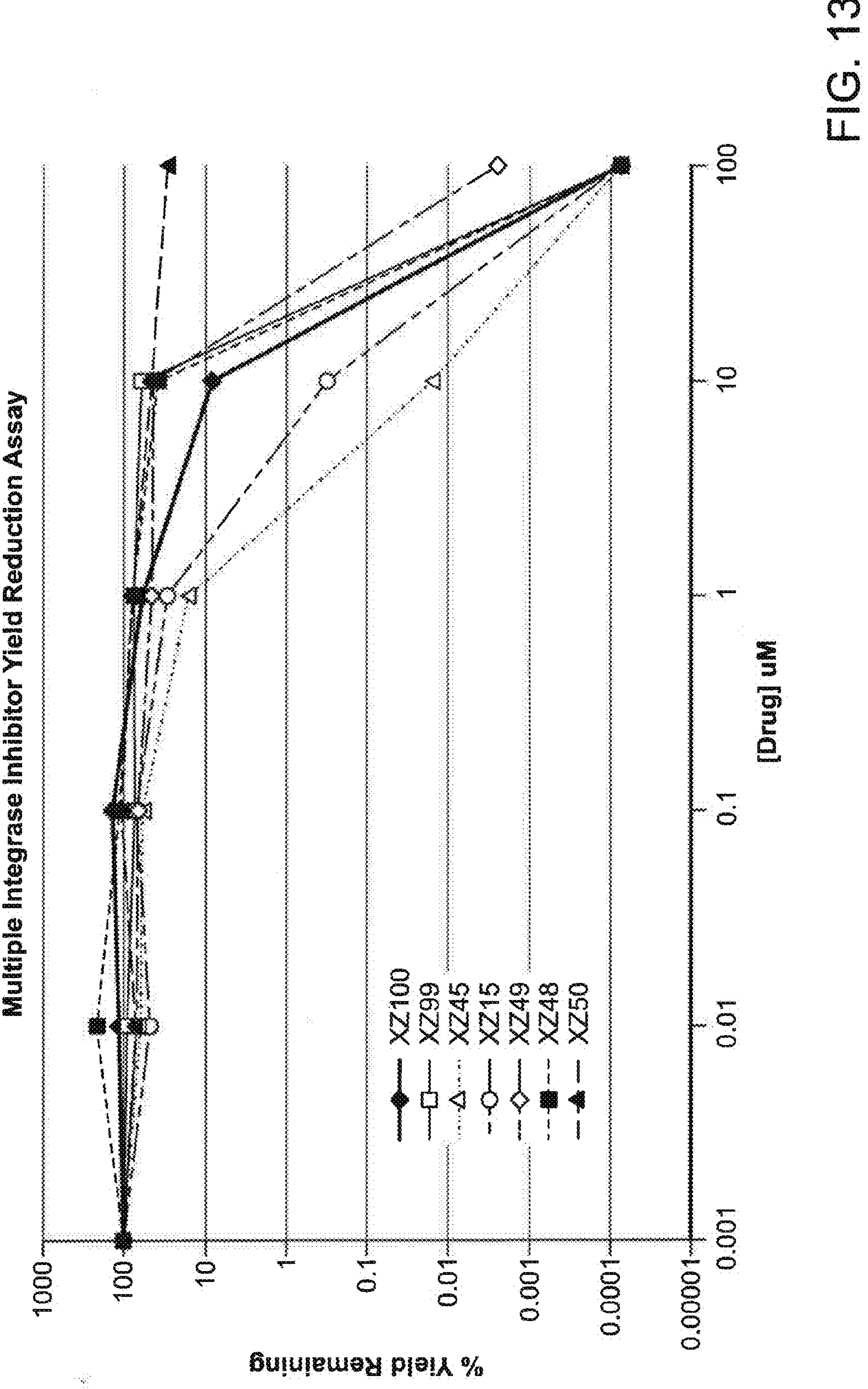

FIG. 13

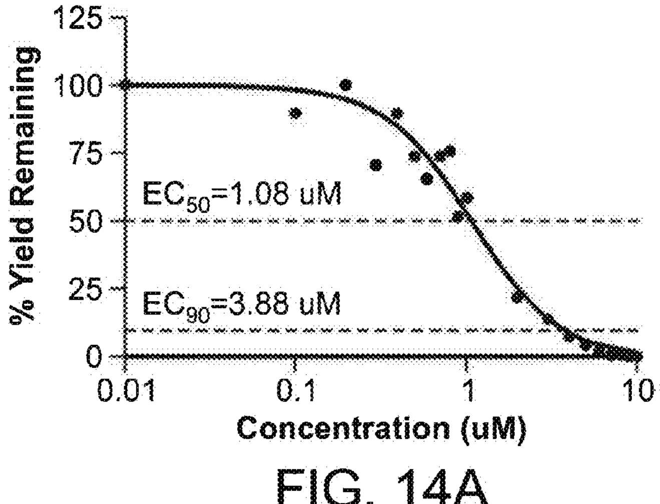

FIG. 14A

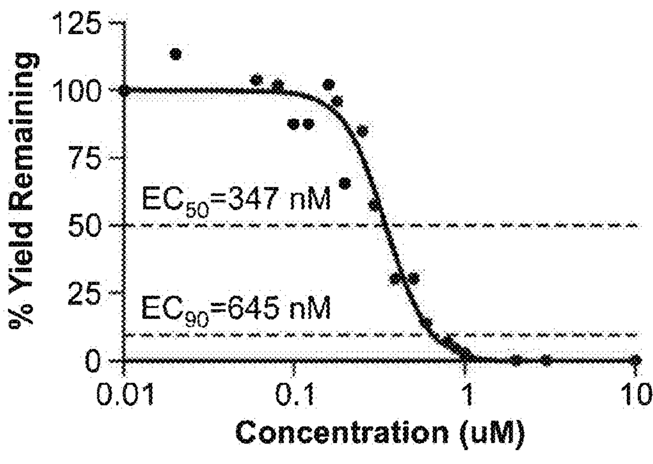

FIG. 14B

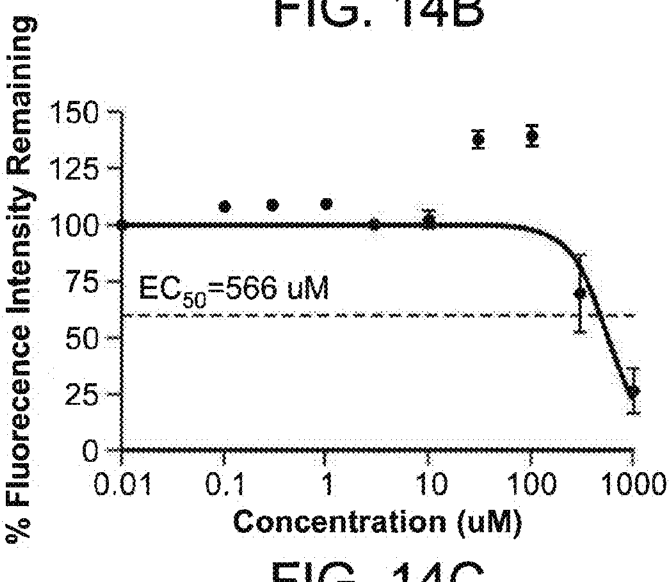

FIG. 14C

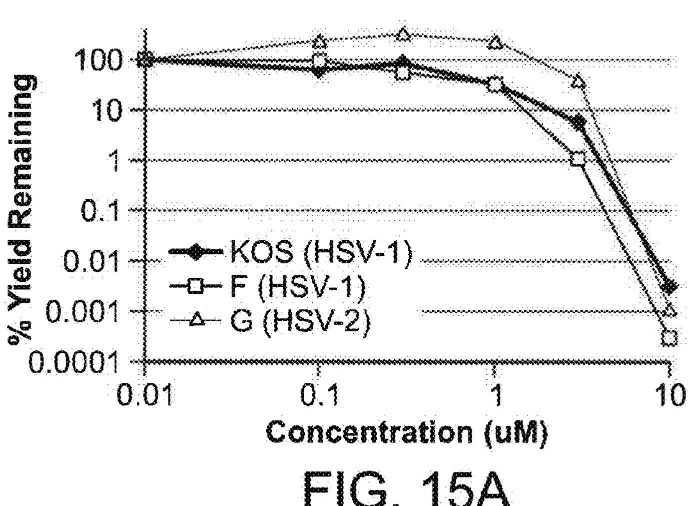

FIG. 15A

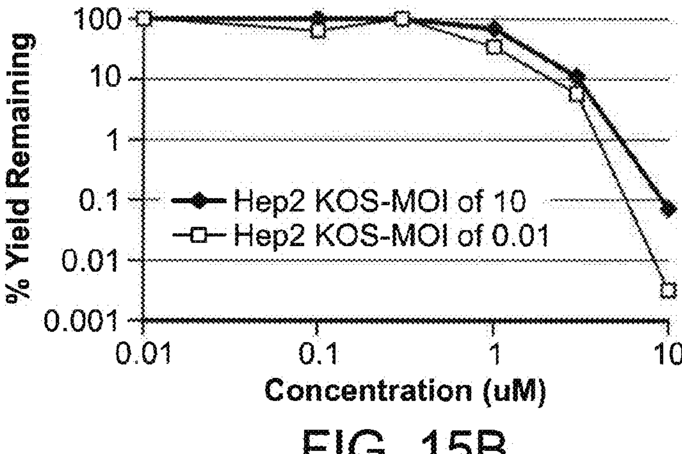

FIG. 15B

Concentration (uM)

100
10
1
0.1
0.01
0.001

% Yield Remaining

HFF KOS-MOI of 10
HFF KOS-MOI of 0.01

0.01
0.1
1
10

Concentration (uM)

FIG. 15C

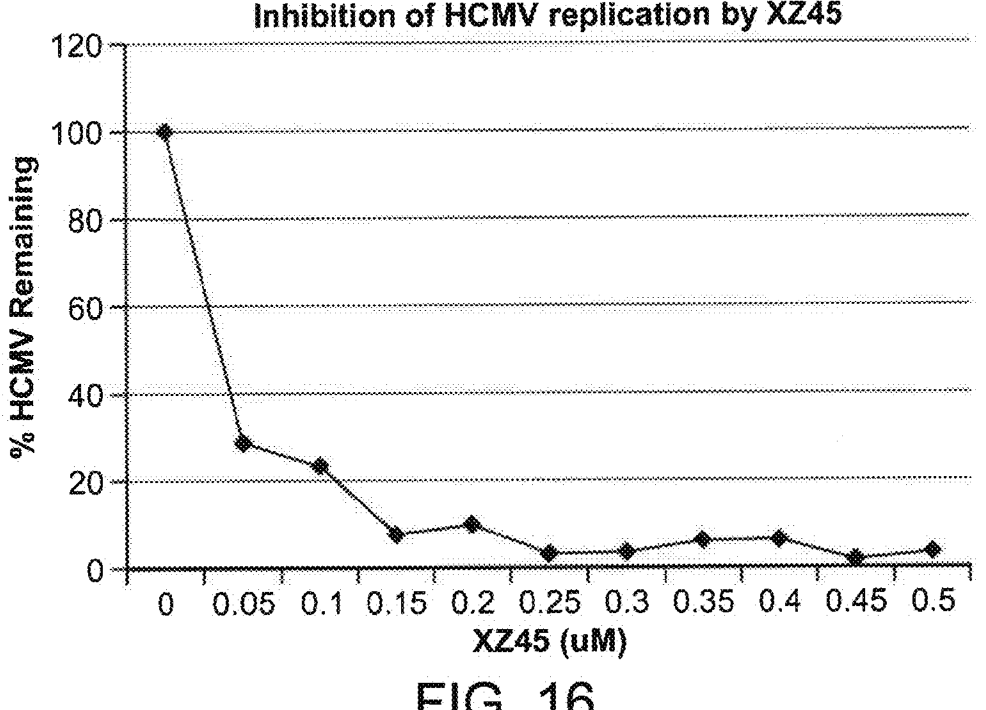

FIG. 16

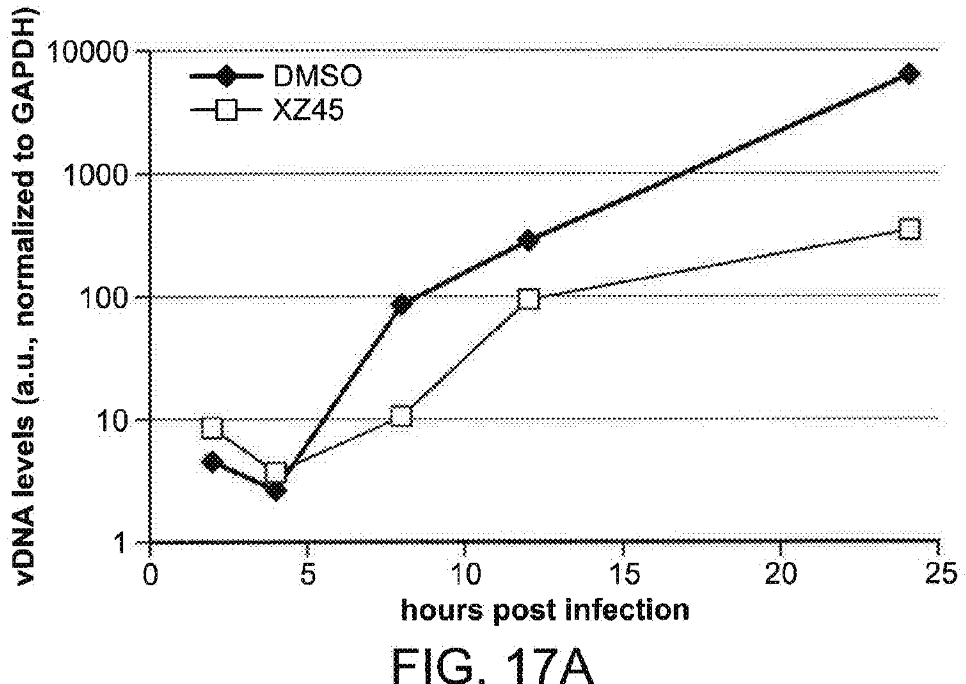

FIG. 17A

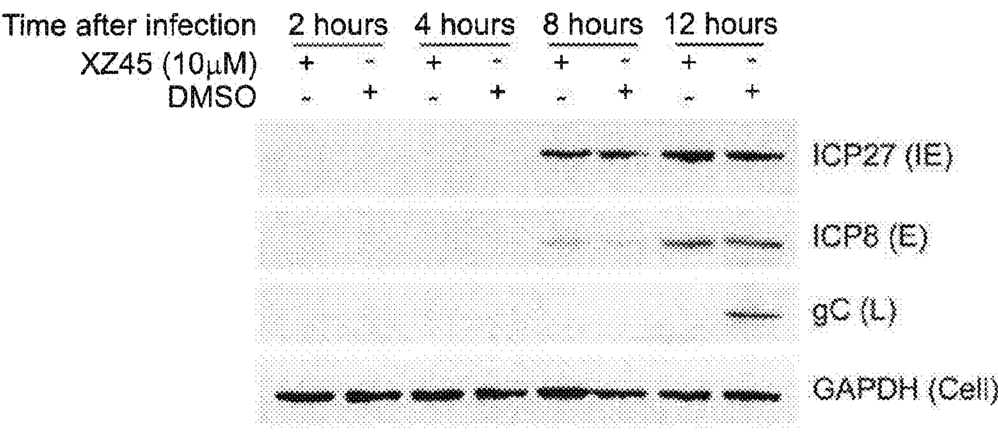

FIG. 17B

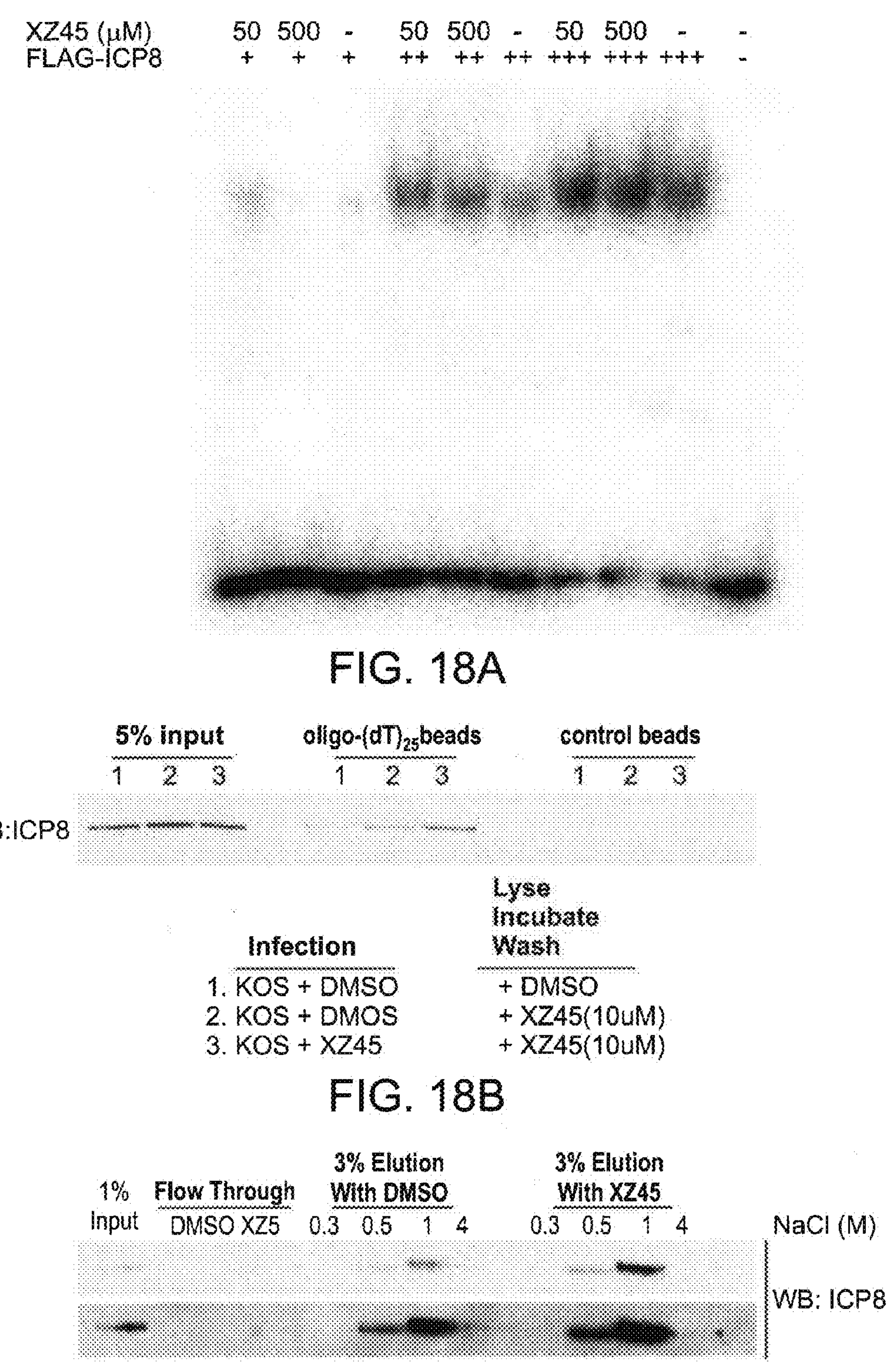

FIG. 18A

FIG. 18B

FIG. 18C

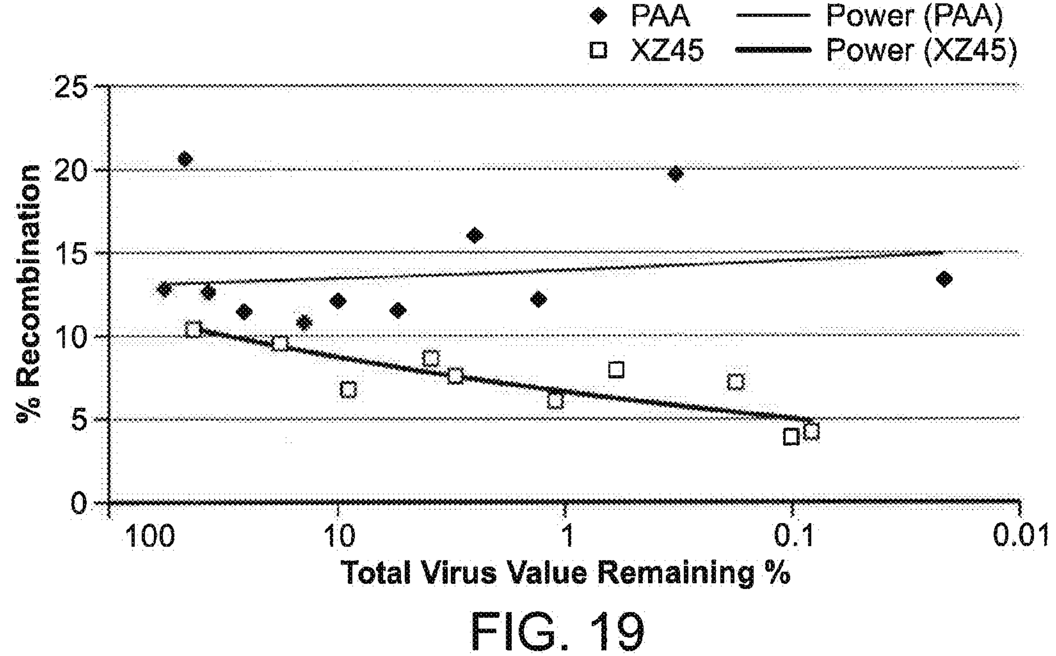

FIG. 19

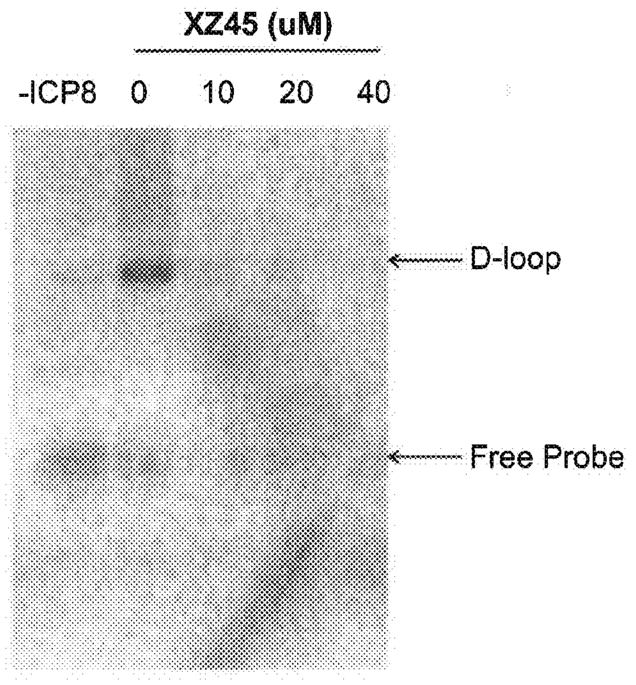

FIG. 20

COMPOSITIONS AND METHODS FOR TREATING HERPES VIRUSES

RELATED APPLICATIONS

[0001] This application is a continuation of PCT Patent Application No. PCT/US2012/047782, filed Jul. 22, 2012, which claims the benefit of and priority to U.S. Provisional Patent Application Ser. No. 61/511,016, filed Jul. 22, 2011. The contents of each of the foregoing applications are incorporated herein by reference in their entirety.

STATEMENT OF RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH

[0002] This work was supported by the following grants from the National Institutes of Health, Grant No's: AI 063106 and AI 081477. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Herpes simplex virus 1 and 2 are ubiquitous human pathogens affecting nineteen percent of the adult U.S. population. The herpes virus is an enveloped virus that contains a 152 kb dsDNA genome that includes eighty-four open reading frames. The primary site of herpes infection is the epithelium and the virus also undergoes replication there. When viral particles are released from the epithelium, they can infect local sensory neurons. The viral particle is transported from the sensory axon back to the cell body of the sensory neuron where it can establish a latent infection.

[0004] Human infection by these herpes viruses typically results in lifelong latent infections that periodically give rise to clinical lesions or asymptomatic viral shedding. Herpes viruses are a major cause of sexually transmitted disease for which no adequate therapies exist. Because transmission of the virus can occur even in the absence of symptoms, public health measures to control the sexual transmission of the virus have been largely ineffective. In addition, chronic infection with the virus lowers immune function and increases the probability that an infected individual will acquire human immunodeficiency virus (HIV).

[0005] Herpes infections can also be transmitted from a mother to her infant during childbirth. The resulting neonatal infections have a fifty percent mortality rate and even when the neonate survives the infection, neurological sequelae are common. Better methods of treating and preventing herpes infection are urgently required.

SUMMARY OF THE INVENTION

[0006] The invention generally provides therapeutic and prophylactic compositions that include an ICP8 or ICP8 homolog inhibitor that reduces or eliminates viral replication of a Herpes virus, including but not limited to herpes simplex virus (HSV) (e.g., HSV-1 or HSV-2) and/or or related double stranded DNA virus.

[0007] In one aspect, the invention provides a method of inhibiting Herpes virus (e.g., herpes simplex virus) replication in a cell, the method comprising contacting the cell with an agent that inhibits a DDE recombinase, thereby inhibiting herpes virus replication in the cell.

[0008] In another aspect, the invention provides a method of inhibiting Herpes virus (e.g., herpes simplex virus) replication in a cell, the method comprising contacting the cell with an agent that reduces the biological activity of a herpes virus polypeptide having functional and/or structural homology to a human immunodeficiency virus (HIV) integrase, thereby inhibiting herpes virus replication in the cell.

[0009] In certain embodiments, the polypeptide is ICP8 or an ICP8 homolog (e.g., a homologous viral recombinase of the herpes virus alpha, beta, gamma family or a related double stranded DNA virus). In certain embodiments, the agent is a small compound that inhibits Human Immunodeficiency Virus (HIV) integrase enzymatic activity. In certain embodiments, the agent is selected from the group consisting of Raltegravir, 118-D-24, L-841411, elvitegrevir, MK-2048, XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50; or a derivative or analog thereof.

[0010] In another aspect, the invention provides a method of inhibiting Herpes virus (e.g., herpes simplex virus) replication in a cell, the method comprising contacting the cell with Raltegravir or 118-D-24, thereby inhibiting herpes virus replication in the cell.

[0011] In another aspect, the invention provides a method of Herpes virus (e.g., herpes simplex virus) replication in a cell, the method comprising contacting the cell with an agent that inhibits Infected Cell Protein 8 (ICP8) biological activity or expression in the cell, thereby inhibiting herpes virus replication in the cell.

[0012] In certain embodiments, the agent is selected from the group consisting of Raltegravir, 118-D-24, L-841411, elvitegrevir, MK-2048, XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50; or a derivative or analog thereof.

[0013] In another aspect, the invention provides a method of treating or preventing a Herpes virus (e.g., herpes simplex virus) infection in a subject, the method comprising administering to the subject an effective amount of an agent that inhibits a DDE recombinase, thereby treating or preventing a herpes virus infection in the subject.

[0014] In another aspect, the invention provides a method of treating or preventing a Herpes virus (e.g., herpes simplex virus) infection in a subject, the method comprising administering to the subject an effective amount of an agent that reduces the biological activity of a herpes virus polypeptide having functional and/or structural homology to a human immunodeficiency virus (HIV) integrase, thereby treating or preventing a herpes virus infection in a subject.

[0015] In certain embodiments, the agent reduces herpes virus replication. In certain embodiments, the effective amount is sufficient to reduce viral replication by at least about 85% or more.

[0016] In other embodiments of the invention the herpes virus is an alphaherpesvirus, a betaherpesvirus, or a gammaherpesvirus. In certain embodiments the herpes virus of the invention is capable of infecting a human cell. In other embodiments the herpes virus of the invention is capable of infecting a non-human mammal cell. In yet other embodiments, the herpes virus is Herpes simplex virus 1 (HSV-1), Herpes simplex virus 2 (HSV-2), Epstein Barr virus (EBV), Cytomegalovirus (CMV), Varicella Zoster Virus (VZV), Herpes lymphotropic virus, Human herpes virus 6 (HHV-6), Human herpes virus 7 (HHV-7), Human herpes virus 8 (HHV-8), or Kaposi's sarcoma-associated herpes virus (KSHV).

[0017] In another aspect, the invention provides a method of treating or preventing a Herpes virus (e.g., herpes simplex virus) infection in a subject, the method comprising administering to the subject an effective amount of an agent selected from the group consisting of Raltegravir 118-D-24, XZ100,

XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50; or a derivative or analog thereof, thereby treating or preventing a herpes virus infection in the subject.

[0018] In yet another aspect, the invention provides a method of inhibiting Herpes virus (e.g., herpes simplex virus) replication in a subject, the method comprising administering to the subject an effective amount of a compound capable of inhibiting a viral DDE recombinase, such that replication of herpes virus in the subject is inhibited.

[0019] In certain embodiments of the above methods, the method further comprises identifying the subject as having or at risk of developing a herpes virus infection. In certain embodiments, the method further comprises identifying the subject as testing negative for an HIV infection.

[0020] In another aspect, the invention provides a method of treating or preventing a Herpes virus (e.g., herpes simplex virus) infection in a subject, the method comprising

[0021] diagnosing the subject as having a herpes virus infection; and

[0022] administering to the subject an effective amount of an agent selected from the group consisting of Raltegravir, 118-D-24, XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50; or a derivative or analog thereof, thereby treating or preventing a herpes virus infection in the subject.

[0023] In certain embodiments, the subject is identified as testing negative for an HIV infection.

In certain embodiments, the effective amount is sufficient to reduce viral replication by at least about 85% or more.

[0024] In certain embodiments, the subject is identified as having an acyclovir-resistant herpes virus infection.

[0025] In yet another aspect, the invention provides a method of inhibiting the re-activation of a latent Herpes virus (e.g., herpes simplex virus) in a subject, the method comprising administering to a subject identified as having a latent herpes virus infection an effective amount of an agent that reduces the biological activity of a herpes virus polypeptide having functional and/or structural homology to a human immunodeficiency virus (HIV) integrase, thereby inhibiting the re-activation of the latent herpes virus in the subject.

[0026] In another aspect, the invention provides a method of reducing the propensity of a subject to acquire an HIV infection, the method comprising: diagnosing the subject as having a herpes virus infection; and administering to the subject an effective amount of an agent selected from the group consisting of Raltegravir, 118-D-24 XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50; or a derivative or analog thereof; or an agent that reduces the biological activity of a herpes virus polypeptide having functional and/or structural homology to a human immunodeficiency virus (HIV) integrase, thereby treating or preventing a herpes virus infection in the subject.

[0027] In certain embodiments of the methods described above, the herpes virus is HSV1 or HSV2.

[0028] In another aspect, the invention provides a pharmaceutical composition comprising an effective amount of an agent selected from the group consisting of Raltegravir, 118-D-24, XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50; or a derivative or analog thereof; or an agent that reduces the biological activity of a herpes virus polypeptide having functional and/or structural homology to a human immunodeficiency virus (HIV) integrase formulated for topical administration.

[0029] In another aspect, the invention provides an isolated herpes virus comprising an alteration in an ICP8 nucleic acid sequence, wherein the alteration decreases viral replication in a cell.

[0030] In another aspect, the invention provides a cell infected with the herpes virus comprising an alteration in an ICP8 nucleic acid sequence, wherein the alteration decreases viral replication in a cell.

[0031] In still another aspect, the invention provides an immunogenic composition comprising an effective amount of the herpes virus comprising an alteration in an ICP8 nucleic acid sequence, wherein the alteration decreases viral replication in a cell.

[0032] In another aspect, the invention provides a method of generating an HSV-specific immune response in a subject, the method comprising administering to the subject an effective amount of the herpes virus comprising an alteration in an ICP8 nucleic acid sequence, wherein the alteration decreases viral replication in a cell in a pharmaceutically acceptable excipient.

[0033] In still another aspect, the invention provides a method of identifying a compound that inhibits Herpes virus (e.g., herpes simplex virus) replication in a cell, the method comprising:

[0034] contacting a herpes virus infected cell with a test compound, and comparing viral DDE recombinase activity in said cell relative to a reference, wherein a reduction in DDE recombinase activity in said cell identifies the compound as capable of inhibiting herpes virus replication in a cell.

[0035] In yet another aspect, the invention provides a method of identifying a compound that treats or prevents a Herpes virus (e.g., herpes simplex virus) infection in a subject, the method comprising:

[0036] contacting a Herpes virus (e.g., herpes simplex virus) infected cell with a compound that inhibits HIV integrase;

[0037] and comparing Herpes virus (e.g., herpes simplex virus) replication in said cell with a reference, wherein a compound that inhibits herpes virus replication is identified as useful for treating or preventing herpes virus infection.

[0038] In still another aspect, the invention provides a method of identifying a compound that inhibits herpes virus replication in a cell, the method comprising:

[0039] a) obtaining a crystal structure of HSV ICP8 or obtaining information relating to the crystal structure of HSV ICP8, and

[0040] b) modeling a test compound into or on the crystal structure coordinates to determine whether the compound inhibits HSV ICP8 and inhibits replication of Herpes virus (e.g., herpes simplex virus, HSV) in a cell.

[0041] In yet another aspect, the invention features a method of inhibiting recombination mediated by ICP8 or an ICP8 homolog involving contacting the ICP8 or ICP8 homolog with an effective amount of Raltegravir, 118-D-24, L-841411, elvitegrevir, MK-2048, XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, or XZ50; or a derivative or analog thereof.

[0042] In another aspect, the invention features a method of inhibiting expression of a herpes virus late gene (or inhibiting production of a herpes virus late gene protein product) involving contacting a cell infected with a herpes virus with an agent that inhibits DDE recombinase, thereby inhibiting expression of the herpes virus late gene.

[0043] In one embodiment the agent is Raltegravir, 118-D-24, L-841411, elvitegrevir, MK-2048, XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, or XZ50; or a derivative or analog thereof.

[0044] By "ICP8 polypeptide" is meant a protein having at least about 85% identity to NCBI Accession No. P17470, or a fragment thereof, having recombinase activity and/or DNA binding activity. In certain embodiments, an ICP8 polypeptide has amino acid sequence identity to NCBI Accession No. BAA01507.1. In other embodiments, a fragment of ICP8 comprises an ICP8 DDE domain or DNA binding domain.

[0045] HSV-1 wild type strain KOS ICP8 amino acid sequence:

METKPKTATTIKVPPGPLGYVYARACPSEGIELLALLSARSGDADVAVAP

LVVGLTVESGFEANVAVVVGSRTTGLGGTAVSLKLTPSHYSSSVYVFHGG

RHLDPSTQAPNLTRLCERARRHFGFSDYTPRPGDLKHETTGEALCERLGL

DPDRALLYLVVTEGFKEAVCINNTFLHLGGSDKVTIGGAEVHRIPVYPLQ

LFMPDFSRVIAEPFNANHRSIGENFTYPLPFFNRPLNRLLFEAVVGPAAV

ALRCRNVDAVARAAAHLAFDENHEGAALPADITFTAFEASQGKTPRGGRD

GGGKGPAGGPEQRLASVMAGDAALALESIVSMAVFDEPPTDISAWPLCEG

QDTAAARANAVGAYLARAAGLVGAMVFSTNSALHLTEVDDAGPADPKDHS

KPSFYRFFLVPGTHVAANPQVDREGHVVPGFEGRPTAPLVGGTQEFAGEH

LAMLCGFSPALLAKMLFYLERCDGGVIVGRQEMDVFRYVADSNQTDVPCN

LCTFDTRHACVHTTLMRLRARHPKFASAARGAIGVFGTMNSMYSDCDVLG

NYAAFSALKRADGSETARTIMQETYRAATERVMAELETLQYVDQAVPTAM

GRLETIITNREALHTVVNNVRQVVDREVEQLMRNLVEGRNFKFRDGLGEA

NHAMSLTLDPYACGPCPLLQLLGRRSNLAVYQDLALSQCHGVFAGQSVEG

RNFRNQFQPVLRRRVMDMFNNGFLSAKTLTVALSEGAAICAPSLTAGQTA

PAESSFEGDVARVTLGFPKELRVKSRVLFAGASANASEAAKARVASLQSA

YQKPDKRVDILLGPLGFLLKQFHAAIFPNGKPPGSNQPNPQWFWTALQRN

QLPARLLSREDIETIAFIKKFSLDYGAINFINLAPNNVSELAMYYMANQI

LRYCDHSTYFINTLTAIIAGSRRPPSVQAAAAWSAQGGAGLEAGARALMD

AVDAHPGAWTSMFASCNLLRPVMAARPMVVLGLSISKYYGMAGNDRVFQA

GNWASLMGGKNACPLLIFDRTRKFVLACPRAGFVCAASNLGGGAHESSLC

EQLRGIISEGGAAVASSVFVATVKSLGPRTQQLQIEDWLALLEDEYLSEE

MMELTARALERGNGEWSTDAALEVAHEAEALVSQLGNAGEVFNFGDFGCE

DDNATPFGGPGAPGPAFAGRKRAFHGDDPFGEGPPDKKGDLTLDML

[0046] By "ICP8 DDE domain" is meant a portion of the ICP8 polypeptide having recombinase activity and comprising at least amino acid 1087. It is further contemplated that amino acids 860 and 861 may contribute to the structure and/or activity of the DDE domain. ICP8 DDE domain described herein was based on an analysis of amino acid homology of different recombinase proteins.

[0047] By "ICP8 biological activity" is meant DNA binding activity, recombinase activity, or any other activity required for viral replication.

[0048] By "ICP8 nucleic acid molecule" is meant any nucleic acid molecule that encodes an ICP8 polypeptide. An exemplary ICP8 nucleotide sequence follows: Nucleotide sequence of the ICP8 open reading frame from HSV-1 wild type strain KOS

atggagacaaagcccaagacggcaaccaccatcaaggtcccccccgggcc

cctgggatacgtgtacgctcgcgcgtgtccgtccgaaggcatcgagcttc

tggcgttactgtcggcgcgcagcggcgatgccgacgtcgccgtggcgccc

ctggtcgtgggcctgaccgtggagagcggctttgaggccaacgtagccgt

ggtcgtgggactcgcacgacggggctcgggggtaccgcggtgtccctgaa

actgacgccatcgcactacagctcgtccgtgtacgtattcacggcggccg

gcacctggaccccagcacccaggccccaaacctgacgcgactctgcgagc

gggcacgccgccattttggcttttcggactacacccccccggcccggcgac

ctcaaacacgagacgacgggggaggcgctgtgtgagcgcctcggcctgga

cccggaccgcgccctcctgtatctggtcgttaccgagggcttcaaggagg

ccgtgtgcatcaacaacacctactgcacctgggaggctcggacaaggtaa

ccataggcggggcggaggtgcaccgcatacccgtgtatccgttgcagctg

acatgccggatatagccgggtcatcgccgagccgttcaacgccaaccacc

gatcgatcggggagaatatacctacccgcaccgttattaaccgcccccctc

aaccgcctcctg

ttcgaggcggtcgtgggacccgccgccgtggcactgcgatgccgaaacgt

ggacgccgtggcccgcgcggccgcccacctggcgtagacgaaaaccacga

gggcgccgccctccccgccgacattacgttcacggccacgaagccagcca

gggtaagaccccgcggggtgggcgcgacggcggcggcaagggcccggcgg

gcgggttcgaacagcgcctggcctccgtcatggccggagacgccgccctg

gccctcgagtctatcgtgtcgatggccgtcttcgacgagccgcccaccga

catctccgcgtggccgctgtgcgagggccaggacacggccgcggcccgcg

ccaacgccgtcggggcgtacctggcgcgcgccgcgggactcgtgggggcc

atggtatttagcaccaactcggccctccatctcaccgaggtggacgacgc

cggtccggcggacccaaaggaccacagcaaaccctcctttttaccgcttct

tcctcgtgcccgggacccacgtggcggccaacccacaggtggaccgcgag

ggacacgtggtgcccgggttcgagggtcggcccaccgcgcccctcgtcgg

cggaacccaggaatttgccggcgagcacctggccatgctgtgtgggtttt

ccccggcgctgctggccaagatgctgttttacctggagcgctgcgacggc

ggcgtgatcgtcgggcgccaggagatggacgtgtttcgatacgtcgcgga

ctccaaccagaccgacgtgccctgcaacctgtgcaccttcgacacgcgcc

acgcctgcgtacacacgacgctcatgcgcctccgggcgcgccatcccaag

ttcgccagcgccgcccgcggagccatcggcgtcttcgggaccatgaacag

catgtacagcgactgcgacgtgctgggaaactacgccgccttctcggccc

tgaagcgcgcggacggatccgagaccgcccggaccatcatgcaggagacg

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taccgcgcggcgaccgagcgcgtcatggccgaactcgagaccctgcagta

cgtggaccaggcggtccccacggccatggggcggctggagaccatcatca

ccaaccgcgaggccctgcatacggtggtgaacaacgtcaggcaggtcgtg

gaccgcgaggtggagcagctgatgcgcaacctggtggaggggaggaactt

caagtttcgcgacggtctgggcgaggccaaccacgccatgtccctgacgc

tggacccgtacgcgtgcgggccatgcccctgcttcagcttctcgggcgg

cgatccaacctcgccgtgtatcaggacctggccctgagccagtgccacgg

ggtgttcgccgggcagtcggtcgaggggcgcaactttcgcaatcaattcc

aaccggtgctgcggcggcgcgtgatggacatgtttaacaacgggtttctg

tcggccaaaacgctgacggtcgcgctctcggagggggcggctatctgcgc

ccccagcctaacggccggccagacggcccccgccgagagcagcttcgagg

gcgacgttgcccgcgtgaccctggggtttcccaaggagctgcgcgtcaag

agccgcgtgttgttcgcgggcgcgagcgccaacgcgtccgaggccgccaa

ggcgcgggtcgccagcctccagagcgcctaccagaagcccgacaagcgcg

tggacatcctcctcggaccgctgggctttctgctgaagcagttccacgcg

gccatcttccccaacggcaagcccccggggtccaaccagccgaacccgca

gtggttctggacggccctccaacgcaaccagcttcccgcccggctcctgt

cgcgcgaggacatcgagaccatcgcgttcattaaaaagttttccctggac

tacggcgcgataaactttattaacctggcccccaacaacgtgagcgagct

ggcgatgtactacatggcaaaccagattctgcggtactgcgatcactcga

catacttcatcaacaccctcacggccatcatcgcggggtcccgccgtccc

cccagcgtgcaggcggcggccgcgtggtccgcgcagggcggggcgggcct

ggaggccggggcccgcgcgctgatggacgccgtggacgcgcatccgggcg

cgtggacgtccatgttcgccagctgcaacctgctgcggcccgtcatggcg

gcgcgccccatggtcgtgttggggttgagcatcagcaaatactacggcat

ggccggcaacgaccgtgtgtttcaggccgggaactgggccagcctgatgg

gcggcaaaaacgcgtgcccgctccttatttttgaccgcacccgcaagttc

gtcctggcctgtccccgggccgggtttgtgtgcgcggcctcgaacctcgg

cggcggagcgcacgaaagctcgctgtgcgagcagctccggggcattatct

ccgagggcggggcggccgtcgccagtagcgtgttcgtggcgaccgtgaaa

agcctggggccccgcacccagcagctgcagatcgaggactggctggcgct

cctggaggacgagtacctaagcgaggagatgatggagctgaccgcgcgtg

ccctggagcgcggcaacggcgagtggtcgacggacgcggccctggaggtg

gcgcacgaggccgaggccctagtcagccaactcggcaacgccggggaggt

gtttaactttggggattttggctgcgaggacgacaacgcgacgccgttcg

gcggcccgggggccccgggaccggcatttgccggccgcaaacgggcgttc

cacggggatgacccgtttggggagggcccccccgacaaaaagggagacct

gacgttggatatgctgtga
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[0049] By "ICP8 homolog" is meant a viral recombinase of the alphaherpesvirus, betaherpesvirus, gammaherpesvirus, or a related double stranded DNA virus that is homologous to ICP8 from HSV-1. The amino acid sequences of several non-limiting illustrative examples of ICP8 homologs are shown in FIG. **1**B.

[0050] A "DDE recombinase" is a polypeptide that contains a DDE domain or site, a magnesium ion binding site composed of aspartic acid and glutamic acid amino acids.

[0051] A "Herpes virus" is a virus belonging to the Herpesviridae family of DNA viruses, and includes members of the three Herpesviridae subfamilies: Alphaherpesvirinae, Betaherpesvirinae, and Gammaherpesvirinae. A herpes virus can be a human virus affecting humans or a virus affecting non-human animals (e.g., mammals). Illustrative non-limiting examples of herpes virus include Herpes simplex virus Type 1 (HSV-1), Herpes simplex virus Type 2 (HSV-2), Epstein Barr virus (EBV), Cytomegalovirus (CMV), Varicella Zoster Virus (VZV), Herpes lymphotropic virus, Human herpes virus 6 (HHV-6), Human herpes virus 7 (HHV-7), Human herpes virus 8 (HHV-8), and Kaposi's sarcoma-associated herpes virus (KSHV).

[0052] By "functional homology" is meant an activity or function that is shared between two or more nucleotides or polypeptides, and which may or may not be associated with a shared or conserved primary nucleic acids or amino acid sequence.

[0053] By "structural homology" is meant a three dimensional structure that is shared between two or more nucleic acids or polypeptides, and which may or may not be associated with a shared or conserved primary amino acid or nucleotide sequence.

[0054] By "integrase activity" is meant an enzymatic activity that catalyzes the integration of one segment of DNA into another.

[0055] A subject is "diagnosed as having a Herpes infection" by methods known in the art. For example, a fluid sample from a blister of a subject may be tested by PCR to detect viral DNA. As another example, a subject may be tested for the presence of antibodies specific to the herpes virus.

[0056] A subject is "diagnosed as having HIV" if they test positive by an HIV ELISA, an HIV Western Blot, or by PCR. A subject is "negative for an HIV infection" if they do not test positive on two or more of these tests.

[0057] By "agent" is meant any small molecule chemical compound, antibody, nucleic acid molecule, or polypeptide, or fragments thereof. A "small molecule" or "small compound" is a chemical compound, preferably non-peptidic, having a molecular weight of less than about 1000 atomic mass units, in certain embodiments, less than about 800 a.m.u. or less than about 600 a.m.u. or less than about 500 a.m.u. or less than about 400 a.m.u.

[0058] By "alteration" is meant a change (increase or decrease) in the expression levels or activity of a gene or polypeptide as detected by standard art known methods such as those described herein. As used herein, an alteration includes a 10% change in expression levels, preferably a 25% change, more preferably a 40% change, and most preferably a 50% or greater change in expression levels."

[0059] By "ameliorate" is meant decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease.

[0060] By "analog" is meant a molecule that is not identical, but has analogous functional or structural features. For example, an analog or derivative of a compound disclosed herein (e.g., analogs or derivatives of raltegravir) have ICP8-

binding and/or ICP8-inhibitory activity analogous to the disclosed compound(s); e.g., an analog or derivative of raltegravir has ICP8-inhibitory activity analogous to raltegravir or have a chemical structure analogous to raltegravir. Such analogs are encompasessed within the scope fo the present invention. As a further example, a polypeptide analog retains the biological activity of a corresponding naturally-occurring polypeptide, while having certain biochemical modifications that enhance the analog's function relative to a naturally occurring polypeptide. Such biochemical modifications could increase the analog's protease resistance, membrane permeability, or half-life, without altering, for example, ligand binding. A polypeptide analog may include an unnatural amino acid.

[0061] By "binding to" a molecule is meant having a physicochemical affinity for that molecule. Binding may be measured by any of the methods of the invention, e.g., using an in vitro translation binding assay.

[0062] By "computer modeling" is meant the application of a computational program to determine one or more of the following: the location and binding proximity of a ligand to a binding moiety, the occupied space of a bound ligand, the amount of complementary contact surface between a binding moiety and a ligand, the deformation energy of binding of a given ligand to a binding moiety, and some estimate of hydrogen bonding strength, van der Waals interaction, hydrophobic interaction, and/or electrostatic interaction energies between ligand and binding moiety. Computer modeling can also provide comparisons between the features of a model system and a candidate compound. For example, a computer modeling experiment can compare a pharmacophore model of the invention with a candidate compound to assess the fit of the candidate compound with the model.

[0063] By a "computer system" is meant the hardware means, software means and data storage means used to analyze atomic coordinate data. The minimum hardware means of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means and data storage means. Desirably a monitor is provided to visualize structure data. The data storage means may be RAM or means for accessing computer readable media of the invention. Examples of such systems are microcomputer workstations available from Silicon Graphics Incorporated and Sun Microsystems running Unix based, Windows NT or IBM OS/2 operating systems.

[0064] By "computer readable media" is meant any media which can be read and accessed directly by a computer e.g. so that the media is suitable for use in the above-mentioned computer system. The media include, but are not limited to: magnetic storage media such as floppy discs, hard disc storage medium and magnetic tape; optical storage media such as optical discs or CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media.

[0065] In this disclosure, "comprises," "comprising," "containing" and "having" and the like can have the meaning ascribed to them in U.S. Patent law and can mean "includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments.

[0066] "Detect" refers to identifying the presence, absence or amount of the analyte to be detected.

[0067] By "disease" is meant any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

[0068] By "effective amount" is meant the amount required to ameliorate the symptoms of a disease relative to an untreated patient. The effective amount of active compound (s) used to practice the present invention for therapeutic treatment of a disease varies depending upon the manner of administration, the age, body weight, and general health of the subject. Ultimately, the attending physician or veterinarian will decide the appropriate amount and dosage regimen. Such amount is referred to as an "effective" amount. An effective amount of a compound described herein may range from about 1 μg/Kg to about 5000 mg/Kg body weight.

[0069] The invention provides a number of targets that are useful for the development of highly specific drugs to treat a disorder characterized by the methods delineated herein. In addition, the methods of the invention provide a facile means to identify therapies that are safe for use in subjects. In addition, the methods of the invention provide a route for analyzing virtually any number of compounds for effects on a disease described herein with high-volume throughput, high sensitivity, and low complexity.

[0070] By "fitting", is meant determining by automatic, or semi-automatic means, interactions between one or more atoms of an agent molecule and one or more atoms or binding sites of DDE domains of ICP8, and determining the extent to which such interactions are stable. Various computer-based methods for fitting are described further herein.

[0071] By "fragment" is meant a portion of a polypeptide or nucleic acid molecule. This portion contains, preferably, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the entire length of the reference nucleic acid molecule or polypeptide. A fragment may contain 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 nucleotides or amino acids.

[0072] By "isolated polynucleotide" is meant a nucleic acid (e.g., a DNA) that is free of the genes which, in the naturally-occurring genome of the organism from which the nucleic acid molecule of the invention is derived, flank the gene. The term therefore includes, for example, a recombinant DNA that is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote; or that exists as a separate molecule (for example, a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. In addition, the term includes an RNA molecule that is transcribed from a DNA molecule, as well as a recombinant DNA that is part of a hybrid gene encoding additional polypeptide sequence.

[0073] By an "isolated polypeptide" is meant a polypeptide of the invention that has been separated from components that naturally accompany it. Typically, the polypeptide is isolated when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, a polypeptide of the invention. An isolated polypeptide of the invention may be obtained, for example, by extraction from a natural source, by expression of a recombinant nucleic acid encoding such a polypeptide; or by chemically synthesizing the protein. Purity can be measured by any

appropriate method, for example, column chromatography, polyacrylamide gel electrophoresis, or by HPLC analysis.

[0074] As used herein, "obtaining" as in "obtaining an agent" includes synthesizing, purchasing, or otherwise acquiring the agent.

[0075] As used herein, the terms "prevent," "preventing," "prevention," "prophylactic treatment" and the like refer to reducing the probability of developing a disorder or condition in a subject, who does not have, but is at risk of or susceptible to developing a disorder or condition.

[0076] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50.

[0077] By "reduces" is meant a negative alteration of at least 10%, 25%, 50%, 75%, or 100%.

[0078] By "reference" is meant a standard or control condition.

[0079] A "reference sequence" is a defined sequence used as a basis for sequence comparison. A reference sequence may be a subset of or the entirety of a specified sequence; for example, a segment of a full-length cDNA or gene sequence, or the complete cDNA or gene sequence. For polypeptides, the length of the reference polypeptide sequence will generally be at least about 16 amino acids, preferably at least about 20 amino acids, more preferably at least about 25 amino acids, and even more preferably about 35 amino acids, about 50 amino acids, or about 100 amino acids. For nucleic acids, the length of the reference nucleic acid sequence will generally be at least about 50 nucleotides, preferably at least about 60 nucleotides, more preferably at least about 75 nucleotides, and even more preferably about 100 nucleotides or about 300 nucleotides or any integer thereabout or there between.

[0080] By "root mean square deviation" is meant the square root of the arithmetic mean of the squares of the deviations from the mean.

[0081] Nucleic acid molecules useful in the methods of the invention include any nucleic acid molecule that encodes a polypeptide of the invention or a fragment thereof. Such nucleic acid molecules need not be 100% identical with an endogenous nucleic acid sequence, but will typically exhibit substantial identity. Polynucleotides having "substantial identity" to an endogenous sequence are typically capable of hybridizing with at least one strand of a double-stranded nucleic acid molecule. Nucleic acid molecules useful in the methods of the invention include any nucleic acid molecule that encodes a polypeptide of the invention or a fragment thereof. Such nucleic acid molecules need not be 100% identical with an endogenous nucleic acid sequence, but will typically exhibit substantial identity. Polynucleotides having "substantial identity" to an endogenous sequence are typically capable of hybridizing with at least one strand of a double-stranded nucleic acid molecule. By "hybridize" is meant pair to form a double-stranded molecule between complementary polynucleotide sequences (e.g., a gene described herein), or portions thereof, under various conditions of stringency. (See, e.g., Wahl, G. M. and S. L. Berger (1987) Methods Enzymol. 152:399; Kimmel, A. R. (1987) Methods Enzymol. 152:507).

[0082] For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and more preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and more preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30° C., more preferably of at least about 37° C., and most preferably of at least about 42° C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred: embodiment, hybridization will occur at 30° C. in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37° C. in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42° C. in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50% formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

[0083] For most applications, washing steps that follow hybridization will also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include a temperature of at least about 25° C., more preferably of at least about 42° C., and even more preferably of at least about 68° C. In a preferred embodiment, wash steps will occur at 25° C. in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42° C. in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 68° C. in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art. Hybridization techniques are well known to those skilled in the art and are described, for example, in Benton and Davis (Science 196:180, 1977); Grunstein and Hogness (Proc. Natl. Acad. Sci., USA 72:3961, 1975); Ausubel et al. (Current Protocols in Molecular Biology, Wiley Interscience, New York, 2001); Berger and Kimmel (Guide to Molecular Cloning Techniques, 1987, Academic Press, New York); and Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York.

[0084] By "substantially identical" is meant a polypeptide or nucleic acid molecule exhibiting at least 50% identity to a reference amino acid sequence (for example, any one of the amino acid sequences described herein) or nucleic acid sequence (for example, any one of the nucleic acid sequences described herein). Preferably, such a sequence is at least 60%, more preferably 80% or 85%, and more preferably 90%, 95% or even 99% identical at the amino acid level or nucleic acid to the sequence used for comparison.

[0085] Sequence identity is typically measured using sequence analysis software (for example, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wis. 53705, BLAST, BESTFIT, GAP, or PILEUP/PRETTYBOX programs). Such software matches identical or similar sequences by assigning degrees of homology to various substitutions, deletions, and/or other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid, asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. In an exemplary approach to determining the degree of identity, a BLAST program may be used, with a probability score between e^{-3} and e^{-100} indicating a closely related sequence.

[0086] By "subject" is meant a mammal, including, but not limited to, a human or non-human mammal, such as a bovine, equine, canine, ovine, or feline.

[0087] As used herein, the terms "treat," "treated," "treating," "treatment," and the like refer to reducing or ameliorating a disorder and/or symptoms associated therewith (e.g. HSV1 or HSV2). By "ameliorate" is meant decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g. infection by a Herpes virus such as HSV1 or HSV2). It will be appreciated that, although not precluded, treating a disorder or condition does not require that the disorder, condition, or symptoms associated therewith be completely eliminated.

[0088] Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. Unless specifically stated or obvious from context, as used herein, the terms "a," "an," and "the" are understood to be singular or plural.

[0089] Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein are modified by the term about.

[0090] The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[0091] Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0092] FIGS. **1**A and **1**B show the alignment of ICP8 and several ICP8 homolog sequences. Amino acid sequences for HSV-1 ICP8 and ICP8 homologs from representative viruses in each of the three subfamilies of herpesviruses (alphaherpesvirus, betaherpesvirus, and gammaherpesvirus) were aligned using the T-Coffee alignment algorithm (Di Tommaso, P., et al., Nucleic Acids Res., vol. 39, pages W13-W17 (Web Server Version)). The ICP8 homologs included in the analysis were from HSV-1 strain KOS(NCBI accession number P17470), varicella-zoster virus (AEW89446), Marek's disease virus (Q9E6P0), Epstein-Barr virus (P03227), human cytomegalovirus (P17147), murine cytomegalovirus (MCMV) (P30672), human herpesvirus 7(O56282), and Kaposi's sarcoma-associated herpesvirus (ADQ57880). Sites with similar amino acids in 4 or more ICP8 homologs are in black letters highlighted in light gray; sites with identical amino acids in 4 or more ICP8 homologs are in white letters highlighted in black; and sites with identical amino acids in all 9 ICP8 homologs are in white letters highlighted in dark gray. In FIG. **1**A, two regions are shown, identifying conserved amino acids at positions 545 and 547 (based on their position in HSV-1 ICP8) and the complete conservation of an aspartic acid residue at position 1087. FIG. **1**B shows the full alignment.

[0093] FIG. **2** shows a schematic depicting five steps of HSV DNA replication. In Step 1, the origin binding protein, UL9, binds to specific sites at an origin (either oriL or oriS) and starts to unwind the DNA. In Step 2, the single-stranded DNA binding protein, ICP8, is recruited to the unwound DNA. Step 3, UL9 and ICP8 recruit the five remaining replication proteins to the replication forks. In Step 4, DNA synthesis initially proceeds via a theta replication mechanism, but then switches to a rolling-circle replication mechanism as shown in Step 5.

[0094] FIG. **3**A-**3**D shows a Western Blot, two bar graphs, and a gel-shift, respectively. FIG. **2**A is a Western Blot showing the expression of the E860A/D861A and E1086A/D1087A mutants. FIG. **2**B is a bar graph that shows the ability of the E860A/D861A and E1086A/D1087A mutants to complement an ICP8 mutant virus. FIG. **2**C shows a bar graph depicting the effect of ICP8 DDE mutant plasmids on complementation of an ICP8 mutant virus. Cells were either mock transfected, transfected with an empty vector (pCIΔ), or transfected with plasmids expressing wild type ICP8, the ICP8 d105 deletion mutant, or with the codons that encode the indicated amino acids in ICP8 mutated to encode alanine. At 24 hours post transfection, the cells were infected with the ICP8 mutant 8lacZ. Viral yield samples were harvested at 24 hours post infection and viral yield was determined by plaque assay. The reported values are percent complementation, relative to cells transfected with the plasmid encoding wild type ICP8. FIG. **2**D shows the effect of ICP8 DDE mutation on DNA binding. Wild type and DDE mutant ICP8 were expressed from recombinant baculoviruses and purified from infected Sf21 cells. The indicated concentration of each protein was incubated with 40 fmol radiolabeled oligo(dT)25 DNA and resolved on a 5% native polyacrylamide gel.

[0095] FIG. **4**A-**4**C shows a bar graph and two line graphs, respectively. FIG. **3**A is a bar graph that shows the effect of an ICP8 DDE mutant on viral yield. FIG. **3**B shows a line graph that depicts the effect of an ICP8 DDE mutant on viral DNA levels, as normalized to a GAPDH control. FIG. **3**C shows the effect of ICP8 DDE mutant on viral DNA replication. Cells were infected with either wild type virus HSV-1 (strain KOS), the ICP8 DDEm mutant, or the ICP8 mutant pm1.a, which is defective for DNA binding and therefore defective for replication of viral DNA. Total DNA was harvested at the times indicated, and viral DNA levels in each sample was determined by real time PCR and normalized to the levels of cellular DNA.

[0096] FIG. **5** shows a Western Blot (top) and a Northern Blot (bottom). The Western Blot shows the effect of ICP8 DDE mutant on viral protein expression. The Northern Blot shows the effect of ICP8 DDE mutant on viral gene expres-

sion. Cells were infected with either wild type HSV-1 or the ICP8 DDEm mutant, and total RNA was purified from cells at the indicated times. RNA was resolved by agarose gel electrophoresis, transferred to a charged nylon membrane, and probes for representative immediate-early (ICP27), early (ICP8), and late (gC) were hybridized to the membrane.

[0097] FIG. **6** is a bar graph that depicts the effects of Raltegravir and 118-D-24 on viral replication at 100 μM and 1 mM, respectively.

[0098] FIG. **7** is a line graph that depicts the effect of the HIV integrase inhibitor 118-D-24 on viral yield. Cells were infected with wild type HSV-1 at a multiplicity of infection of 0.01 plaque forming units per cell and treated with the indicated concentration of the HIV integrase inhibitor 118-D-24. At 48 hours post infection, viral yield samples were harvested and the yield was determined by plaque assay. Values are presented as the percent yield remaining, relative to the DMSO vehicle control treatment.

[0099] FIG. **8** is a ribbon diagram depicting the structure of the ICP8 polypeptide.

[0100] FIG. **9** is a bar graph that shows the effect of the HIV integrase inhibitors on viral yield. Cells were infected with wild type HSV-1 at a multiplicity of infection of 0.01 plaque-forming units per cell and treated with the indicated concentration of the HIV integrase inhibitor specified. At 48 hours post infection, viral yield samples were harvested and the yield was determined by plaque assay. Values are presented as the percent yield remaining, relative to the DMSO vehicle control treatment.

[0101] FIG. **10** is a line graph that depicts the effect of the HIV integrase inhibitor 118-D-24 on viral DNA replication. Cells were infected with wild type HSV-1 and were treated with either 1 mM 118-D-24 or DMSO for the time indicated. Total DNA was harvested at the times indicated, and viral DNA levels in each sample was determined by real time PCR and normalized to the levels of cellular DNA.

[0102] FIG. **11** shows a Western Blot depicting the effect of the HIV integrase inhibitor 118-D-24 on viral gene expression. Cells were infected with wild type HSV-1 and were treated with either 1 mM 118-D-24 or DMSO for the time indicated.

[0103] Total protein samples were harvested, resolved by SDS-PAGE, transferred to a PVDF membrane, and probed with antibodies for representative immediate-early (ICP27), early (ICP8), and late (gC) gene products. Samples were also probed for cellular GAPDH as a loading control.

[0104] FIG. **12** is a graph showing the effects of 118-D-24 derivates on HSV replication.

[0105] FIG. **13** is a graph showing the effect of various 118-D-24 derivatives on HSV replication over a range of drug concentrations.

[0106] FIGS. **14**A-**14**C are a set of graphs that show the effects of XZ45 on HSV-1 replication in Hep2 cells (FIG. **14**A) and normal human foreskin fibroblasts (FIG. **14**B). A graph showing the cytotoxicity of XZ45 on Hep2 cells is shown in FIG. **14**C.

[0107] FIGS. **15**A-**15**C are a set of graphs showing the effects of XZ45 on HSV-1 and HSV-2 replication in Hep2 cells (FIGS. **15**A and **15**B) and human foreskin fibroblasts (FIG. **15**C).

[0108] FIG. **16** is a graph showing the effect of XZ45 on human cytomegalovirus (HCMV) replication.

[0109] FIGS. **17**A and **17**B show the effects of XZ45 on viral DNA synthesis (FIG. **17**A) and late gene expression (FIG. **17**B).

[0110] FIGS. **18**A-**18**C show that XZ45 does not decrease ssDNA binding to ICP8 as measured by mobility shift assay (FIG. **18**A), ssDNA bead pull down assay (FIG. **18**B), and ICP8 binding to ssDNA-cellulose (FIG. **18**C).

[0111] FIG. **19** is a graph showing that XZ45 inhibits HSV recombination.

[0112] FIG. **20** is a gel showing the results of a D-loop assay that demonstrates that XZ45 inhibits HSV recombination.

DETAILED DESCRIPTION OF THE INVENTION

[0113] The invention features compositions and methods that are useful for the treatment and prevention of herpes viruses, including but not limited to Herpes Simplex virus (e.g., HSV-1 and/or HSV-2).

[0114] The invention is based, at least in part, on the discovery that HIV integrase inhibitors (e.g., Raltegravir and 118-D-24) also inhibit Herpes Simplex Virus (HSV) replication.

Herpes Virus

[0115] Herpes viruses are enveloped viruses having a double stranded DNA genome that bud from the inner nuclear membrane which has become modified by the insertion of herpes glycoproteins. There are at least 25 viruses in the family Herpesviridae which is currently divided into three subfamilies: alphaherpesvirus, betaherpesvirus, and gammaherpesvirus. Eight or more herpes virus types are known to infect man frequently: Herpes simplex virus 1 (HSV-1), Herpes simplex virus 2 (HSV-2), Epstein Barr virus (EBV), Cytomegalovirus (CMV), Varicella Zoster Virus (VZV), Herpes lymphotropic virus, Human herpes virus 6 (HHV-6), Human herpes virus 7 (HHV-7), Human herpes virus 8 (HHV-8), and Kaposi's sarcoma-associated herpes virus (KSHV).

[0116] Herpes simplex virus 1 (HSV-1) is a double stranded DNA virus that replicates its genome in the nucleus of infected cells. The HSV-1 genome encodes seven gene products that are directly involved in the replication of viral DNA, all of which are essential for HSV-1 DNA replication. These proteins are the DNA polymerase (which consists of the catalytic subunit UL30 and its processivity factor UL42), an origin binding protein (UL9), a single-stranded DNA binding protein (ICP8, also known as UL29), and a helicase/primase complex (which consists of the proteins UL5, UL52, and UL8).

[0117] Without wishing to be bound be theory, it is likely that HSV DNA replication involves a DNA recombination-based mechanism. In support of this model, viral DNA has been observed as a branched structure in infected cells, indicating that recombination likely occurred to create these molecules, and that recombination would likely be required to resolve them. Homologous recombination of the HSV-1 DNA is also known to occur at high frequency, for example to result in the isomerization of the viral genome, which produces 4 different isomers generated by recombination within the terminal and internal repeat sequences. It is clear that recombination of the viral genome occurs during viral infection. However, the viral and cellular proteins required for recombination, as well as the role recombination plays in the HSV-1 life cycle, have yet to be delineated.

[0118] One viral protein proposed to be involved in recombination is ICP8, which is a single stranded DNA binding protein that is necessary for viral DNA replication and that exhibits recombinase activity in vitro. The crystal structure of ICP8 revealed that it shares similarities with enzymes in the DDE family of recombinases, such as RAG-1 and HIV Integrase. These proteins utilize conserved D and E residues to coordinate magnesium ions that are involved in catalyzing their enzymatic activities. ICP8 contains two regions of conserved D and E residues, amino acids E860/D861 and E1086/D1087, which are structurally similar to the active D and E residues of other known DDE recombinases.

[0119] As described in the Examples below, a genetic approach was used to determine whether these residues were necessary complement the replication of an ICP8 mutant virus. Mutation of the E860/D861 amino acids (e.g. E860A/D861A) complemented replication of an ICP8 mutant virus to only ~37% the level of wild type ICP8, and a E1086A/D1087A mutant did not complement above background levels, indicating that both regions are important for ICP8 function. A mutant virus with the E1086A/D1087A mutation in ICP8 was created, and this mutant virus was defective for viral DNA replication and both late gene transcript and protein accumulation. It was further shown that D1087A, as a single mutation, recapitulated the phenotype of the double mutant. Taken together, these results indicate that the DDE residues in ICP8 are important for its function during infection, and likely operate by mediating the previously observed recombinase activity of this viral protein.

[0120] ICP8 has been shown to mediate several activities involved in DNA recombination in vitro, including strand exchange and strand invasion. Furthermore, ICP8 has been shown to interact with the HSV-encoded alkaline nuclease UL12, which is proposed to play a role in the initiation and/or the resolution of the DNA recombination mechanism.

[0121] ICP8 is a major component of HSV-1 replication compartments, which are nuclear domains where viral DNA replication and late gene expression occur. ICP8 also interacts with several cellular proteins known to be involved in recombination and recruits these proteins to viral replication compartments, where they may play important roles in mediating recombination of the HSV-1 genome.

[0122] As described in the working Examples below, conserved residues in ICP8 that share structural homology with catalytic residues of enzymes in the DDE family of recombinases, including most notably RAG-1, have been identified and shown to be important for ICP8-mediated recombination. Enzymes in the DDE recombinase family perform recombination reactions using a catalytic triad of aspartic acid (D) and glutamic acid (E) residues that coordinate divalent metal cations. As described in the working Examples below, these putative DDE residues in ICP8 are important for its activity, and a mutant virus with DDE residues in ICP8 mutated is defective for viral DNA replication. These results identify ICP8 residues that are likely required for HSV-1 DNA recombination and indicate that recombination of the viral genome is likely required for viral DNA replication.

[0123] Several other viruses encode proteins that contain DDE motifs, such as HIV integrase and HCMV UL89. Antiviral compounds have been developed to inhibit the activity of the HIV integrase enzyme, and one of these compounds, Raltegravir, can also inhibit HCMV UL89 activity. Surprisingly, as reported herein, these compounds, including L-841411, Raltegravir, and 118-D-24, inhibit HSV replication, likely by inhibiting the virally encoded HSV DDE recombinase, ICP8.

[0124] As used herein, the terms "treat," treating," "treatment," and the like refer to reducing or ameliorating a disorder and/or symptoms associated therewith. It will be appreciated that, although not precluded, treating a disorder or condition does not require that the disorder, condition or symptoms associated therewith be completely eliminated.

[0125] As used herein, the terms "prevent," "preventing," "prevention," "prophylactic treatment" and the like refer to reducing the probability of developing a disorder or condition in a subject, who does not have, but is at risk of or susceptible to developing a disorder or condition.

[0126] The therapeutic methods of the invention (which include prophylactic treatment) in general comprise administration of a therapeutically effective amount of the compounds herein, such as a compound of the formulae herein to a subject (e.g., animal, human) in need thereof, including a mammal, particularly a human. Such treatment will be suitably administered to subjects, particularly humans, suffering from, having, susceptible to, or at risk for a disease, disorder, or symptom thereof due to viral infection (e.g., with HSV1 or HSV2). Determination of those subjects "at risk" can be made by any objective or subjective determination by a diagnostic test or opinion of a subject or health care provider (e.g., genetic test, enzyme or protein marker, Marker (as defined herein), family history, and the like). The compounds herein may be also used in the treatment of any other disorders in which Raltegravir, 118-D-24, L-841411, elvitegrevir, or MK-2048 may be implicated.

[0127] In one embodiment, the invention provides a method of monitoring treatment progress. The method includes the step of determining a level of diagnostic marker (Marker) (e.g., any target delineated herein modulated by a compound herein, a protein or indicator thereof, etc.) or diagnostic measurement (e.g., screen, assay) in a subject suffering from or susceptible to a disorder or symptoms thereof associated with herpes, in which the subject has been administered a therapeutic amount of a compound herein sufficient to treat the disease or symptoms thereof. The level of Marker determined in the method can be compared to known levels of Marker in either healthy normal controls or in other afflicted patients to establish the subject's disease status. In preferred embodiments, a second level of Marker in the subject is determined at a time point later than the determination of the first level, and the two levels are compared to monitor the course of disease or the efficacy of the therapy. In certain preferred embodiments, a pre-treatment level of Marker in the subject is determined prior to beginning treatment according to this invention; this pre-treatment level of Marker can then be compared to the level of Marker in the subject after the treatment commences, to determine the efficacy of the treatment.

Compounds of the Invention

[0128] Compounds of the invention were found to inhibit Herpes virus replication, and in particular HSV replication. Without wishing to be bound by any particular theory, these compounds may be particularly effective for the treatment of HSV. In one approach, compounds useful for the treatment of HSV are selected using a molecular docking program to identify compounds that are expected to bind to an ICP8 DDE domain. In certain embodiments, a compound of the inven-

tion can bind to ICP8 and reduce ICP8 biological activity and/or disrupt HSV replication.

[0129] In certain embodiments, a compound of the invention can prevent, inhibit, disrupt, or reduce by at least 10%, 25%, 50%, 75%, or 100% of the expression and/or biological activity of ICP8.

[0130] In certain embodiments, a compound of the invention is a small molecule having a molecular weight less than about 1000 daltons, less than 800, less than 600, less than 500, less than 400, or less than about 300 daltons. Examples of compounds of the invention include Raltegravir, 118-D-24, Elvitegravir (also known as GS 9137 or JTK-303), dolutegravir, MK-2048, L841411, XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50 and pharmaceutically acceptable salts thereof. Compounds of the invention also include analogs or derivatives of compounds disclosed herein.

[0131] The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound of the invention having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)-amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N,N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)-amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound disclosed herein or any other compound delineated herein, having a basic functional group, such as an amino functional group, and a pharmaceutically acceptable inorganic or organic acid. Suitable acids include, but are not limited to, hydrogen sulfate, citric acid, acetic acid, oxalic acid, hydrochloric acid, hydrogen bromide, hydrogen iodide, nitric acid, phosphoric acid, isonicotinic acid, lactic acid, salicylic acid, tartaric acid, ascorbic acid, succinic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucaronic acid, saccharic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid.

In Silico Screening Methods and Systems

[0132] In another aspect, the invention provides a machine readable storage medium which comprises the structural coordinates of an ICP8 polypeptide (e.g., ICP8 DDE domain or an amino acid corresponding to positions 547, 623, 645, 735, 860, 861, 1086, and 1087 of HSV protein ICP8). A storage medium encoded with these data is capable of displaying a three-dimensional graphical representation of a molecule or molecular complex which comprises such binding sites on a computer screen or similar viewing device.

[0133] The invention also provides methods for designing, evaluating and identifying compounds that bind to the aforementioned binding site. Such compounds are expected to inhibit HSV replication. The invention provides a computer for producing a) a three-dimensional representation of a molecule or molecular complex, wherein said molecule or molecular complex comprises a binding site; or b) a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding site that has a root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 (more preferably not more than 1.5) angstroms, wherein said computer comprises:

[0134] (i) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of amino acid residues in the ICP8 DDE domain, or other ICP8 binding site;

[0135] (ii) a working memory for storing instructions for processing said machine-readable data;

[0136] (iii) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

[0137] (iv) a display coupled to said central-processing unit for displaying said three-dimensional representation.

[0138] Thus, the computer produces a three-dimensional graphical structure of a molecule or a molecular complex which comprises a binding site.

[0139] In another embodiment, the invention provides a computer for producing a three-dimensional representation of a molecule or molecular complex defined by structure coordinates of all of the ICP8 amino acids, or a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding site that has a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably not more than 1.5) angstroms.

[0140] In exemplary embodiments, the computer or computer system can include components that are conventional in the art, e.g., as disclosed in U.S. Pat. No. 5,978,740 and/or 6,183,121 (incorporated herein by reference). For example, a computer system can includes a computer comprising a central processing unit ("CPU"), a working memory (which may be, e.g., RAM (random-access memory) or "core" memory), a mass storage memory (such as one or more disk drives or CD-ROM drives), one or more cathode-ray tube (CRT) or liquid crystal display (LCD) display terminals, one or more keyboards, one or more input lines, and one or more output lines, all of which are interconnected by a conventional system bus.

[0141] Machine-readable data of this invention may be inputted to the computer via the use of a modem or modems connected by a data line. Alternatively or additionally, the input hardware may include CD-ROM drives, disk drives or flash memory. In conjunction with a display terminal, a keyboard may also be used as an input device.

[0142] Output hardware coupled to the computer by output lines may similarly be implemented by conventional devices. By way of example, output hardware may include a CRT or LCD display terminal for displaying a graphical representation of a binding pocket of this invention using a program such as QUANTA or PYMOL. Output hardware might also include a printer, or a disk drive to store system output for later use.

[0143] In operation, the CPU coordinates the use of the various input and output devices, coordinates data accesses from the mass storage and accesses to and from working memory, and determines the sequence of data processing

steps. A number of programs may be used to process the machine-readable data of this invention, including commercially-available software.

[0144] A magnetic storage medium for storing machine-readable data according to the invention can be conventional. A magnetic data storage medium can be encoded with a machine-readable data that can be carried out by a system such as the computer system described above. The medium can be a conventional floppy diskette or hard disk, having a suitable substrate which may be conventional, and a suitable coating, which may also be conventional, on one or both sides, containing magnetic domains whose polarity or orientation can be altered magnetically. The medium may also have an opening (not shown) for receiving the spindle of a disk drive or other data storage device.

[0145] The magnetic domains of the medium are polarized or oriented so as to encode in a manner which may be conventional, machine readable data such as that described herein, for execution by a system such as the computer system described herein.

[0146] An optically-readable data storage medium also can be encoded with machine-readable data, or a set of instructions, which can be carried out by a computer system. The medium can be a conventional compact disk read only memory (CD-ROM) or a rewritable medium such as a magneto-optical disk which is optically readable and magneto-optically writable.

[0147] In the case of CD-ROM, as is well known, a disk coating is reflective and is impressed with a plurality of pits to encode the machine-readable data. The arrangement of pits is read by reflecting laser light off the surface of the coating. A protective coating, which preferably is substantially transparent, is provided on top of the reflective coating.

[0148] In the case of a magneto-optical disk, as is well known, a data-recording coating has no pits, but has a plurality of magnetic domains whose polarity or orientation can be changed magnetically when heated above a certain temperature, as by a laser. The orientation of the domains can be read by measuring the polarization of laser light reflected from the coating. The arrangement of the domains encodes the data as described above.

[0149] Structure data, when used in conjunction with a computer programmed with software to translate those coordinates into the 3-dimensional structure of a molecule or molecular complex comprising a binding pocket may be used for a variety of purposes, such as drug discovery.

[0150] For example, the structure encoded by the data may be computationally evaluated for its ability to associate with chemical entities. Chemical entities that associate with a DDE domain or a binding site of an ICP8 protein are expected to inhibit Herpes virus replication (e.g. HSV1 and HSV2), to inhibit ICP8 biological activity, and/or to disrupt ICP8 subcellular localization. Such compounds are potential drug candidates. Alternatively, the structure encoded by the data may be displayed in a graphical three-dimensional representation on a computer screen. This allows visual inspection of the structure, as well as visual inspection of the structure's association with chemical entities.

[0151] Thus, according to another embodiment, the invention relates to a method for evaluating the potential of a chemical entity to associate with a) a molecule or molecular complex comprising a binding site defined by structure coordinates and/or amino acid positions in ICP8, as described herein, or b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably 1.5) angstroms.

[0152] This method comprises the steps of:

[0153] i) employing computational means to perform a fitting operation between the chemical entity and a binding site of the ICP8 polypeptide or fragment thereof or molecular complex; and

[0154] ii) analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket. This embodiment relates to evaluating the potential of a chemical entity to associate with or bind to a binding site of an ICP8 polypeptide or fragment thereof.

[0155] The term "chemical entity", as used herein, refers to chemical compounds, complexes of at least two chemical compounds, and fragments of such compounds or complexes.

[0156] In certain embodiments, the method evaluates the potential of a chemical entity to associate with a molecule or molecular complex defined by structure coordinates of all of the amino acids of an ICP8 protein, as described herein, or a homologue of said molecule or molecular complex having a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably not more than 1.5) angstroms.

[0157] In a further embodiment, the structural coordinates one of the binding sites described herein can be utilized in a method for identifying an antagonist of a molecule comprising an ICP8 binding site (e.g., a DDE domain or DNA binding domain). This method comprises the steps of:

[0158] a) using the atomic coordinates of ICP8; and

[0159] b) employing the three-dimensional structure to design or select the potential agonist or antagonist. One may obtain the compound by any means available. By "obtaining" is meant, for example, synthesizing, buying, or otherwise procuring the agonist or antagonist. If desired, the method further involves contacting the agonist or antagonist with an ICP8 polypeptide or a fragment thereof to determine the ability of the potential agonist or antagonist to interact with the molecule. If desired, the method also further involves the step of contacting a Herpes infected with an ICP8 binding compound and evaluating inhibition of viral replication, evaluating viral DNA production, cell death, ICP8 biological activity, ICP8 DNA binding activity, ICP8 recombinase activity, ICP8 expression and/or levels, or ICP8 subcellular localization.

[0160] In another embodiment, the invention provides a method for identifying a potential agonist or antagonist of an ICP8 polypeptide, the method comprising the steps of:

[0161] a) using the atomic coordinates of the ICP8 polypeptide (e.g., DDE domain or DNA binding domain); and

[0162] b) employing the three-dimensional structure to design or select the potential agonist or antagonist.

[0163] The present inventors' elucidation of heretofore unidentified binding sites of ICP8 polypeptides provides the necessary information for designing new chemical entities and compounds that may interact with ICP8 proteins, in whole or in part, and may therefore modulate (e.g., inhibit) the activity of ICP8 proteins.

[0164] The design of compounds that bind to an ICP8 DDE domain sequence, that are cytotoxic to a cell infected with Herpes (e.g. HSV1 or HSV2), that reduce ICP8 expression and/or levels or biological activity, or that disrupt ICP8 sub-

cellular localization, according to this invention generally involves consideration of several factors. In one embodiment, the compound physically and/or structurally associates with at least a fragment of an ICP8 polypeptide, such as a binding site within a DDE domain sequence. Non-covalent molecular interactions important in this association include hydrogen bonding, van der Waals interactions, hydrophobic interactions and electrostatic interactions. Desirably, the compound assumes a conformation that allows it to associate with the ICP8 binding site(s) directly. Although certain portions of the compound may not directly participate in these associations, those portions of the entity may still influence the overall conformation of the molecule. This, in turn, may have a significant impact on the compound's potency. Such conformational requirements include the overall three-dimensional structure and orientation of the chemical compound in relation to all or a portion of the binding site, or the spacing between functional groups comprising several chemical compound that directly interact with the binding site or a homologue thereof.

[0165] The potential inhibitory or binding effect of a chemical compound on an ICP8 binding site may be analyzed prior to its actual synthesis and testing by the use of computer modeling techniques. If the theoretical structure of the given compound suggests insufficient interaction and association between it and the target binding site, testing of the compound is obviated. However, if computer modeling indicates a strong interaction, the molecule is synthesized and tested for its ability to bind a DDE domain sequence and/or a DNA binding domain sequence, or to test its biological activity by assaying for example, viral replication by a Herpes infected cell (e.g. a cell infected with HSV1 or HSV2), by assaying a reduction in ICP8 expression and/or levels or biological activity, or by assaying ICP8 subcellular localization. Candidate compounds may be computationally evaluated by means of a series of steps in which chemical entities or fragments are screened and selected for their ability to associate with the ICP8 DDE domain and/or DNA binding domain.

[0166] One skilled in the art may use one of several methods to screen chemical compounds, or fragments for their ability to associate with an ICP8 binding site. This process may begin by visual inspection of, for example, an ICP8 binding site on the computer screen based on the ICP8 structure coordinates described herein, or other coordinates which define a similar shape generated from the machine-readable storage medium. Selected fragments or chemical compounds are then positioned in a variety of orientations, or docked, within that binding site as defined supra. Docking may be accomplished using software such as Quanta and DOCK, followed by energy minimization and molecular dynamics with standard molecular mechanics force fields, such as CHARMM and AMBER.

[0167] Specialized computer programs (e.g., as known in the art and/or commercially available and/or as described herein) may also assist in the process of selecting fragments or chemical entities.

[0168] Once suitable chemical entities or fragments have been selected, they can be assembled into a single compound or complex. Assembly may be preceded by visual inspection of the relationship of the fragments to each other on the three-dimensional image displayed on a computer screen in relation to the structure coordinates of the target binding site.

[0169] Instead of proceeding to build an inhibitor of a binding pocket in a step-wise fashion one fragment or chemical entity at a time as described above, inhibitory or other binding compounds may be designed as a whole or "de novo" using either an empty binding site or optionally including some portion(s) of a known inhibitor(s). There are many de novo ligand design methods known in the art, some of which are commercially available (e.g., LeapFrog, available from Tripos Associates, St. Louis, Mo.).

[0170] Other molecular modeling techniques may also be employed in accordance with this invention (see, e.g., N. C. Cohen et al., "Molecular Modeling Software and Methods for Medicinal Chemistry, J. Med. Chem., 33, pp. 883-894 (1990); see also, M. A. Navia and M. A. Murcko, "The Use of Structural Information in Drug Design", Current Opinions in Structural Biology, 2, pp. 202-210 (1992); L. M. Balbes et al., "A Perspective of Modern Methods in Computer-Aided Drug Design", in Reviews in Computational Chemistry, Vol. 5, K. B. Lipkowitz and D. B. Boyd, Eds., VCH, New York, pp. 337-380 (1994); see also, W. C. Guida, "Software For Structure-Based Drug Design", Curr. Opin. Struct. Biology, 4, pp. 777-781 (1994)).

[0171] Once a compound has been designed or selected, the efficiency with which that entity may bind to a binding site may be tested and optimized by computational evaluation.

[0172] Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interactions. Examples of programs designed for such uses include: AMBER; QUANTA/CHARMM (Accelrys, Inc., Madison, Wis.) and the like. These programs may be implemented, for instance, using a commercially-available graphics workstation. Other hardware systems and software packages will be known to those skilled in the art.

[0173] Another technique involves the in silico screening of virtual libraries of compounds, e.g., as described herein (see, e.g., Examples). Many thousands of compounds can be rapidly screened and the best virtual compounds can be selected for further screening (e.g., by synthesis and in vitro or in vivo testing). Small molecule databases can be screened for chemical entities or compounds that can bind, in whole or in part, to an ICP8 DDE domain and/or DNA binding site. In this screening, the quality of fit of such entities to the binding site may be judged either by shape complementarity or by estimated interaction energy.

[0174] A computer for producing a three-dimensional representation of:

[0175] a) a molecule or molecular complex, wherein said molecule or molecular complex comprises a DDE domain and/or a DNA binding domain of an ICP8 polypeptide defined by structure coordinates of amino acid residues in DDE domain and/or a DNA binding domain of an ICP8 polypeptide; or

[0176] b) a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding site that has a root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 (more preferably not more than 1.5) angstroms, wherein said computer comprises:

[0177] (i) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of structure coordinates of amino acid residues in the DDE domain and/or a DNA binding domain of an ICP8 polypeptide;

[0178] (ii) a working memory for storing instructions for processing said machine-readable data;

[0179] (iii) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

[0180] (iv) a display coupled to said central-processing unit for displaying said three-dimensional representation. As described in the Examples, compounds identified using in silico methods may optionally be tested in vitro or in vivo, for example, using the "Additional Screening Methods" described below, or any other method known in the art.

Additional Screening Methods

[0181] As described above, the invention provides specific examples of chemical compounds, including, but not limited to, Raltegravir, L-841411, 118-D-24, Elvitegravir (also known as GS 9137 or JTK-303), dolutegravir, and MK-2048, that inhibit the biological activity (e.g. recombinase activity and/or DNA binding activity) of an ICP8 polypeptide, as well as the replication of a Herpes virus (e.g. HSV1 or HSV2). However, the invention is not so limited. The invention further provides a simple means for identifying agents (including nucleic acids, peptides, small molecule inhibitors, and mimetics) that are capable of binding to an ICP8 polypeptide, that can inhibit viral replication in an infected cell, that reduce ICP8 expression and/or levels or biological activity, or that disrupt ICP8 subcellular localization. Such compounds are also expected to be useful for the treatment or prevention of a Herpes infection.

[0182] Virtually any agent that specifically binds to an ICP8 polypeptide or that modulates ICP8 expression and/or levels or biological activity may be employed in the methods of the invention. Methods of the invention are useful for the high-throughput low-cost screening of candidate agents that reduce, slow, or eliminate replication of a Herpes virus in an infected cell, in particular a cell infected with HSV1 and/or HSV2. A candidate agent that specifically binds to ICP8 is then isolated and tested for activity in an in vitro assay or in vivo assay for its ability to reduce Herpes viral replication, reduce ICP8 recombinase activity, or reduce ICP8 DNA binding activity. One skilled in the art appreciates that the effects of a candidate agent on a cell is typically compared to a corresponding control cell not contacted with the candidate agent. Thus, the screening methods include comparing the proliferation of a virus in an infected cell contacted by a candidate agent to the proliferation of an untreated control cell.

[0183] In other embodiments, the expression or activity of ICP8 in a cell treated with a candidate agent is compared to untreated control samples to identify a candidate compound that decreases the expression or biological activity of an ICP8 polypeptide in the contacted cell. Polypeptide expression or activity can be compared by procedures well known in the art, such as Western blotting, flow cytometry, immunocytochemistry, binding to magnetic and/or ICP8-specific antibody-coated beads, in situ hybridization, fluorescence in situ hybridization (FISH), ELISA, microarray analysis, RT-PCR, Northern blotting, or colorimetric assays, such as the Bradford Assay and Lowry Assay.

[0184] In one working example, one or more candidate agents are added at varying concentrations to the culture medium containing a Herpes infected cell. An agent that reduces the expression of an ICP8 or gC polypeptide expressed in the cell, or viral DNA replication, is considered useful in the invention; such an agent may be used, for example, as a therapeutic to prevent, delay, ameliorate, stabilize, or treat a Herpes infection of a cell. Once identified, agents of the invention (e.g., agents that specifically bind to and/or antagonize ICP8) may be used to treat a Herpes infected cell. An agent identified according to a method of the invention is locally or systemically delivered to treat a Herpes infection in situ.

[0185] In one embodiment, the effect of a candidate agent may, in the alternative, be measured at the level of ICP8 polypeptide production using the same general approach and standard immunological techniques, such as Western blotting or immunoprecipitation with an antibody specific for ICP8. For example, immunoassays may be used to detect or monitor the expression of ICP8 in a Herpes infected cell. In one embodiment, the invention identifies a polyclonal or monoclonal antibody (produced as described herein) that is capable of binding to and blocking the biological activity or disrupting the subcellular localization of an ICP8 polypeptide. A compound that disrupts the subcellular localization, or reduces the expression or activity of an ICP8 polypeptide is considered particularly useful. Again, such an agent may be used, for example, as a therapeutic to prevent or treat a Herpes infection.

[0186] Alternatively, or in addition, candidate compounds may be identified by first assaying those that specifically bind to and antagonize an ICP8 polypeptide of the invention and subsequently testing their effect on a Herpes infected cells as described in the Examples. In one embodiment, the efficacy of a candidate agent is dependent upon its ability to interact with the ICP8 polypeptide. Such an interaction can be readily assayed using any number of standard binding techniques and functional assays (e.g., those described in Ausubel et al., supra). For example, a candidate compound may be tested in vitro for interaction and binding with a polypeptide of the invention and its ability to modulate Herpes viral replication may be assayed by any standard assays (e.g., those described herein). In one embodiment, viral replication is determined by a viral replication assay, or a viral DNA replication assay. In another embodiment, ICP8 expression is monitored immunohistochemically.

[0187] Potential ICP8 antagonists include organic molecules, peptides, peptide mimetics, polypeptides, nucleic acid ligands, aptamers, and antibodies that bind to an ICP8 polypeptide and reduce its activity. In one particular example, a candidate compound that binds to an ICP8 polypeptide may be identified using a chromatography-based technique. For example, a recombinant ICP8 polypeptide of the invention may be purified by standard techniques from cells engineered to express the polypeptide, or may be chemically synthesized, once purified the peptide is immobilized on a column. A solution of candidate agents is then passed through the column, and an agent that specifically binds the ICP8 polypeptide or a fragment thereof is identified on the basis of its ability to bind to an ICP8 polypeptide and to be immobilized on the column. To isolate the agent, the column is washed to remove non-specifically bound molecules, and the agent of interest is then released from the column and collected. Agents isolated by this method (or any other appropriate method) may, if desired, be further purified (e.g., by high performance liquid chromatography). In addition, these candidate agents may be tested for their ability to reduce Herpes replication. Agents isolated by this approach may also be used, for example, as therapeutics to treat or prevent a Herpes infection. Compounds that are identified as binding to an

ICP8 polypeptide with an affinity constant less than or equal to 1 nM, 5 nM, 10 nM, 100 nM, 1 μM or 10 μM are considered particularly useful in the invention.

Test Compounds and Extracts

[0188] In general, ICP8 antagonists (e.g., agents that specifically bind and reduce the activity of an ICP8 polypeptide) are identified from large libraries of natural product or synthetic (or semi-synthetic) extracts or chemical libraries or from polypeptide or nucleic acid libraries, according to methods known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the screening procedure(s) of the invention. Agents used in screens may include known those known as therapeutics for the treatment of other types of viral infection (e.g. HIV). Alternatively, virtually any number of unknown chemical extracts or compounds can be screened using the methods described herein. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or animal-based extracts, fermentation broths, and synthetic compounds, as well as the modification of existing polypeptides.

[0189] Libraries of natural polypeptides in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova (Slough, UK), Harbor Branch Oceangraphics Institute (Ft. Pierce, Fla.), and PharmaMar, U.S.A. (Cambridge, Mass.). Such polypeptides can be modified to include a protein transduction domain using methods known in the art and described herein. In addition, natural and synthetically produced libraries are produced, if desired, according to methods known in the art, e.g., by standard extraction and fractionation methods. Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al., *Proc. Natl. Acad. Sci. U.S.A.* 90:6909, 1993; Erb et al., *Proc. Natl. Acad. Sci. USA* 91:11422, 1994; Zuckermann et al., *J. Med. Chem.* 37:2678, 1994; Cho et al., *Science* 261:1303, 1993; Carrell et al., *Angew. Chem. Int. Ed. Engl.* 33:2059, 1994; Carell et al., *Angew. Chem. Int. Ed. Engl.* 33:2061, 1994; and Gallop et al., *J. Med. Chem.* 37:1233, 1994. Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

[0190] Numerous methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of polypeptides, chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid-based compounds. Synthetic compound libraries are commercially available from Brandon Associates (Merrimack, N.H.) and Aldrich Chemical (Milwaukee, Wis.). Alternatively, chemical compounds to be used as candidate compounds can be synthesized from readily available starting materials using standard synthetic techniques and methodologies known to those of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds identified by the methods described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

[0191] Libraries of compounds may be presented in solution (e.g., Houghten, *Biotechniques* 13:412-421, 1992), or on beads (Lam, *Nature* 354:82-84, 1991), chips (Fodor, *Nature* 364:555-556, 1993), bacteria (Ladner, U.S. Pat. No. 5,223,409), spores (Ladner U.S. Pat. No. 5,223,409), plasmids (Cull et al., *Proc Natl Acad Sci USA* 89:1865-1869, 1992) or on phage (Scott and Smith, *Science* 249:386-390, 1990; Devlin, *Science* 249:404-406, 1990; Cwirla et al. *Proc. Natl. Acad. Sci.* 87:6378-6382, 1990; Felici, *J. Mol. Biol.* 222:301-310, 1991; Ladner supra.).

[0192] In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (e.g., taxonomic dereplication, biological dereplication, and chemical dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known for their activity should be employed whenever possible.

When a crude extract is found to have an ICP8 binding activity, further fractionation of the positive lead extract is necessary to isolate molecular constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and identification of a chemical entity within the crude extract that reduces ICP8 recombinase activity, DNA binding activity, and/or Herpes viral replication. Methods of fractionation and purification of such heterogeneous extracts are known in the art. If desired, compounds shown to be useful as therapeutics are chemically modified according to methods known in the art.

[0193] The present invention provides methods of treating disease (e.g. Herpes infection) and/or disorders or symptoms thereof which comprise administering a therapeutically effective amount of a pharmaceutical composition comprising a compound of the formulae herein to a subject (e.g., a mammal such as a human). Thus, one embodiment is a method of treating a subject suffering from or susceptible to a disease (e.g. Herpes infection) or symptom thereof. The method includes the step of administering to the mammal a therapeutic amount of an amount of a compound herein sufficient to treat the disease or disorder or symptom thereof, under conditions such that the disease or disorder is treated.

[0194] The methods herein include administering to the subject (including a subject identified as in need of such treatment) an effective amount of a compound described herein, or a composition described herein to produce such effect. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

[0195] The therapeutic methods of the invention (which include prophylactic treatment) in general comprise administration of a therapeutically effective amount of the compounds herein, such as a compound of the formulae herein to a subject (e.g., animal, human) in need thereof, including a mammal, particularly a human. Such treatment will be suitably administered to subjects, particularly humans, suffering from, having, susceptible to, or at risk for a disease, disorder, or symptom thereof. Determination of those subjects "at risk" can be made by any objective or subjective determination by a diagnostic test or opinion of a subject or health care provider (e.g., genetic test, enzyme or protein marker, Marker (as

defined herein), family history, and the like). The compounds herein may be also used in the treatment of any other disorders in which a Herpes infection may be implicated.

[0196] In one embodiment, the invention provides a method of monitoring treatment progress. The method includes the step of determining a level of diagnostic marker (Marker) (e.g. a Herpes polypeptide such as ICP8 or gC, or any target delineated herein modulated by a compound herein, a protein or indicator thereof, etc.) or diagnostic measurement (e.g., screen, assay) in a subject suffering from or susceptible to a disorder or symptoms thereof associated with a Herpes infection, in which the subject has been administered a therapeutic amount of a compound herein sufficient to treat the disease or symptoms thereof. The level of Marker determined in the method can be compared to known levels of Marker in either healthy normal controls or in other afflicted patients to establish the subject's disease status. In preferred embodiments, a second level of Marker in the subject is determined at a time point later than the determination of the first level, and the two levels are compared to monitor the course of disease or the efficacy of the therapy. In certain preferred embodiments, a pre-treatment level of Marker in the subject is determined prior to beginning treatment according to this invention; this pre-treatment level of Marker can then be compared to the level of Marker in the subject after the treatment commences, to determine the efficacy of the treatment.

Pharmaceutical Therapeutics

[0197] In other embodiments, agents discovered to have medicinal value using the methods described herein are useful as a drug or as information for structural modification of existing compounds, e.g., by rational drug design. Such methods are useful for screening agents having an effect on an ICP8 recombinase or DNA binding activity, or Herpes viral replication.

[0198] For therapeutic uses, the compositions or agents identified using the methods disclosed herein may be administered systemically, for example, formulated in a pharmaceutically-acceptable buffer such as physiological saline. Preferable routes of administration include, for example, oral, subcutaneous, intravenous, interperitoneally, intramuscular, or intradermal injections that provide continuous, sustained levels of the drug in the patient. In certain embodiments, the route of administration is oral administration; in other embodiments, topical administration is preferred. Compounds of the invention can be administered by a combination of routes, such as combined oral and topical administration.

[0199] Treatment of human patients or other animals will be carried out using a therapeutically effective amount of a therapeutic identified herein in a physiologically-acceptable carrier. Suitable carriers and their formulation are described, for example, in Remington's Pharmaceutical Sciences by E. W. Martin. The amount of the therapeutic agent to be administered varies depending upon the manner of administration, the age and body weight of the patient, and with the clinical symptoms of the Herpes infection. Generally, amounts will be in the range of those used for other agents used in the treatment of other diseases associated with Herpes infections, or infection by other similar viruses, although in certain instances lower amounts will be needed because of the increased specificity of the compound. A compound is administered at a dosage that inhibits Herpes viral replication, or that reduces ICP8 expression and/or levels or biological activity as determined by a method known to one skilled in the art, or using any assay that measures the expression or the biological activity of an ICP8 polypeptide.

Formulation of Pharmaceutical Compositions

[0200] The administration of a compound for the treatment of a Herpes infection may be by any suitable means that results in a concentration of the therapeutic that, combined with other components, is effective in ameliorating, reducing, or stabilizing a Herpes infection. The compound may be contained in any appropriate amount in any suitable carrier substance, and is generally present in an amount of 1-95% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for parenteral (e.g., subcutaneously, intravenously, intramuscularly, or intraperitoneally) administration route. The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice (see, e.g., Remington: The Science and Practice of Pharmacy (20th ed.), ed. A. R. Gennaro, Lippincott Williams & Wilkins, 2000 and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York).

[0201] Human dosage amounts can initially be determined by extrapolating from the amount of compound used in mice, as a skilled artisan recognizes it is routine in the art to modify the dosage for humans compared to animal models. In certain embodiments it is envisioned that the dosage may vary from between about 1 μg compound/Kg body weight to about 5000 mg compound/Kg body weight; or from about 5 mg/Kg body weight to about 4000 mg/Kg body weight or from about 10 mg/Kg body weight to about 3000 mg/Kg body weight; or from about 50 mg/Kg body weight to about 2000 mg/Kg body weight; or from about 100 mg/Kg body weight to about 1000 mg/Kg body weight; or from about 150 mg/Kg body weight to about 500 mg/Kg body weight, per day. In other embodiments this dose may be about 1, 5, 10, 25, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350, 1400, 1450, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, 3500, 4000, 4500, or 5000 mg/Kg body weight, per day. In other embodiments, it is envisaged that doses may be in the range of about 5 mg compound/Kg body to about 20 mg compound/Kg body. In other embodiments the doses may be about 8, 10, 12, 14, 16 or 18 mg/Kg body weight, per day. In certain embodiments, the dose may be selected to provide a concentration is a body fluid of the subject (e.g., blood, lymph, saliva, etc.) from about 10 μM to about 10 mM, or from about 100 μM to about 1 mM. Doses may be administered once per day, or in divided doses, e.g., twice per day, three times per day, or more frequently as needed. Of course, this dosage amount may be adjusted upward or downward, as is routinely done in such treatment protocols, depending on the results of the initial clinical trials and the needs of a particular patient.

[0202] Pharmaceutical compositions according to the invention may be formulated to release the active compound substantially immediately upon administration or at any predetermined time or time period after administration. The latter types of compositions are generally known as controlled release formulations, which include (i) formulations that create a substantially constant concentration of the drug within the body over an extended period of time; (ii) formulations that after a predetermined lag time create a substantially constant concentration of the drug within the body over an

extended period of time; (iii) formulations that sustain action during a predetermined time period by maintaining a relatively, constant, effective level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active substance (sawtooth kinetic pattern); (iv) formulations that localize action by, e.g., spatial placement of a controlled release composition adjacent to or in contact with the thymus; (v) formulations that allow for convenient dosing, such that doses are administered, for example, once every one or two weeks; and (vi) formulations that target a Herpes infection by using carriers or chemical derivatives to deliver the therapeutic agent to a particular cell type (e.g. sensory neurons). For some applications, controlled release formulations obviate the need for frequent dosing during the day to sustain the plasma level at a therapeutic level.

[0203] Any of a number of strategies can be pursued in order to obtain controlled release in which the rate of release outweighs the rate of metabolism of the compound in question. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients, including, e.g., various types of controlled release compositions and coatings. Thus, the therapeutic is formulated with appropriate excipients into a pharmaceutical composition that, upon administration, releases the therapeutic in a controlled manner. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, molecular complexes, nanoparticles, patches, and liposomes.

Parenteral Compositions

[0204] The pharmaceutical composition may be administered parenterally by injection, infusion or implantation (subcutaneous, intravenous, intramuscular, intraperitoneal, or the like) in dosage forms, formulations, or via suitable delivery devices or implants containing conventional, non-toxic pharmaceutically acceptable carriers and adjuvants. The formulation and preparation of such compositions are well known to those skilled in the art of pharmaceutical formulation. Formulations can be found in Remington: The Science and Practice of Pharmacy, supra.

[0205] Compositions for parenteral use may be provided in unit dosage forms (e.g., in single-dose ampoules), or in vials containing several doses and in which a suitable preservative may be added (see below). The composition may be in the form of a solution, a suspension, an emulsion, an infusion device, or a delivery device for implantation, or it may be presented as a dry powder to be reconstituted with water or another suitable vehicle before use. Apart from the active agent that reduces or ameliorates a Herpes infection, the composition may include suitable parenterally acceptable carriers and/or excipients. The active therapeutic agent(s) may be incorporated into microspheres, microcapsules, nanoparticles, liposomes, or the like for controlled release. Furthermore, the composition may include suspending, solubilizing, stabilizing, pH-adjusting agents, tonicity adjusting agents, and/or dispersing, agents.

[0206] As indicated above, the pharmaceutical compositions according to the invention may be in the form suitable for sterile injection. To prepare such a composition, the suitable active antineoplastic therapeutic(s) are dissolved or suspended in a parenterally acceptable liquid vehicle. Among acceptable vehicles and solvents that may be employed are water, water adjusted to a suitable pH by addition of an appropriate amount of hydrochloric acid, sodium hydroxide or a suitable buffer, 1,3-butanediol, Ringer's solution, and isotonic sodium chloride solution and dextrose solution. The aqueous formulation may also contain one or more preservatives (e.g., methyl, ethyl or n-propyl p-hydroxybenzoate). In cases where one of the compounds is only sparingly or slightly soluble in water, a dissolution enhancing or solubilizing agent can be added, or the solvent may include 10-60% w/w of propylene glycol or the like.

Controlled Release Parenteral Compositions

[0207] Controlled release parenteral compositions may be in form of aqueous suspensions, microspheres, microcapsules, magnetic microspheres, oil solutions, oil suspensions, or emulsions. Alternatively, the active drug may be incorporated in biocompatible carriers, liposomes, nanoparticles, implants, or infusion devices.

[0208] Materials for use in the preparation of microspheres and/or microcapsules are, e.g., biodegradable/bioerodible polymers such as polygalactin, poly-(isobutyl cyanoacrylate), poly(2-hydroxyethyl-L-glutaminine) and, poly(lactic acid). Biocompatible carriers that may be used when formulating a controlled release parenteral formulation are carbohydrates (e.g., dextrans), proteins (e.g., albumin), lipoproteins, or antibodies. Materials for use in implants can be non-biodegradable (e.g., polydimethyl siloxane) or biodegradable (e.g., poly(caprolactone), poly(lactic acid), poly(glycolic acid) or poly(ortho esters) or combinations thereof).

Solid Dosage Forms for Oral Use

[0209] Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. Such formulations are known to the skilled artisan. Excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.

[0210] The tablets may be uncoated or they may be coated by known techniques, optionally to delay disintegration and absorption in the gastrointestinal tract and thereby providing a sustained action over a longer period. The coating may be adapted to release the active drug in a predetermined pattern (e.g., in order to achieve a controlled release formulation) or it may be adapted not to release the active drug until after passage of the stomach (enteric coating). The coating may be a sugar coating, a film coating (e.g., based on hydroxypropyl methylcellulose, methylcellulose, methyl hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, acry-

late copolymers, polyethylene glycols and/or polyvinylpyrrolidone), or an enteric coating (e.g., based on methacrylic acid copolymer, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, and/or ethylcellulose). Furthermore, a time delay material, such as, e.g., glyceryl monostearate or glyceryl distearate may be employed.

[0211] The solid tablet compositions may include a coating adapted to protect the composition from unwanted chemical changes, (e.g., chemical degradation prior to the release of the active anti-Herpes therapeutic substance). The coating may be applied on the solid dosage form in a similar manner as that described in Encyclopedia of Pharmaceutical Technology, supra.

[0212] At least two anti-Herpes therapeutics may be mixed together in the tablet, or may be partitioned. In one example, the first active anti-Herpes therapeutic is contained on the inside of the tablet, and the second active anti-Herpes therapeutic is on the outside, such that a substantial portion of the second anti-Herpes therapeutic is released prior to the release of the first anti-Herpes therapeutic.

[0213] Formulations for oral use may also be presented as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (e.g., potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders and granulates may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment.

Controlled Release Oral Dosage Forms

[0214] Controlled release compositions for oral use may, e.g., be constructed to release the active anti-Herpes therapeutic by controlling the dissolution and/or the diffusion of the active substance. Dissolution or diffusion controlled release can be achieved by appropriate coating of a tablet, capsule, pellet, or granulate formulation of compounds, or by incorporating the compound into an appropriate matrix. A controlled release coating may include one or more of the coating substances mentioned above and/or, e.g., shellac, beeswax, glycowax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitostearate, ethylcellulose, acrylic resins, dl-polylactic acid, cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylmethacrylate, 2-hydroxymethacrylate, methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol methacrylate, and/or polyethylene glycols. In a controlled release matrix formulation, the matrix material may also include, e.g., hydrated methylcellulose, carnauba wax and stearyl alcohol, carbopol 934, silicone, glyceryl tristearate, methyl acrylate-methyl methacrylate, polyvinyl chloride, polyethylene, and/or halogenated fluorocarbon.

[0215] A controlled release composition containing one or more therapeutic compounds may also be in the form of a buoyant tablet or capsule (i.e., a tablet or capsule that, upon oral administration, floats on top of the gastric content for a certain period of time). A buoyant tablet formulation of the compound(s) can be prepared by granulating a mixture of the compound(s) with excipients and 20-75% w/w of hydrocolloids, such as hydroxyethylcellulose, hydroxypropylcellulose, or hydroxypropylmethylcellulose. The obtained granules can then be compressed into tablets. On contact with the gastric juice, the tablet forms a substantially water-impermeable gel barrier around its surface. This gel barrier takes part in maintaining a density of less than one, thereby allowing the tablet to remain buoyant in the gastric juice.

Combination Therapies

[0216] Optionally, an anti-Herpes therapeutic may be administered in combination with any other standard anti-Herpes therapy; such methods are known to the skilled artisan and described in Remington's Pharmaceutical Sciences by E. W. Martin. If desired, agents of the invention (including Raltegravir, 118-D-24, Elvitegravir (also known as GS 9137 or JTK-303), dolutegravir, MK-2048, L841411, and pharmaceutically acceptable salts thereof) are administered in combination with any conventional anti-neoplastic therapy, including but not limited to, surgery, radiation therapy, or chemotherapy. In one preferred embodiment, an agent of the invention is administered in combination with temozolomide.

Kits or Pharmaceutical Systems

[0217] The present compositions may be assembled into kits or pharmaceutical systems for use in ameliorating a Herpes infection. Kits or pharmaceutical systems according to this aspect of the invention comprise a carrier means, such as a box, carton, tube or the like, having in close confinement therein one or more container means, such as vials, tubes, ampoules, bottles and the like. The kits or pharmaceutical systems of the invention may also comprise associated instructions for using the agents of the invention.

[0218] The practice of the present invention employs, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are well within the purview of the skilled artisan. Such techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", second edition (Sambrook, 1989); "Oligonucleotide Synthesis" (Gait, 1984); "Animal Cell Culture" (Freshney, 1987); "Methods in Enzymology" "Handbook of Experimental Immunology" (Weir, 1996); "Gene Transfer Vectors for Mammalian Cells" (Miller and Calos, 1987); "Current Protocols in Molecular Biology" (Ausubel, 1987); "PCR: The Polymerase Chain Reaction", (Mullis, 1994); "Current Protocols in Immunology" (Coligan, 1991). These techniques are applicable to the production of the polynucleotides and polypeptides of the invention, and, as such, may be considered in making and practicing the invention. Particularly useful techniques for particular embodiments will be discussed in the sections that follow.

[0219] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the assay, screening, and therapeutic methods of the invention, and are not intended to limit the scope of what the inventors regard as their invention.

[0220] The practice of the present invention employs, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are well within the purview of the skilled artisan. Such

techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", second edition (Sambrook, 1989); "Oligonucleotide Synthesis" (Gait, 1984); "Animal Cell Culture" (Freshney, 1987); "Methods in Enzymology" "Handbook of Experimental Immunology" (Weir, 1996); "Gene Transfer Vectors for Mammalian Cells" (Miller and Calos, 1987); "Current Protocols in Molecular Biology" (Ausubel, 1987); "PCR: The Polymerase Chain Reaction", (Mullis, 1994); "Current Protocols in Immunology" (Coligan, 1991). These techniques are applicable to the production of the polynucleotides and polypeptides of the invention, and, as such, may be considered in making and practicing the invention. Particularly useful techniques for particular embodiments will be discussed in the sections that follow.

[0221] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the assay, screening, and therapeutic methods of the invention, and are not intended to limit the scope of what the inventors regard as their invention.

EXAMPLES

Example 1

ICP8 with Variations of the DDE Residues have Decreased Ability to Complement Replication of an ICP8 Mutant Virus

[0222] To identify highly conserved regions (and therefore new functional domains) in HSV-1 ICP8 and its homologs in other herpesviruses, an alignment of amino acid sequences from nine ICP8 homologs was performed, with representatives from alpha-, beta-, and gamma-herpesviruses. Numerous aspartic acid (D) and glutamic acid (E) residues were identified that were conserved in many or all of the ICP8 homologs (FIGS. **1**A and **1**B). The conservation of these residues in the homologs suggests that they are important for ICP8 function. Several of these conserved residues were located in or near the DNA binding groove in the ICP8 crystal structures (Mapelli, M., et al., J. Biol. Chem., vol. 280, pages 2990-2997), suggesting that they would be available to carry out enzymatic functions on bound DNA. Interestingly, members of a family of enzymes called DDE recombinases, including transposases, RAG-1, and retroviral integrases, also have conserved D and E residues that coordinate magnesium ions that are important for mediating the recombination reactions, leading to the notion that ICP8 may share biochemical and pharmacological properties with these will-studied proteins. Numerous ICP8 residues were further investigated, including D545 (amino acid positions are based on KOS ICP8 sequence)$_m$ D547, D625, E627, D645, E735, E860, D861, E1086, and D1087.

[0223] To determine whether the D643, E735, D860/E861 and E1086/D1087 DDE recombinase residues identified above are required for ICP8 function during HSV-1 infection, they were mutated to alanine and tested for their ability to complement the replication of an ICP8 mutant virus. FIG. **2** shows a schematic of the HSV-1 replication process. As shown in FIG. **3**A, all mutant forms of ICP8 were expressed at similar levels in transiently transfected Vero cells. At 24 hours after transfection, Vero cells were infected with the ICP8 null virus 8lacZ at a multiplicity of infection (MOI) of 20. Samples were harvested at 24 hours post infection and the viral yield was determined by performing plaque assays on V529 cells, which stably express ICP8 to complement replication of 8lacZ. The viral yield observed in cells transfected with the plasmid expressing wild type ICP8 was designated as 100% complementation, and all of the ICP8 mutants were compared to that value. As shown in FIGS. **3**B and **3**C, the D860A/E861A mutant form of ICP8 complemented 8lacZ replication to approximately 37% the level of wild type ICP8, indicating that residues 860 and 861 are required for wild type activity of ICP8. The E1086A/D1087A mutant form of ICP8 did not complement replication of 8lacZ to above the background levels observed when cells were transfected with the empty vector plasmid, as shown in FIG. **3**B. The d105 mutant form of ICP8, which fails to complement replication of an ICP8 mutant virus, also did not complement 8lacZ replication to above background levels. These results indicate that either residues 1086 and/or 1087 are very important for ICP8 function during HSV-1 replication.

[0224] To determine whether both residues 1086 and 1087 are required for ICP8 activity, each amino acid was mutated to alanine individually. FIG. **3**C shows that E1086A displayed significant levels of complementation (~60%), while D1087A displayed no detectable complementation, thereby indicating that D1087 plays a very important role in ICP8 function.

[0225] Additionally, mutations at two other locations in ICP8, E735 and D645, were also mutated to assess whether they were important for ICP8 function. As shown in FIG. **3**C, E735A and D645A displayed complementation levels of ~90% and ~70%, respectively. This data indicates that these positions are less important for ICP8 function than position D1087.

[0226] To rule out that the possibility that mutation of the putative DDE residues in ICP8 did not reduce the activity of ICP8 by simply destroying the overall folding of the protein, we investigated their ability to bind DNA. As shown in FIG. **3**D, shows that the DDE mutant is able to bind DNA, indicating that it possesses the requisite structure required to bind DNA. Additionally, Vero cells were either mock infected or infected with either wild type HSV-1 or the ICP8 DDE mutant at an MOI of 10. At 8 hours post infection, cells were fixed and stained for immunofluorescence with the ICP8-specific antibody 39S, which specifically recognizes active ICP8 in viral replication compartments. The DDE mutant of ICP8 was recognized by a conformation specific antibody (data not shown).

Example 2

The DDE Residues in ICP8 are Required for HSV-1 Replication and Viral DNA Replication

[0227] KOS.DDEm, a mutant virus containing the E1086A/D1087A mutation in ICP8, was constructed to investigate whether this mutant form of ICP8 affected HSV-1 replication when expressed from the viral genome. As shown in FIG. **4**A, replication of this mutant virus was indistinguishable from the ICP8-null virus 8lacZ in non-complementing Vero cells. KOS.DDEm replicated to nearly wild type levels in the complementing V529 cells, suggesting that while this DDE mutation in ICP8 cannot support viral replication, it does not have a dominant negative phenotype, which is different from the d105 mutation.

[0228] The levels of viral DNA replication in Vero cells infected with either the KOS.DDEm mutant virus or wild

type KOS were investigated. No viral DNA replication was observed between 4 and 12 hours post infection in cells infected with the KOS.DDEm mutant virus. In contrast, as shown in FIG. **4**B, a more than 20-fold increase in HSV-1 DNA was observed by 12 hours post infection in cells infected with wild type virus. FIG. **4**C further shows the effect of the KOS.DDEm mutant virus relative to another independent control, pm1.a., which is completely defective for DNA replication. These data indicate that the DDE residues in ICP8 are very important for HSV-1 DNA replication, and that these residues likely promote recombination activity on the viral genome.

Example 3

Effect of DDE Residues on Viral Gene Expression

[0229] As described above, the KOS.DDEm mutant virus exhibited defects in viral replication and DNA replication; consequently, KOS.DDEm mutant virus was also tested for an effect on viral gene expression. The accumulation of the immediate-early gene products ICP27 and ICP4, the early gene product ICP8, and the late gene product glycoprotein C (gC), was assayed by performing immunoblot assays with Vero cells that were infected with either wild type HSV-1 or the ICP8 mutant virus KOS.DDEm. As shown in FIG. **5**, slightly higher levels of ICP27, ICP4, and ICP8 were observed in KOS.DDEm-infected Vero cells, relative to Vero cells infected with wild type HSV-1, suggesting that the putative DDE recombinase residues in ICP8 are not required for expression of viral immediate-early or early genes. Although accumulation of the immediate-early and early gene products tested was not dependent on the DDE residues in ICP8, the late gene product gC was observed to accumulate to lower levels at 12 hours post infection in Vero cells infected with the KOS.DDEm relative to cells infected with wild type HSV-1, as shown in FIG. **5**. Patterns of viral transcript accumulation observed in RNA hybridization assays were similar to the patterns of accumulation of viral proteins observed in immunoblot assays. It is known that expression of gC requires HSV-1 DNA replication, and the decreased levels of gC are consistent with the observed defect in viral DNA replication.

Example 4

Raltegravir, LL841411, and 118-D-24 Inhibit HSV-1 Replication with High Efficiency

[0230] The HIV integrase structurally similar to ICP8, and can be inhibited by specific drugs such as Raltegravir and 118-D-24. These drugs were tested to determine whether they could inhibit HSV replication.

[0231] Raltegravir and 118-D-24, which have been shown to inhibit HIV replication by inhibiting the activity of the HIV integrase enzyme, inhibited the replication of HSV-1 with high efficacy in cell culture-based assays. As shown in FIG. **6**, Raltegravir at a concentration of 100 μM reduced HSV viral yield by greater than 96%, and 118-D-24 at a concentration of 1 mM reduced HSV yield by greater than 99.99%. 118-D-24 was studied further because it appeared to inhibit HSV replication very strongly. As shown in FIG. **7**, a dose-response curve with 118-D-24 demonstrated that the concentration required for 50% inhibition of HSV yield (IC50) was approximately 0.4 mM. The inhibition of HSV replication is likely due to the inhibition of the HSV protein ICP8, which shares structural homology with HIV integrase. FIG. **8** shows a ribbon structure of the ICP8 protein. Additionally, FIG. **9** shows that L-841411, another inhibitor, also shows significant reduction of HSV viral yield, albeit to a lesser extent than Raltegravir and 118-D-24.

Example 5

118-D-24 Inhibit HSV-1 Replication with High Efficiency

[0232] In view of the high efficiency of 118-D-24 as an HSV replication inhibitor, the effective concentration range of 118-D-24 was tested over a concentration range of 0-1 mM. FIG. **7** shows the dose response curve of 118-D-24 as tested in an HSV yield reduction assay. 118-D-24 reduces HSV yield by about 50% at a concentration of 0.4 mM, and completely, or nearly completely, eliminates HSV yield at a concentration of 1 mM.

[0233] The effect of 118-D-24 on viral DNA replication was also tested. As shown in FIG. **10**, **118**-D-24 decreased viral DNA replication by about 50% relative to a DMSO control.

[0234] The effect of 118-D-24 on viral gene expression was also tested. As shown in FIG. **11**, the accumulation of the immediate-early gene product ICP27, and the early gene product ICP8, was moderately reduced at 5 hours post-treatment relative to a DMSO control, however, accumulation of the late gene product gC was eliminated.

Example 6

118-D-24 Derivatives Inhibit HSV Replication

[0235] To evaluate the effects of 118-D-24 derivatives on HSV replication, a panel of derivatives (Table 1) (Zhao, X. Z., 2008, *J. Med. Chem., vol.* 51, pages 251-259) were screened for their ability to inhibit HSV-1 KOS virus replication in Hep2 cells. Hep2 cells were plated in a 6-well plate and incubated overnight to reach confluency. The cells were then inoculated with HSV-1 KOS virus at MOI=0.01 for 1 hour. Following inoculation, the virus inoculum was replaced with DMEV medium containing 118-D-24 or a derivative of 118-D-24. After 48 hours, samples were harvested by adding an equal volume of 10% non-fat milk and immediately frozen at −80° C. Samples were freeze-thawed three times to rupture the cell membranes and allow the release of virus. Virus titers were determined by titration on Vero cells. The 100% yield represents the viral titer in samples without drug treatment. As shown in FIG. **12**, 250 μM of the 118-D-24 derivatives XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50 resulted in significant reductions in viral yield. Dose response curves for these 118-D-24 derivatives on viral replication are shown in FIG. **13**. Hep2 cells or (FIG. **14**A) or HFF cells (FIG. **14**B) were infected with HSV-1 virus (KOS strain) at MOI of 0.01. Samples were then processed and percent yield remaining values were calculated. EC50 and EC90 values were calculated using nonlinear regression curve fit with a variable slope. GaraphPad Prism 5 software was used for all analyses. (FIG. **14**C) Cytotoxicity of XZ45 on the viability of Hep2 cells during a 48-hour incubation period was evaluated using the Promega cell titer glo assay, as described by the manufacturer. The reported values are percent fluorescence intensity remaining relative to the fluorescence intensity from cells grown in media containing DMSO alone. CC50 value was determined as described above. FIGS. **14**A and **14**B show the effects of XZ45 on HSV-1 replication in Hep2 cells (14A)

and normal human foreskin fibroblasts (14B) and the cytotoxicity of XZ45 in Hep2 cells is shown in FIG. **14**C. These results indicate that XZ45 has a therapeutic index of ~500 for HSV-1 in the Hep2 cell system.

TABLE 1

NO	STRUCTURE
	118-D-24 derivatives
XZ319	Chemical Formula: $C_{11}H_9N_3O_4$ Molecular Weight: 247.2069
XZ320	Chemical Formula: $C_{24}H_{20}O_6$ Molecular Weight: 404.4120
XZ89	Chemical Formula: $C_{15}H_9ClFNO_4$ Molecular Weight: 321.6877
XZ90	Chemical Formula: $C_{15}H_{11}ClFNO_3$ Molecular Weight: 307.7041

TABLE 1-continued

NO	STRUCTURE
	118-D-24 derivatives
XZ259	Chemical Formula: $C_{17}H_{16}ClFN_2O_5S$ Molecular Weight: 414.8357
XZ100	Chemical Formula: $C_{16}H_{12}N_4O_4$ Molecular Weight: 324.2909
XZ99	Chemical Formula: $C_{16}H_{14}N_4O_3$ Molecular Weight: 310.3074
XZ45	Chemical Formula: $C_{14}H_{12}N_2O_5$ Molecular Weight: 288.2555
XZ15	Chemical Formula: $C_{14}H_{12}N_2O_6$ Molecular Weight: 304.2549

TABLE 1-continued

118-D-24 derivatives	
NO	STRUCTURE
XZ49	Chemical Formula: $C_{15}H_{12}N_2O_6$ Molecular Weight: 316.2656
XZ48	Chemical Formula: $C_{16}H_{12}N_2O_6$ Molecular Weight: 328.2763
XZ50	Chemical Formula: $C_{16}H_{10}N_2O_7$ Molecular Weight: 342.2598
XZ199	Chemical Formula: $C_{18}H_{14}ClFN_2O_4$ Molecular Weight: 376.7662
XZ202	Chemical Formula: $C_{16}H_{12}ClFN_2O_4$ Molecular Weight: 350.7289

TABLE 1-continued

118-D-24 derivatives	
NO	STRUCTURE
XZ201	Chemical Formula: $C_{21}H_{14}ClFN_2O_4$ Molecular Weight: 412.7983
XZ220	Chemical Formula: $C_{21}H_{20}ClFN_2O_6$ Molecular Weight: 450.8447
XZ256	Chemical Formula: $C_{19}H_{15}ClFN_3O_5$ Molecular Weight: 419.7909
XZ242	Chemical Formula: $C_{16}H_{12}ClFN_2O_4$ Molecular Weight: 350.7289

TABLE 1-continued

118-D-24 derivatives	
NO	STRUCTURE
XZ248	Chemical Formula: $C_{18}H_{18}N_2O_4$ Molecular Weight: 326.3465
XZ235	Chemical Formula: $C_{18}H_{17}ClFN_3O_4$ Molecular Weight: 393.7967
XZ236	Chemical Formula: $C_{21}H_{23}ClFN_3O_4$ Molecular Weight: 435.8764

Example 7

XZ45 Inhibits the Replication of HSV-1, HSV-2, and Human Cytomegalovirus (HCMV)

[0236] Hep2 cells were infected with HSV-1 strain KOS, strain F, or HSV-2 strain G at MOI of 0.01. The infected cells were grown in media containing increasing concentrations of XZ45 or DMSO for 48 hours. Samples were harvested and viral yield was determined by plaque assay on Vero cells. The reported values are percent yield remaining relative to cells grown in media containing DMSO alone (FIG. **15**A). Hep2 cells (FIG. **15**B) or HFF cells (FIG. **15**C) were infected with HSV-1 virus (KOS strain) at MOI of 10 or 0.01 or with human cytomegalovirus (HCMV) (FIG. **16**). Samples were then processed and percent yield remaining values were calculated as describe above. The results demonstrate that XZ45 inhibits the replication of HSV-1, HSV-2, and HCMV.

Example 8

XZ45 Inhibits Viral DNA Synthesis and Late Gene Expression

[0237] FIG. **17**A shows the effect of XZ45 on viral DNA synthesis. Hep2 cells were infected with HSV-1 KOS at an MOI=10 in the presence or absence of 10 μM XZ45. Total DNA was harvested at the times indicated, and viral DNA levels in each sample were determined by real-time PCR and were normalized to the levels of cellular DNA. FIG. **17**B shows the effect of XZ45 on viral gene expression. Hep2 cells were infected with HSV-1 KOS in the presence or absence of 10 μM XZ45. Lysates were prepared for immunoblotting at the indicated times. Polypeptides were resolved by SDS-PAGE, transferred to a PVDF membrane, and probed for representative immediate-early (ICP27), early (ICP8), and late (gC) gene products. As shown, XZ45 significantly inhibited the expression of the late gene (gC) products.

Example 9

XZ45 does not Decrease ssDNA Binding by ICP8

[0238] The effect of XZ45 on ssDNA binding by ICP8 was measured by EMSA assay with purified ICP8 protein using ^{32}P-labled polynucleotide ssDNA probe (FIG. **18**A); ssDNA beads pull down assay (FIG. **18**B), and ICP8 binding to ssDNA-cellulose (FIG. **18**C). As shown, XZ45 does not affect ssDNA binding by ICP8 as determined using the three assays.

Example 10

XZ45 Inhibits Viral Recombination in Infected Cells

[0239] To test the effect of XZ45 on HSV recombination during viral replication, 8LacZ (deletion of ul29) and hr99 (deletion of ul5) virus were used to coinfect Hep2 cells in the presence of XZ45 or PAA. At 20 hours after infection, samples were harvested and progeny virus were tittered on Vero cells and V529 cells to determine the viral titer of recombinated virus and total virus. The recombination rate reflects the ratio between the titer of recombinated virus and total virus. As shown in FIG. **19**, XZ45 significantly inhibited HSV recombination compared to PAA.

[0240] To further test the effect of XZ45 on ICP8 mediated recombination a D-loop assay was used. A double stranded DNA probe was mixed with a single stranded DNA oligonucleotide in the presence or absence of ICP8 with 0, 10, 20, or 40 μM XZ45. Following incubation, the reaction products were analyzed by electrophoresis through a native gel. As shown in FIG. **20**, ICP8 is able to catalyze recombination between a double stranded DNA probe and a single stranded DNA oligonucleotide. However, XZ45 inhibited the ICP8 mediated formation of D-loops between the double stranded DNA template and the single stranded DNA probe, thereby demonstrating that XZ45 inhibited the ability of ICP8 to mediate recombination.

The results described above were obtained using the following methods and materials.

[0241] Cells and Viruses.

[0242] Vero cells were obtained from American Type Cell Culture (Manassas, Va.). V529 cells were generated as described by, hereby incorporated by reference in its entirety. Cells were maintained in Dulbecco's Modification of Eagle's Medium (DMEM) supplemented with 5% heat-inactivated fetal bovine serum and 5% heat-inactivated newborn calf serum (NCS). Medium for the V529 cells was also supplemented with 500 μg/mL G418.

[0243] All experiments were performed with HSV-1 wild type strain KOS or mutant viruses 8lacZ, hereby incorporated by reference in its entirety) and KOS.8DDEm, which were derived from strain KOS. Viruses were propagated and titrated on Vero or V529 cells following standard procedures.

[0244] Plasmids.

[0245] The DDE mutations in ICP8 were generated by performing PCR-based site-directed mutagenesis.

[0246] Complementation Assay.

[0247] Vero cells, which do not complement the replication of the ICP8 mutant virus 8lacZ, were transfected with the indicated plasmid using standard transfection reagents known in the art (e.g. Effectene transfection reagents (Qiagen) according to the manufacturer's instructions). At 24 hours post transfection, the transfected cells were infected with 8lacZ at an MOI of 10 pfu/cell. At 24 hours post infection, viral yield samples were harvested by scraping the infected cell monolayer and collecting both the cells and the supernatant. Samples were frozen at −80° C., thawed, and cell-free supernatant was collected following centrifugation of the samples. Viral yield in each sample was determined by performing plaque assays on V529 cells, which express ICP8 and thus complement replication of the ICP8 mutant 8lacZ. Complementation was compared to the viral yield seen following transfection with the plasmid expressing wild type ICP8, and this value was set to be 100% complementation.

[0248] Construction of Mutant Viruses.

[0249] The plasmid p8-8GFP, which encodes ICP8 fused to GFP at its C terminus (described above), was linearized by digesting with EcoRI co-transfected into V529 cells with HSV-1 strain KOS infectious DNA, which was prepared using standard methods, to generate the recombinant virus KOS.8GFP. Plaques expressing GFP were identified by fluorescence microscopy and these recombinant viruses were plaque purified at least 3 times prior to use in experiments. To generate KOS.8DDEm, KOS.8GFP infectious DNA was co-transfected into V529 cells together with EcoRI linearized pBS.8flank8. Plaques that did not express GFP were identified by fluorescent microscopy and plaque purified 3 times prior to use in experiments. The presence of the DDE mutation in ICP8 was confirmed by sequencing a PCR product from the appropriate region of ICP8.

[0250] Viral Replication Assay.

[0251] Vero or V529 cells were infected with the indicated virus at an MOI of 10 in phosphate-buffered saline supplemented with calcium and magnesium (PBS-ABC) containing 1% FBS and 0.1% glucose for one hour in a shaking incubator at 37° C. Following the one hour adsorption step, cells were washed twice with acid wash buffer (recipe), once with DMEM containing 1% FBS, and then DMEM containing 1% FBS was added. Viral yields were harvested at the indicated time post infection by scraping the infected cell monolayer and collecting the cells and supernatant. Samples were frozen at −80° C. following harvesting. Viral yield was determined by performing plaque assays on Vero or V529 cells, as indicated.

[0252] Viral DNA Replication Assay.

[0253] Vero or V529 cells were infected with the indicated virus as described above for the viral replication assay. Following infection for the indicated time, samples were harvested by washing the cell monolayers with PBS-ABC, the cells were scraped in PBS-ABC, and the cells were then collected by centrifugation. Total DNA (including both cellular and viral DNA) was purified using standard methods (e.g. the Generation Capture Column Kit (Qiagen), according to the manufacturer's instructions). Viral DNA was quantified by performing real time PCR using primers specific for the ICP27 promoter. The Real time PCR was performed using standard reagents and methods known in the art (e.g. PowerSYBR Green reagents (Applied Biosystems) and an Applied Biosystems 7X00 Sequence Detection System, according to the manufacturer's instructions). The viral DNA levels were normalized to the levels of a GAPDH pseudogene in each sample.

[0254] Immunoblotting.

[0255] Vero or V529 cells were infected with the indicated virus as described above. Cell monolayers were washed with PBS-ABC, and lysates were prepared by scraping the cells in 2×SDS-PAGE loading buffer and boiling for 5 minutes. Polypeptides were resolved by SDS-PAGE and transferred to a polyvinylidene difluoride (PVDF) membrane. Membranes were blocked for 1 hour at room temperature with 5% milk in Tris-buffered saline with 0.1% Tween 20 (TBST). Blocked membranes were reacted with primary antibodies diluted in 5% milk in TBST.

Other Embodiments

[0256] From the foregoing description, it will be apparent that variations and modifications may be made to the invention described herein to adopt it to various usages and conditions. Such embodiments are also within the scope of the following claims.

[0257] The recitation of a listing of elements in any definition of a variable herein includes definitions of that variable as any single element or combination (or subcombination) of listed elements. The recitation of an embodiment herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[0258] All patents and publications mentioned in this specification are herein incorporated by reference to the same extent as if each independent patent and publication was specifically and individually indicated to be incorporated by reference.

SEQUENCE LISTING

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<160> NUMBER OF SEQ ID NOS: 29

<210> SEQ ID NO 1
<211> LENGTH: 1196
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<212> TYPE: PRT
<213> ORGANISM: Herpes simplex virus

<400> SEQUENCE: 1

Met Glu Thr Lys Pro Lys Thr Ala Thr Thr Ile Lys Val Pro Pro Gly
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Pro Leu Gly Tyr Val Tyr Ala Arg Ala Cys Pro Ser Glu Gly Ile Glu
            20   25   30

Leu Leu Ala Leu Leu Ser Ala Arg Ser Gly Asp Ala Asp Val Ala Val
        35   40   45

Ala Pro Leu Val Val Gly Leu Thr Val Glu Ser Gly Phe Glu Ala Asn
    50   55   60

Val Ala Val Val Val Gly Ser Arg Thr Thr Gly Leu Gly Gly Thr Ala
65   70   75   80

Val Ser Leu Lys Leu Thr Pro Ser His Tyr Ser Ser Ser Val Tyr Val
                85   90   95

Phe His Gly Gly Arg His Leu Asp Pro Ser Thr Gln Ala Pro Asn Leu
            100   105   110

Thr Arg Leu Cys Glu Arg Ala Arg Arg His Phe Gly Phe Ser Asp Tyr
        115   120   125

Thr Pro Arg Pro Gly Asp Leu Lys His Glu Thr Thr Gly Glu Ala Leu
    130   135   140

Cys Glu Arg Leu Gly Leu Asp Pro Asp Arg Ala Leu Leu Tyr Leu Val
145   150   155   160

Val Thr Glu Gly Phe Lys Glu Ala Val Cys Ile Asn Asn Thr Phe Leu
                165   170   175

His Leu Gly Gly Ser Asp Lys Val Thr Ile Gly Gly Ala Glu Val His
            180   185   190

Arg Ile Pro Val Tyr Pro Leu Gln Leu Phe Met Pro Asp Phe Ser Arg
        195   200   205

Val Ile Ala Glu Pro Phe Asn Ala Asn His Arg Ser Ile Gly Glu Asn
    210   215   220

Phe Thr Tyr Pro Leu Pro Phe Phe Asn Arg Pro Leu Asn Arg Leu Leu
225   230   235   240

Phe Glu Ala Val Val Gly Pro Ala Ala Val Ala Leu Arg Cys Arg Asn
                245   250   255

Val Asp Ala Val Ala Arg Ala Ala Ala His Leu Ala Phe Asp Glu Asn
            260   265   270

His Glu Gly Ala Ala Leu Pro Ala Asp Ile Thr Phe Thr Ala Phe Glu
        275   280   285

Ala Ser Gln Gly Lys Thr Pro Arg Gly Gly Arg Asp Gly Gly Gly Lys
    290   295   300

Gly Pro Ala Gly Gly Phe Glu Gln Arg Leu Ala Ser Val Met Ala Gly
305   310   315   320

Asp Ala Ala Leu Ala Leu Glu Ser Ile Val Ser Met Ala Val Phe Asp
                325   330   335

Glu Pro Pro Thr Asp Ile Ser Ala Trp Pro Leu Cys Glu Gly Gln Asp
            340   345   350

Thr Ala Ala Ala Arg Ala Asn Ala Val Gly Ala Tyr Leu Ala Arg Ala
        355   360   365

Ala Gly Leu Val Gly Ala Met Val Phe Ser Thr Asn Ser Ala Leu His
    370   375   380

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Leu Thr Glu Val Asp Asp Ala Gly Pro Ala Asp Pro Lys Asp His Ser
385                 390                 395                 400

Lys Pro Ser Phe Tyr Arg Phe Phe Leu Val Pro Gly Thr His Val Ala
                405                 410                 415

Ala Asn Pro Gln Val Asp Arg Glu Gly His Val Val Pro Gly Phe Glu
            420                 425                 430

Gly Arg Pro Thr Ala Pro Leu Val Gly Gly Thr Gln Glu Phe Ala Gly
        435                 440                 445

Glu His Leu Ala Met Leu Cys Gly Phe Ser Pro Ala Leu Leu Ala Lys
    450                 455                 460

Met Leu Phe Tyr Leu Glu Arg Cys Asp Gly Gly Val Ile Val Gly Arg
465                 470                 475                 480

Gln Glu Met Asp Val Phe Arg Tyr Val Ala Asp Ser Asn Gln Thr Asp
                485                 490                 495

Val Pro Cys Asn Leu Cys Thr Phe Asp Thr Arg His Ala Cys Val His
            500                 505                 510

Thr Thr Leu Met Arg Leu Arg Ala Arg His Pro Lys Phe Ala Ser Ala
        515                 520                 525

Ala Arg Gly Ala Ile Gly Val Phe Gly Thr Met Asn Ser Met Tyr Ser
    530                 535                 540

Asp Cys Asp Val Leu Gly Asn Tyr Ala Ala Phe Ser Ala Leu Lys Arg
545                 550                 555                 560

Ala Asp Gly Ser Glu Thr Ala Arg Thr Ile Met Gln Glu Thr Tyr Arg
                565                 570                 575

Ala Ala Thr Glu Arg Val Met Ala Glu Leu Glu Thr Leu Gln Tyr Val
            580                 585                 590

Asp Gln Ala Val Pro Thr Ala Met Gly Arg Leu Glu Thr Ile Ile Thr
        595                 600                 605

Asn Arg Glu Ala Leu His Thr Val Val Asn Asn Val Arg Gln Val Val
    610                 615                 620

Asp Arg Glu Val Glu Gln Leu Met Arg Asn Leu Val Glu Gly Arg Asn
625                 630                 635                 640

Phe Lys Phe Arg Asp Gly Leu Gly Glu Ala Asn His Ala Met Ser Leu
                645                 650                 655

Thr Leu Asp Pro Tyr Ala Cys Gly Pro Cys Pro Leu Leu Gln Leu Leu
            660                 665                 670

Gly Arg Arg Ser Asn Leu Ala Val Tyr Gln Asp Leu Ala Leu Ser Gln
        675                 680                 685

Cys His Gly Val Phe Ala Gly Gln Ser Val Glu Gly Arg Asn Phe Arg
    690                 695                 700

Asn Gln Phe Gln Pro Val Leu Arg Arg Arg Val Met Asp Met Phe Asn
705                 710                 715                 720

Asn Gly Phe Leu Ser Ala Lys Thr Leu Thr Val Ala Leu Ser Glu Gly
                725                 730                 735

Ala Ala Ile Cys Ala Pro Ser Leu Thr Ala Gly Gln Thr Ala Pro Ala
            740                 745                 750

Glu Ser Ser Phe Glu Gly Asp Val Ala Arg Val Thr Leu Gly Phe Pro
        755                 760                 765

Lys Glu Leu Arg Val Lys Ser Arg Val Leu Phe Ala Gly Ala Ser Ala
    770                 775                 780
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```
Asn Ala Ser Glu Ala Ala Lys Ala Arg Val Ala Ser Leu Gln Ser Ala
785                 790                 795                 800

Tyr Gln Lys Pro Asp Lys Arg Val Asp Ile Leu Leu Gly Pro Leu Gly
                805                 810                 815

Phe Leu Leu Lys Gln Phe His Ala Ala Ile Phe Pro Asn Gly Lys Pro
            820                 825                 830

Pro Gly Ser Asn Gln Pro Asn Pro Gln Trp Phe Trp Thr Ala Leu Gln
        835                 840                 845

Arg Asn Gln Leu Pro Ala Arg Leu Leu Ser Arg Glu Asp Ile Glu Thr
    850                 855                 860

Ile Ala Phe Ile Lys Lys Phe Ser Leu Asp Tyr Gly Ala Ile Asn Phe
865                 870                 875                 880

Ile Asn Leu Ala Pro Asn Asn Val Ser Glu Leu Ala Met Tyr Tyr Met
                885                 890                 895

Ala Asn Gln Ile Leu Arg Tyr Cys Asp His Ser Thr Tyr Phe Ile Asn
            900                 905                 910

Thr Leu Thr Ala Ile Ile Ala Gly Ser Arg Arg Pro Pro Ser Val Gln
        915                 920                 925

Ala Ala Ala Ala Trp Ser Ala Gln Gly Gly Ala Gly Leu Glu Ala Gly
    930                 935                 940

Ala Arg Ala Leu Met Asp Ala Val Asp Ala His Pro Gly Ala Trp Thr
945                 950                 955                 960

Ser Met Phe Ala Ser Cys Asn Leu Leu Arg Pro Val Met Ala Ala Arg
                965                 970                 975

Pro Met Val Val Leu Gly Leu Ser Ile Ser Lys Tyr Tyr Gly Met Ala
            980                 985                 990

Gly Asn Asp Arg Val Phe Gln Ala  Gly Asn Trp Ala Ser  Leu Met Gly
        995                 1000                1005

Gly Lys  Asn Ala Cys Pro Leu  Leu Ile Phe Asp Arg  Thr Arg Lys
    1010                1015                1020

Phe Val  Leu Ala Cys Pro Arg  Ala Gly Phe Val Cys  Ala Ala Ser
    1025                1030                1035

Asn Leu  Gly Gly Gly Ala His  Glu Ser Ser Leu Cys  Glu Gln Leu
    1040                1045                1050

Arg Gly  Ile Ile Ser Glu Gly  Gly Ala Ala Val Ala  Ser Ser Val
    1055                1060                1065

Phe Val  Ala Thr Val Lys Ser  Leu Gly Pro Arg Thr  Gln Gln Leu
    1070                1075                1080

Gln Ile  Glu Asp Trp Leu Ala  Leu Leu Glu Asp Glu  Tyr Leu Ser
    1085                1090                1095

Glu Glu  Met Met Glu Leu Thr  Ala Arg Ala Leu Glu  Arg Gly Asn
    1100                1105                1110

Gly Glu  Trp Ser Thr Asp Ala  Ala Leu Glu Val Ala  His Glu Ala
    1115                1120                1125

Glu Ala  Leu Val Ser Gln Leu  Gly Asn Ala Gly Glu  Val Phe Asn
    1130                1135                1140

Phe Gly  Asp Phe Gly Cys Glu  Asp Asp Asn Ala Thr  Pro Phe Gly
    1145                1150                1155

Gly Pro  Gly Ala Pro Gly Pro  Ala Phe Ala Gly Arg  Lys Arg Ala
    1160                1165                1170

Phe His  Gly Asp Asp Pro Phe  Gly Glu Gly Pro Pro  Asp Lys Lys
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    1175                1180                1185

Gly Asp  Leu Thr Leu Asp Met  Leu
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```

<210> SEQ ID NO 2
<211> LENGTH: 3591
<212> TYPE: DNA
<213> ORGANISM: Herpes simplex virus

<400> SEQUENCE: 2

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gtgtccctga aactgacgcc atcgcactac agctcgtccg tgtacgtctt tcacggcggc    300

cggcacctgg accccagcac ccaggcccca aacctgacgc gactctgcga gcgggcacgc    360

cgccattttg gcttttcgga ctacaccccc cggcccggcg acctcaaaca cgagacgacg    420

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gttaccgagg gcttcaagga ggccgtgtgc atcaacaaca cctttctgca cctgggaggc    540

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gtgtttaact ttggggattt tggctgcgag gacgacaacg cgacgccgtt cggcggcccg 3480

ggggccccgg gaccggcatt tgccggccgc aaacgggcgt tccacgggga tgacccgttt 3540

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<210> SEQ ID NO 3
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 3

tttttttttt tttttttttt ttttt 25

<210> SEQ ID NO 4
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Herpes simplex virus

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<400> SEQUENCE: 4

Leu Met Arg Leu Arg Ala Arg His Pro Lys Phe Ala Ser Ala Ala Arg
1               5                   10                  15

Gly Ala Ile Gly Val Phe Gly Thr Met Asn Ser Met Tyr Ser Asp Cys
            20                  25                  30

Asp Val Leu Gly Asn Tyr Ala Ala Phe Ser Ala Leu Lys Arg Ala Asp
        35                  40                  45

Gly Ser
    50


<210> SEQ ID NO 5
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Herpes simplex virus

<400> SEQUENCE: 5

Leu Met Arg Leu Arg Ala Arg His Pro Lys Phe Ala Ser Ala Ala Arg
1               5                   10                  15

Gly Ala Ile Gly Val Phe Gly Thr Met Asn Ser Ala Tyr Ser Asp Cys
            20                  25                  30

Asp Val Leu Gly Asn Tyr Ala Ala Phe Ser Ala Leu Lys Arg Ala Asp
        35                  40                  45

Gly Ser
    50


<210> SEQ ID NO 6
<211> LENGTH: 51
<212> TYPE: PRT
<213> ORGANISM: Varicella-zoster virus

<400> SEQUENCE: 6

Val His Arg Leu Arg Gln Arg Met Pro Arg Phe Gly Gln Ala Thr Arg
1               5                   10                  15

Gln Pro Ile Gly Val Phe Gly Thr Met Asn Ser Gln Tyr Ser Asp Cys
            20                  25                  30

Asp Pro Leu Gly Asn Tyr Ala Pro Tyr Leu Ile Leu Arg Lys Pro Gly
        35                  40                  45

Asp Gln Thr
    50


<210> SEQ ID NO 7
<211> LENGTH: 49
<212> TYPE: PRT
<213> ORGANISM: Marek's disease virus

<400> SEQUENCE: 7

Ile Lys Arg Leu Val Tyr Arg Leu Pro Lys Phe Gly Tyr Gln Met Arg
1               5                   10                  15

Gly Ala Met Gly Leu Phe Gly Ala Met Thr Asn Asn Tyr Cys Asp Val
            20                  25                  30

Asn Ala Leu Gly Ser Tyr Ala Gln Phe Ser Thr Leu Lys Arg Ser Glu
        35                  40                  45

Gly


<210> SEQ ID NO 8
<211> LENGTH: 48
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-continued

<212> TYPE: PRT
<213> ORGANISM: Epstein-Barr virus

<400> SEQUENCE: 8

```
Phe Phe Arg Leu Arg Asp Arg Phe Pro Pro Val Met Ser Thr Gln Arg
1               5                   10                  15

Arg Asp Pro Tyr Val Ile Ser Gly Ala Ser Gly Ser Tyr Asn Glu Thr
            20                  25                  30

Asp Phe Leu Gly Asn Phe Leu Asn Phe Ile Asp Lys Glu Asp Asp Gly
        35                  40                  45
```

<210> SEQ ID NO 9
<211> LENGTH: 59
<212> TYPE: PRT
<213> ORGANISM: Human cytomegalovirus

<400> SEQUENCE: 9

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Phe Val Arg Val Arg Thr Arg Leu Pro Val Val Pro Lys Gln Pro Lys
1               5                   10                  15

Lys Glu Pro Cys Val Ile Thr Val Gln Ser Arg Phe Leu Asn Asp Val
            20                  25                  30

Asp Ile Leu Gly Ser Phe Gly Arg Arg Tyr Asn Val Asp Ala Lys Asp
        35                  40                  45

Gly Gly Leu Asp Gly Lys Gly Asp Asp Gly Val
    50                  55
```

<210> SEQ ID NO 10
<211> LENGTH: 53
<212> TYPE: PRT
<213> ORGANISM: Murine cytomegalovirus

<400> SEQUENCE: 10

```
Phe Ile Arg Val Asn Thr Arg Leu Pro Gly Ile Pro Lys Gln Ile Lys
1               5                   10                  15

Lys Glu Pro Val Val Val Thr Leu Leu Ser Arg Ala Phe Ala Asp Ala
            20                  25                  30

Asp Leu Leu Gly Asn Tyr Gly Lys Arg Tyr Gly Leu Glu Ser Arg Glu
        35                  40                  45

Ala Gly Asp Gly Gly
    50
```

<210> SEQ ID NO 11
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Human herpesvirus

<400> SEQUENCE: 11

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Leu Ile Arg Ile Asn Ser Arg Leu Pro Gln Ile Ser Lys Thr Thr Lys
1               5                   10                  15

Lys Glu Pro Ile Val Met Thr Met Phe Ser Arg Phe Tyr Ala Asp Val
            20                  25                  30

Asp Val Leu Gly Ser Phe Gly Lys Lys Gly Val Asn Glu Ser Lys Asp
        35                  40                  45

Pro Met
    50
```

<210> SEQ ID NO 12

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<211> LENGTH: 48
<212> TYPE: PRT
<213> ORGANISM: Kaposi's sarcoma-associated herpesvirus

<400> SEQUENCE: 12

Phe Tyr Arg Met Lys Asp Arg Phe Pro Pro Val Leu Ser Asn Val Lys
1 5 10 15

Arg Asp Pro Tyr Val Ile Thr Gly Thr Ala Gly Thr Tyr Asn Asp Leu
20 25 30

Glu Ile Leu Gly Asn Phe Ala Thr Phe Arg Glu Arg Glu Glu Glu Gly
35 40 45

<210> SEQ ID NO 13
<211> LENGTH: 57
<212> TYPE: PRT
<213> ORGANISM: Herpes simplex virus

<400> SEQUENCE: 13

Ala Gly Phe Val Cys Ala Ala Ser Asn Leu Gly Gly Gly Ala His Glu
1 5 10 15

Ser Ser Leu Cys Glu Gln Leu Arg Gly Ile Ile Ser Glu Gly Gly Ala
20 25 30

Ala Val Ala Ser Ser Val Phe Val Ala Thr Val Lys Ser Leu Gly Pro
35 40 45

Arg Thr Gln Gln Leu Gln Ile Glu Asp
50 55

<210> SEQ ID NO 14
<211> LENGTH: 57
<212> TYPE: PRT
<213> ORGANISM: Herpes simplex virus

<400> SEQUENCE: 14

Ala Gly Phe Val Cys Ala Ala Ser Ser Leu Gly Gly Gly Ala His Glu
1 5 10 15

His Ser Leu Cys Glu Gln Leu Arg Gly Ile Ile Ala Glu Gly Gly Ala
20 25 30

Ala Val Ala Ser Ser Val Phe Val Ala Thr Val Lys Ser Leu Gly Pro
35 40 45

Arg Thr Gln Gln Leu Gln Ile Glu Asp
50 55

<210> SEQ ID NO 15
<211> LENGTH: 57
<212> TYPE: PRT
<213> ORGANISM: Varicella-zoster virus

<400> SEQUENCE: 15

Gly Gly Phe Ile Cys Pro Val Thr Gly Pro Ser Ser Gly Asn Arg Glu
1 5 10 15

Thr Thr Leu Ser Asp Gln Val Arg Gly Ile Ile Val Ser Gly Gly Ala
20 25 30

Met Val Gln Leu Ala Ile Tyr Ala Thr Val Val Arg Ala Val Gly Ala
35 40 45

Arg Ala Gln His Met Ala Phe Asp Asp
50 55

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<210> SEQ ID NO 16
<211> LENGTH: 57
<212> TYPE: PRT
<213> ORGANISM: Marek's disease virus

<400> SEQUENCE: 16

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Val Gly Phe Val Ala Glu Gln Pro Ile Phe Ser Ser Gly Ile Lys Glu
1               5                   10                  15

Thr Thr Leu Ile Asp Arg Val Arg Met Val Leu Ser Glu Glu Ser Ala
            20                  25                  30

Ala Pro His Ala Ala Val Tyr Met Leu Ala Leu Lys Met Val Gly Asp
        35                  40                  45

Arg Val Arg Gln Met Glu Leu Glu Asp
    50                  55
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<210> SEQ ID NO 17
<211> LENGTH: 59
<212> TYPE: PRT
<213> ORGANISM: Epstein-Barr virus

<400> SEQUENCE: 17

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Leu Gly Leu Thr Val Lys Arg Arg Thr Gln Ala Ala Thr Thr Tyr Glu
1               5                   10                  15

Ile Glu Asn Ile Arg Ala Gly Leu Glu Ala Ile Ile Ser Gln Lys Gln
            20                  25                  30

Glu Glu Asp Cys Val Phe Asp Val Val Cys Asn Leu Val Asp Ala Met
        35                  40                  45

Gly Glu Ala Cys Ala Ser Leu Thr Arg Asp Asp
    50                  55
```

<210> SEQ ID NO 18
<211> LENGTH: 57
<212> TYPE: PRT
<213> ORGANISM: Human cytomegalovirus

<400> SEQUENCE: 18

```
Ala Asp Val Leu Ile Lys Arg Ser Arg Arg Glu Asn Val Leu Phe Asp
1               5                   10                  15

Ala Asp Leu Ile Lys Asn Arg Val Met Leu Ala Leu Asp Ala Glu Asn
            20                  25                  30

Leu Asp Cys Asp Pro Glu Val Met Ala Val Tyr Glu Ile Leu Ser Val
        35                  40                  45

Arg Glu Glu Ile Pro Ala Ser Asp Asp
    50                  55
```

<210> SEQ ID NO 19
<211> LENGTH: 59
<212> TYPE: PRT
<213> ORGANISM: Murine cytomegalovirus

<400> SEQUENCE: 19

```
Val Asp Val Leu Ile Arg Arg Ser Arg Arg Glu Asn Val Met Tyr Asp
1               5                   10                  15

Arg Asp Val Val Arg Ser Arg Val Leu Ala Ala Leu Asp Ser Thr Gly
            20                  25                  30

Leu Asp Val Asp Pro Glu Leu Ala Ala Ile Ala Glu Leu Met Glu Gly
        35                  40                  45
```

-continued

```
Arg Asp Glu Gly Asp Ile Pro Glu Ile Asp Asp
    50                  55


<210> SEQ ID NO 20
<211> LENGTH: 57
<212> TYPE: PRT
<213> ORGANISM: Human herpesvirus

<400> SEQUENCE: 20

Cys Asp Ile Ile Val Lys Lys Val Lys Arg Glu Ala Ile Val Tyr Asp
1               5                   10                  15

Val Glu Val Ile Arg Gly Lys Val Leu Asn Ile Ile Glu Ser Leu Ser
            20                  25                  30

Asn Ser Val Asn Pro Glu Leu Leu Ile Leu Ala Glu Val Met Lys Asp
        35                  40                  45

Arg Asp Ser Lys Pro Thr Met Asp Asp
    50                  55


<210> SEQ ID NO 21
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Kaposi's sarcoma-associated herpesvirus

<400> SEQUENCE: 21

Val Asp Arg Leu Val Lys Arg Ile Val Gly Ile Asn Ser Gly Glu Phe
1               5                   10                  15

Glu Ala Glu Ala Val Lys Arg Ser Val Gln Asn Val Leu Glu Asp Arg
            20                  25                  30

Asp Asn Pro Asn Leu Pro Lys Thr Val Val Leu Glu Leu Val Lys His
        35                  40                  45

Leu Gly Ser Ser Cys Ala Ser Leu Thr Glu Glu Asp
    50                  55                  60


<210> SEQ ID NO 22
<211> LENGTH: 1196
<212> TYPE: PRT
<213> ORGANISM: Herpes simplex virus

<400> SEQUENCE: 22

Met Asp Thr Lys Pro Lys Thr Thr Thr Thr Val Lys Val Pro Pro Gly
1               5                   10                  15

Pro Met Gly Tyr Val Tyr Gly Arg Ala Cys Pro Ala Glu Gly Leu Glu
            20                  25                  30

Leu Leu Ser Leu Leu Ser Ala Arg Ser Gly Asp Ala Asp Val Ala Val
        35                  40                  45

Ala Pro Leu Ile Val Gly Leu Thr Val Glu Ser Gly Phe Glu Ala Asn
    50                  55                  60

Val Ala Ala Val Val Gly Ser Arg Thr Thr Gly Leu Gly Gly Thr Ala
65                  70                  75                  80

Val Ser Leu Lys Leu Met Pro Ser His Tyr Ser Pro Ser Val Tyr Val
                85                  90                  95

Phe His Gly Gly Arg His Leu Ala Pro Ser Thr Gln Ala Pro Asn Leu
            100                 105                 110

Thr Arg Leu Cys Glu Arg Ala Arg Pro His Phe Gly Phe Ala Asp Tyr
        115                 120                 125

Ala Pro Arg Pro Cys Asp Leu Lys His Glu Thr Thr Gly Asp Ala Leu
```

-continued

```
    130                 135                 140

Cys Glu Arg Leu Gly Leu Asp Pro Asp Arg Ala Leu Leu Tyr Leu Val
145                 150                 155                 160

Ile Thr Glu Gly Phe Arg Glu Ala Val Cys Ile Ser Asn Thr Phe Leu
                165                 170                 175

His Leu Gly Gly Met Asp Lys Val Thr Ile Gly Asp Ala Glu Val His
            180                 185                 190

Arg Ile Pro Val Tyr Pro Leu Gln Met Phe Met Pro Asp Phe Ser Arg
        195                 200                 205

Val Ile Ala Asp Pro Phe Asn Cys Asn His Arg Ser Ile Gly Glu Asn
    210                 215                 220

Phe Asn Tyr Pro Leu Pro Phe Phe Asn Arg Pro Leu Ala Arg Leu Leu
225                 230                 235                 240

Phe Glu Ala Val Val Gly Pro Ala Ala Val Ala Leu Arg Ala Arg Asn
                245                 250                 255

Val Asp Ala Val Ala Arg Ala Ala Ala His Leu Ala Phe Asp Glu Asn
            260                 265                 270

His Glu Gly Ala Ala Leu Pro Ala Asp Ile Thr Phe Thr Ala Phe Glu
        275                 280                 285

Ala Ser Gln Gly Lys Pro Gln Arg Gly Ala Arg Asp Ala Gly Asn Lys
    290                 295                 300

Gly Pro Ala Gly Gly Phe Glu Gln Arg Leu Ala Ser Val Met Ala Gly
305                 310                 315                 320

Asp Ala Ala Leu Ala Leu Glu Ser Ile Val Ser Met Ala Val Phe Asp
                325                 330                 335

Glu Pro Pro Pro Asp Ile Thr Thr Trp Pro Leu Leu Glu Gly Gln Glu
            340                 345                 350

Thr Pro Ala Ala Arg Ala Gly Ala Val Gly Ala Tyr Leu Ala Arg Ala
        355                 360                 365

Ala Gly Leu Val Gly Ala Met Val Phe Ser Thr Asn Ser Ala Leu His
    370                 375                 380

Leu Thr Glu Val Asp Asp Ala Gly Pro Ala Asp Pro Lys Asp His Ser
385                 390                 395                 400

Lys Pro Ser Phe Tyr Arg Phe Phe Leu Val Pro Gly Thr His Val Ala
                405                 410                 415

Ala Asn Pro Gln Leu Asp Arg Glu Gly His Val Val Pro Gly Tyr Glu
            420                 425                 430

Gly Arg Pro Thr Ala Pro Leu Val Gly Gly Thr Gln Glu Phe Ala Gly
        435                 440                 445

Glu His Leu Ala Met Leu Cys Gly Phe Ser Pro Ala Leu Leu Ala Lys
    450                 455                 460

Met Leu Phe Tyr Leu Glu Arg Cys Asp Gly Gly Val Ile Val Gly Arg
465                 470                 475                 480

Gln Glu Met Asp Val Phe Arg Tyr Val Ala Asp Ser Gly Gln Thr Asp
                485                 490                 495

Val Pro Cys Asn Leu Cys Thr Phe Glu Thr Arg His Ala Cys Ala His
            500                 505                 510

Thr Thr Leu Met Arg Leu Arg Ala Arg His Pro Lys Phe Ala Ser Ala
        515                 520                 525

Ala Arg Gly Ala Ile Gly Val Phe Gly Thr Met Asn Ser Ala Tyr Ser
    530                 535                 540
```

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```
Asp Cys Asp Val Leu Gly Asn Tyr Ala Ala Phe Ser Ala Leu Lys Arg
545                 550                 555                 560

Ala Asp Gly Ser Glu Asn Thr Arg Thr Ile Met Gln Glu Thr Tyr Arg
                565                 570                 575

Ala Ala Thr Glu Arg Val Met Ala Glu Leu Glu Ala Leu Gln Tyr Val
            580                 585                 590

Asp Gln Ala Val Pro Thr Ala Leu Gly Arg Leu Glu Thr Ile Ile Gly
        595                 600                 605

Asn Arg Glu Ala Leu His Thr Val Val Asn Asn Ile Lys Gln Leu Val
    610                 615                 620

Asp Arg Glu Val Glu Gln Leu Met Arg Asn Leu Ile Glu Gly Arg Asn
625                 630                 635                 640

Phe Lys Phe Arg Asp Gly Leu Ala Glu Ala Asn His Ala Met Ser Leu
                645                 650                 655

Ser Leu Asp Pro Tyr Thr Cys Gly Pro Cys Pro Leu Leu Gln Leu Leu
            660                 665                 670

Ala Arg Arg Ser Asn Leu Ala Val Tyr Gln Asp Leu Ala Leu Ser Gln
        675                 680                 685

Cys His Gly Val Phe Ala Gly Gln Ser Val Glu Gly Arg Asn Phe Arg
    690                 695                 700

Asn Gln Phe Gln Pro Val Leu Arg Arg Arg Val Met Asp Leu Phe Asn
705                 710                 715                 720

Asn Gly Phe Leu Ser Ala Lys Thr Leu Thr Val Ala Leu Ser Glu Gly
                725                 730                 735

Ala Ala Ile Cys Ala Pro Ser Leu Thr Ala Gly Gln Thr Ala Pro Ala
            740                 745                 750

Glu Ser Ser Phe Glu Gly Asp Val Ala Arg Val Thr Leu Gly Phe Pro
        755                 760                 765

Lys Glu Leu Arg Val Lys Ser Arg Val Leu Phe Ala Gly Ala Ser Ala
    770                 775                 780

Asn Ala Ser Glu Ala Ala Lys Ala Arg Val Ala Ser Leu Gln Ser Ala
785                 790                 795                 800

Tyr Gln Lys Pro Asp Lys Arg Val Asp Ile Leu Leu Gly Pro Leu Gly
                805                 810                 815

Phe Leu Leu Lys Gln Phe His Ala Val Ile Phe Pro Asn Gly Lys Pro
            820                 825                 830

Pro Gly Ser Asn Gln Pro Asn Pro Gln Trp Phe Trp Thr Ala Leu Gln
        835                 840                 845

Arg Asn Gln Leu Pro Ala Arg Leu Leu Ser Arg Glu Asp Ile Glu Thr
    850                 855                 860

Ile Ala Phe Ile Lys Arg Phe Ser Leu Asp Tyr Gly Ala Ile Asn Phe
865                 870                 875                 880

Ile Asn Leu Ala Pro Asn Asn Val Ser Glu Leu Ala Met Tyr Tyr Met
                885                 890                 895

Ala Asn Gln Ile Leu Arg Tyr Cys Asp His Ser Thr Tyr Phe Ile Asn
            900                 905                 910

Thr Leu Thr Ala Val Ile Ala Gly Ser Arg Arg Pro Pro Ser Val Gln
        915                 920                 925

Ala Ala Ala Ala Trp Ala Pro Gln Gly Gly Ala Gly Leu Glu Ala Gly
    930                 935                 940
```

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```
Ala Arg Ala Leu Met Asp Ser Leu Asp Ala His Pro Gly Ala Trp Thr
945                 950                 955                 960

Ser Met Phe Ala Ser Cys Asn Leu Leu Arg Pro Val Met Ala Ala Arg
                965                 970                 975

Pro Met Val Val Leu Gly Leu Ser Ile Ser Lys Tyr Tyr Gly Met Ala
            980                 985                 990

Gly Asn Asp Arg Val Phe Gln Ala  Gly Asn Trp Ala Ser  Leu Leu Gly
        995                 1000                1005

Gly Lys  Asn Ala Cys Pro Leu  Leu Ile Phe Asp Arg  Thr Arg Lys
    1010                 1015                1020

Phe Val  Leu Ala Cys Pro Arg  Ala Gly Phe Val Cys  Ala Ala Ser
    1025                 1030                1035

Ser Leu  Gly Gly Gly Ala His  Glu His Ser Leu Cys  Glu Gln Leu
    1040                 1045                1050

Arg Gly  Ile Ile Ala Glu Gly  Gly Ala Ala Val Ala  Ser Ser Val
    1055                 1060                1065

Phe Val  Ala Thr Val Lys Ser  Leu Gly Pro Arg Thr  Gln Gln Leu
    1070                 1075                1080

Gln Ile  Glu Asp Trp Leu Ala  Leu Leu Glu Asp Glu  Tyr Leu Ser
    1085                 1090                1095

Glu Glu  Met Met Glu Phe Thr  Thr Arg Ala Leu Glu  Arg Gly His
    1100                 1105                1110

Gly Glu  Trp Ser Thr Asp Ala  Ala Leu Glu Val Ala  His Glu Ala
    1115                 1120                1125

Glu Ala  Leu Val Ser Gln Leu  Gly Ala Ala Gly Glu  Val Phe Asn
    1130                 1135                1140

Phe Gly  Asp Phe Gly Asp Glu  Asp Asp His Ala Ala  Ser Phe Gly
    1145                 1150                1155

Gly Leu  Ala Ala Ala Ala Gly  Ala Ala Gly Val Ala  Arg Lys Arg
    1160                 1165                1170

Ala Phe  His Gly Asp Asp Pro  Phe Gly Glu Gly Pro  Pro Glu Lys
    1175                 1180                1185

Lys Asp  Leu Thr Leu Asp Met  Leu
    1190                 1195
```

<210> SEQ ID NO 23
<211> LENGTH: 1204
<212> TYPE: PRT
<213> ORGANISM: Varicella-zoster virus

<400> SEQUENCE: 23

```
Met Glu Asn Thr Gln Lys Thr Val Thr Val Pro Thr Gly Pro Leu Gly
1               5                   10                  15

Tyr Val Tyr Ala Cys Arg Val Glu Asp Leu Asp Leu Glu Glu Ile Ser
            20                  25                  30

Phe Leu Ala Ala Arg Ser Thr Asp Ser Asp Leu Ala Leu Leu Pro Leu
        35                  40                  45

Met Arg Asn Leu Thr Val Glu Lys Thr Phe Thr Ser Ser Leu Ala Val
    50                  55                  60

Val Ser Gly Ala Arg Thr Thr Gly Leu Ala Gly Ala Gly Ile Thr Leu
65                  70                  75                  80

Lys Leu Thr Thr Ser His Phe Tyr Pro Ser Val Phe Val Phe His Gly
                85                  90                  95
```

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```
Gly Lys His Val Leu Pro Ser Ser Ala Ala Pro Asn Leu Thr Arg Ala
            100                 105                 110

Cys Asn Ala Ala Arg Glu Arg Phe Gly Phe Ser Arg Cys Gln Gly Pro
        115                 120                 125

Pro Val Asp Gly Ala Val Glu Thr Thr Gly Ala Glu Ile Cys Thr Arg
    130                 135                 140

Leu Gly Leu Glu Pro Glu Asn Thr Ile Leu Tyr Leu Val Val Thr Ala
145                 150                 155                 160

Leu Phe Lys Glu Ala Val Phe Met Cys Asn Val Phe Leu His Tyr Gly
                165                 170                 175

Gly Leu Asp Ile Val His Ile Asn His Gly Asp Val Ile Arg Ile Pro
            180                 185                 190

Leu Phe Pro Val Gln Leu Phe Met Pro Asp Val Asn Arg Leu Val Pro
        195                 200                 205

Asp Pro Phe Asn Thr His His Arg Ser Ile Gly Glu Gly Phe Val Tyr
    210                 215                 220

Pro Thr Pro Phe Tyr Asn Thr Gly Leu Cys His Leu Ile His Asp Cys
225                 230                 235                 240

Val Ile Ala Pro Met Ala Val Ala Leu Arg Val Arg Asn Val Thr Ala
                245                 250                 255

Val Ala Arg Gly Ala Ala His Leu Ala Phe Asp Glu Asn His Glu Gly
            260                 265                 270

Ala Val Leu Pro Pro Asp Ile Thr Tyr Thr Tyr Phe Gln Ser Ser Ser
        275                 280                 285

Ser Gly Thr Thr Thr Ala Arg Gly Ala Arg Arg Asn Asp Val Asn Ser
    290                 295                 300

Thr Ser Lys Pro Ser Pro Ser Gly Gly Phe Glu Arg Arg Leu Ala Ser
305                 310                 315                 320

Ile Met Ala Ala Asp Thr Ala Leu His Ala Glu Val Ile Phe Asn Thr
                325                 330                 335

Gly Ile Tyr Glu Glu Thr Pro Thr Asp Ile Lys Glu Trp Pro Met Phe
            340                 345                 350

Ile Gly Met Glu Gly Thr Leu Pro Arg Leu Asn Ala Leu Gly Ser Tyr
        355                 360                 365

Thr Ala Arg Val Ala Gly Val Ile Gly Ala Met Val Phe Ser Pro Asn
    370                 375                 380

Ser Ala Leu Tyr Leu Thr Glu Val Glu Asp Ser Gly Met Thr Glu Ala
385                 390                 395                 400

Lys Asp Gly Gly Pro Gly Pro Ser Phe Asn Arg Phe Tyr Gln Phe Ala
                405                 410                 415

Gly Pro His Leu Ala Ala Asn Pro Gln Thr Asp Arg Asp Gly His Val
            420                 425                 430

Leu Ser Ser Gln Ser Thr Gly Ser Ser Asn Thr Glu Phe Ser Val Asp
        435                 440                 445

Tyr Leu Ala Leu Ile Cys Gly Phe Gly Ala Pro Leu Leu Ala Arg Leu
    450                 455                 460

Leu Phe Tyr Leu Glu Arg Cys Asp Ala Gly Ala Phe Thr Gly Gly His
465                 470                 475                 480

Gly Asp Ala Leu Lys Tyr Val Thr Gly Thr Phe Asp Ser Glu Ile Pro
                485                 490                 495
```

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```
Cys Ser Leu Cys Glu Lys His Thr Arg Pro Val Cys Ala His Thr Thr
            500                 505                 510

Val His Arg Leu Arg Gln Arg Met Pro Arg Phe Gly Gln Ala Thr Arg
        515                 520                 525

Gln Pro Ile Gly Val Phe Gly Thr Met Asn Ser Gln Tyr Ser Asp Cys
    530                 535                 540

Asp Pro Leu Gly Asn Tyr Ala Pro Tyr Leu Ile Leu Arg Lys Pro Gly
545                 550                 555                 560

Asp Gln Thr Glu Ala Ala Lys Ala Thr Met Gln Asp Thr Tyr Arg Ala
                565                 570                 575

Thr Leu Glu Arg Leu Phe Ile Asp Leu Glu Gln Glu Arg Leu Leu Asp
            580                 585                 590

Arg Gly Ala Pro Cys Ser Ser Glu Gly Leu Ser Ser Val Ile Val Asp
        595                 600                 605

His Pro Thr Phe Arg Arg Ile Leu Asp Thr Leu Arg Ala Arg Ile Glu
    610                 615                 620

Gln Thr Thr Thr Gln Phe Met Lys Val Leu Val Glu Thr Arg Asp Tyr
625                 630                 635                 640

Lys Ile Arg Glu Gly Leu Ser Glu Ala Thr His Ser Met Ala Leu Thr
                645                 650                 655

Phe Asp Pro Tyr Ser Gly Ala Phe Cys Pro Ile Thr Asn Phe Leu Val
            660                 665                 670

Lys Arg Thr His Leu Ala Val Val Gln Asp Leu Ala Leu Ser Gln Cys
        675                 680                 685

His Cys Val Phe Tyr Gly Gln Gln Val Glu Gly Arg Asn Phe Arg Asn
    690                 695                 700

Gln Phe Gln Pro Val Leu Arg Arg Arg Phe Val Asp Leu Phe Asn Gly
705                 710                 715                 720

Gly Phe Ile Ser Thr Arg Ser Ile Thr Val Thr Leu Ser Glu Gly Pro
                725                 730                 735

Val Ser Ala Pro Asn Pro Thr Leu Gly Gln Asp Ala Pro Ala Gly Arg
            740                 745                 750

Thr Phe Asp Gly Asp Leu Ala Arg Val Ser Val Glu Val Ile Arg Asp
        755                 760                 765

Ile Arg Val Lys Asn Arg Val Val Phe Ser Gly Asn Cys Thr Asn Leu
    770                 775                 780

Ser Glu Ala Ala Arg Ala Arg Leu Val Gly Leu Ala Ser Ala Tyr Gln
785                 790                 795                 800

Arg Gln Glu Lys Arg Val Asp Met Leu His Gly Ala Leu Gly Phe Leu
                805                 810                 815

Leu Lys Gln Phe His Gly Leu Leu Phe Pro Arg Gly Met Pro Pro Asn
            820                 825                 830

Ser Lys Ser Pro Asn Pro Gln Trp Phe Trp Thr Leu Leu Gln Arg Asn
        835                 840                 845

Gln Met Pro Ala Asp Lys Leu Thr His Glu Glu Ile Thr Thr Ile Ala
    850                 855                 860

Ala Val Lys Arg Phe Thr Glu Glu Tyr Ala Ala Ile Asn Phe Ile Asn
865                 870                 875                 880

Leu Pro Pro Thr Cys Ile Gly Glu Leu Ala Gln Phe Tyr Met Ala Asn
                885                 890                 895

Leu Ile Leu Lys Tyr Cys Asp His Ser Gln Tyr Leu Ile Asn Thr Leu
```

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```
            900                 905                 910

Thr Ser Ile Ile Thr Gly Ala Arg Arg Pro Arg Asp Pro Ser Ser Val
        915                 920                 925

Leu His Trp Ile Arg Lys Asp Val Thr Ser Ala Ala Asp Ile Glu Thr
    930                 935                 940

Gln Ala Lys Ala Leu Leu Glu Lys Thr Glu Asn Leu Pro Glu Leu Trp
945                 950                 955                 960

Thr Thr Ala Phe Thr Ser Thr His Leu Val Arg Ala Ala Met Asn Gln
                965                 970                 975

Arg Pro Met Val Val Leu Gly Ile Ser Ile Ser Lys Tyr His Gly Ala
            980                 985                 990

Ala Gly Asn Asn Arg Val Phe Gln  Ala Gly Asn Trp Ser  Gly Leu Asn
        995                 1000                1005

Gly Gly  Lys Asn Val Cys Pro  Leu Phe Thr Phe Asp  Arg Thr Arg
    1010                 1015                1020

Arg Phe  Ile Ile Ala Cys Pro  Arg Gly Gly Phe Ile  Cys Pro Val
    1025                 1030                1035

Thr Gly  Pro Ser Ser Gly Asn  Arg Glu Thr Thr Leu  Ser Asp Gln
    1040                 1045                1050

Val Arg  Gly Ile Ile Val Ser  Gly Gly Ala Met Val  Gln Leu Ala
    1055                 1060                1065

Ile Tyr  Ala Thr Val Val Arg  Ala Val Gly Ala Arg  Ala Gln His
    1070                 1075                1080

Met Ala  Phe Asp Asp Trp Leu  Ser Leu Thr Asp Asp  Glu Phe Leu
    1085                 1090                1095

Ala Arg  Asp Leu Glu Glu Leu  His Asp Gln Ile Ile  Gln Thr Leu
    1100                 1105                1110

Glu Thr  Pro Trp Thr Val Glu  Gly Ala Leu Glu Ala  Val Lys Ile
    1115                 1120                1125

Leu Asp  Glu Lys Thr Thr Ala  Gly Asp Gly Glu Thr  Pro Thr Asn
    1130                 1135                1140

Leu Ala  Phe Asn Phe Asp Ser  Cys Glu Pro Ser His  Asp Thr Thr
    1145                 1150                1155

Ser Asn  Val Leu Asn Ile Ser  Gly Ser Asn Ile Ser  Gly Ser Thr
    1160                 1165                1170

Val Pro  Gly Leu Lys Arg Pro  Pro Glu Asp Asp Glu  Leu Phe Asp
    1175                 1180                1185

Leu Ser  Gly Ile Pro Ile Lys  His Gly Asn Ile Thr  Met Glu Met
    1190                 1195                1200

Ile


<210> SEQ ID NO 24
<211> LENGTH: 1191
<212> TYPE: PRT
<213> ORGANISM: Marek's disease virus

<400> SEQUENCE: 24

Met Asp Gly Val Gly Lys Ser Val Lys Leu Cys Gly Gly Pro Ile Gly
1               5                   10                  15

Tyr Ile Tyr Ala Thr Pro Lys Cys Ser Val Pro Val Asp Glu Leu Ala
            20                  25                  30

Ile Leu Ala Ala Lys Ser Asn Asp Cys Asp Asp Ala Val Leu Pro Leu
```

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```
        35                  40                  45

Val Ala Gly Leu Thr Val Glu Ser Asp Phe Val Trp Asn Val Ala Ala
    50                  55                  60

Val Ala Gly Thr Lys Thr Thr Gly Leu Gly Ser Gly Gly Thr Thr Leu
65                  70                  75                  80

Lys Leu Val Pro Thr His Tyr His Pro Cys Val Phe Val Phe Tyr Gly
                85                  90                  95

Gly Asp Cys Ile Lys Pro Cys Thr Lys Ala Pro Asn Leu Thr Lys Ala
            100                 105                 110

Cys Asp Leu Ala Arg Glu Arg Phe Gly Tyr Ser Ala Tyr Ser Ser Pro
        115                 120                 125

Ala Pro Thr Ala Phe Glu Thr Thr Gly Gln Gln Ile Cys Glu Ala Leu
    130                 135                 140

Glu Met Asp Ala Gln Asn Val Met Leu Tyr Leu Val Val Thr Glu Leu
145                 150                 155                 160

Phe Lys Glu Val Ile Tyr Leu Cys Asn Ser Phe Leu His Phe Gly Gly
                165                 170                 175

Ser Asp Val Val Thr Ile Asn Asn Ala Asp Val Arg Arg Ile Pro Ile
            180                 185                 190

Tyr Pro Leu His Leu Val Leu Pro Asp Phe Asn Arg Ile Thr Asn Glu
        195                 200                 205

Pro Phe Ser Glu Lys Pro Arg Ala Leu Gly Glu Gly Ala Ile Met Pro
    210                 215                 220

Lys Ala Phe Tyr Asn Asp Ser Leu Cys Arg Leu Leu His Gly Tyr Val
225                 230                 235                 240

Leu Ser Thr Thr Ala Val Gly Leu Arg Val Arg Asn Ile Asp Ala Ile
                245                 250                 255

Ala Arg Gly Ala Ala His Leu Cys Phe Asp Glu Asn His Glu Gly Thr
            260                 265                 270

Leu Leu Pro Ala Asp Thr Thr Phe Thr Ala Phe Thr Pro Ala Ala Glu
        275                 280                 285

Thr Thr Lys Gly Gln Ser Lys Met Gly Lys Arg Glu Gly Ser Asp Val
    290                 295                 300

Ser Gly Gly Gly Tyr Glu Arg Arg Thr Ala Ser Leu Met Ala Ser Asp
305                 310                 315                 320

Ala Thr Leu Ala Ile Glu Asn Val Ile Ser Ala Ser Val Tyr Glu Asp
                325                 330                 335

Pro Ile Pro Asp Val Asn Lys Trp Pro Ile Tyr Cys Asn Pro Val Gly
            340                 345                 350

Tyr Ala Asp Arg Ile Glu Ala Leu Ser Ala Tyr Met Ala Arg Val Ala
        355                 360                 365

Gly Leu Val Gly Ala Met Val Phe Ser Ser Asn Ser Val Ile Tyr Met
    370                 375                 380

Thr Glu Val Gly Glu Ala Gly Ser Thr Glu Gly Lys Glu Thr Ser Thr
385                 390                 395                 400

Thr Ala Pro Ser Phe Tyr Arg Phe Phe Gln Ile Ala Ala Pro His Leu
                405                 410                 415

Ser Ala Asn Pro Leu Val Asp Arg Asp Gly Lys Pro Val Ser Gly Glu
            420                 425                 430

Asn Leu Ser Lys Ser Thr Ser Ala Ser Gln Ser Glu Tyr Ser Leu Asp
        435                 440                 445
```

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```
Tyr Leu Ile Leu Ala Cys Gly Phe Cys Pro Gln Leu Leu Ala Arg Phe
    450                 455                 460

Leu Phe Tyr Leu Glu Arg Cys Asp Gly Gly Ala Lys Ala Cys His His
465                 470                 475                 480

Asp Leu Asp Thr Val Lys Phe Val Ser Ser Ala Ile Asp Ala Asp Met
                485                 490                 495

Pro Cys Glu Leu Cys Asp Lys Thr Ser Arg Ile Tyr Cys Ala His Thr
            500                 505                 510

Thr Ile Lys Arg Leu Val Tyr Arg Leu Pro Lys Phe Gly Tyr Gln Met
        515                 520                 525

Arg Gly Ala Met Gly Leu Phe Gly Ala Met Thr Asn Asn Tyr Cys Asp
    530                 535                 540

Val Asn Ala Leu Gly Ser Tyr Ala Gln Phe Ser Thr Leu Lys Arg Ser
545                 550                 555                 560

Glu Gly Glu Ala Ser Arg Ser Val Met Gln Asp Thr Tyr Arg Leu Thr
                565                 570                 575

Val Glu Arg Met Met Lys Ala Leu Glu Lys Glu Gly Leu Leu Thr Cys
            580                 585                 590

Asp Asp Pro Thr Asn Met Ala Ser Ala Asp Ala Asn Ile Arg Asp Gly
        595                 600                 605

Asn Ser Phe Ile Arg Ala Ile Ser Thr Met Lys Asn Ile Ile Glu Ser
    610                 615                 620

Glu Ala Ser Gln Leu Met Arg Asn Leu Thr Glu Ile Arg Glu Tyr Asn
625                 630                 635                 640

Ile Arg Glu Gly Leu Gly Asp Ala Asn His Thr Leu Ser Leu Ala Val
                645                 650                 655

Glu Pro Tyr Ala Ser Gly Ile Cys Pro Val Leu Ala Phe Leu Ser Arg
            660                 665                 670

Arg Thr Ile Ile Ala Val Val Gln Asp Met Ala Leu Ser Gln Cys Ser
        675                 680                 685

Ile Val Met Gln Gly Gln Gln Val Glu Ala Arg Asn Phe Arg Thr Gln
    690                 695                 700

Phe Gln Ala Val Leu Lys Arg Arg Val Leu Glu Leu Gln Asn Ala Gly
705                 710                 715                 720

Phe Ile Thr Ser Lys Thr Ile Thr Val Thr Leu Glu Asp Gln Gln Ile
                725                 730                 735

Cys Val Pro Asp Pro Ser Lys Ser Gln Tyr Asp Ser Val Ile Ser Asn
            740                 745                 750

Met Glu Gly Asp Leu Val Lys Val Thr Val Glu Ile Phe Arg Glu Leu
        755                 760                 765

Lys Val Lys Asn Lys Val Leu Phe Gly Gly Gly Ile Ala Gly Ala Ala
    770                 775                 780

Ser Glu Ala Thr Lys Ser Arg Leu Ala Gly Met Val Glu Ala Tyr Gln
785                 790                 795                 800

Arg Pro Thr Lys Thr Met His Val Leu Asn Gly Pro Leu Gly Phe Ala
                805                 810                 815

Val Lys Arg Tyr His Thr Leu Leu Phe Pro Asp Val Lys Met Pro Asn
            820                 825                 830

Gly Ala Thr Pro Asn Ala Leu Trp Phe Trp Ile Leu Leu Leu Arg Asn
        835                 840                 845
```

-continued

```
Gln Leu Pro Ala Gly Ile Leu Ser Lys Glu Glu Glu Asp Lys Ser Leu
    850                 855                 860

Phe Ile Lys Lys Phe Thr Lys Ser Tyr Ala Asp Met Asn Tyr Ile Asn
865                 870                 875                 880

Ile Ser Pro Thr Cys Phe Gly Asp Leu Ala Gln Phe Tyr Leu Ala Asn
                885                 890                 895

Thr Ile Leu Lys Tyr Cys Ser His Lys His Phe Phe Ile Asn Thr Ile
            900                 905                 910

Ser Ala Leu Val Ala Val Ser Arg Arg Pro Arg Asp Pro Ala Ile Val
        915                 920                 925

Leu Pro Trp Ile Glu Arg Pro Ile Thr Lys Gly Gln Asp Val Ala Pro
    930                 935                 940

Ala Ala Gln Gln Leu Ile Ala Ser Met Ser Asp His Lys Asp Ile Trp
945                 950                 955                 960

Cys Ala Thr Phe Ser Ser Thr Asn Leu Val Gly Ser Ile Met Thr Thr
                965                 970                 975

Lys Pro Phe Val Val Ile Gly Ile Ser Ile Ser Lys Tyr His Gly Met
            980                 985                 990

Ala Gly Ser Thr Lys Val Phe Gln  Ser Gly Asn Trp Gly  Asn Ile Met
        995                 1000                 1005

Gly Gly  Arg Asn Val Cys Ser  Leu Met Ser Phe Asp  Arg Thr His
    1010                 1015                 1020

Arg Tyr  Val Met Thr Cys Pro  Arg Val Gly Phe Val  Ala Glu Gln
    1025                 1030                 1035

Pro Ile  Phe Ser Ser Gly Ile  Lys Glu Thr Thr Leu  Ile Asp Arg
    1040                 1045                 1050

Val Arg  Met Val Leu Ser Glu  Glu Ser Ala Ala Pro  His Ala Ala
    1055                 1060                 1065

Val Tyr  Met Leu Ala Leu Lys  Met Val Gly Asp Arg  Val Arg Gln
    1070                 1075                 1080

Met Glu  Leu Glu Asp Trp Met  Glu Ile Thr Asn Asp  Glu Tyr Ile
    1085                 1090                 1095

Ser Ser  Leu Ile Asp Glu Leu  Asn Lys Gln Val Glu  Glu Ala Glu
    1100                 1105                 1110

Gly Gly  Trp Asn Ala Asp Ala  Ala Met Thr Leu Ala  Lys Glu Met
    1115                 1120                 1125

Val Asn  Met Ala Met Ser Ile  Pro Thr Asp Gly Pro  Thr Phe Asp
    1130                 1135                 1140

Phe Asp  Ala Cys Asp Glu Asn  Leu Glu Gly His Ala  Asp Gly Gln
    1145                 1150                 1155

Thr Ile  Ser Glu Thr Asn Leu  Lys Arg Pro Asn Met  Asn Val Phe
    1160                 1165                 1170

Asp Leu  Glu Pro Ile Pro Glu  Lys Arg Val Pro Val  Leu Ser Val
    1175                 1180                 1185

Asp Met  Leu
    1190


<210> SEQ ID NO 25
<211> LENGTH: 1128
<212> TYPE: PRT
<213> ORGANISM: Epstein-Barr virus

<400> SEQUENCE: 25
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```
Met Gln Gly Ala Gln Thr Ser Glu Asp Asn Leu Gly Ser Gln Ser Gln
1               5                   10                  15

Pro Gly Pro Cys Gly Tyr Ile Tyr Phe Tyr Pro Leu Ala Thr Tyr Pro
            20                  25                  30

Leu Arg Glu Val Ala Thr Leu Gly Thr Gly Tyr Ala Gly His Arg Cys
        35                  40                  45

Leu Thr Val Pro Leu Leu Cys Gly Ile Thr Val Glu Pro Gly Phe Ser
    50                  55                  60

Ile Asn Val Lys Ala Leu His Arg Arg Pro Asp Pro Asn Cys Gly Leu
65                  70                  75                  80

Leu Arg Ala Thr Ser Tyr His Arg Asp Ile Tyr Val Phe His Asn Ala
                85                  90                  95

His Met Val Pro Pro Ile Phe Glu Gly Pro Gly Leu Glu Ala Leu Cys
            100                 105                 110

Gly Glu Thr Arg Glu Val Phe Gly Tyr Asp Ala Tyr Ser Ala Leu Pro
        115                 120                 125

Arg Glu Ser Ser Lys Pro Gly Asp Phe Phe Pro Glu Gly Leu Asp Pro
    130                 135                 140

Ser Ala Tyr Leu Gly Ala Val Ala Ile Thr Glu Ala Phe Lys Glu Arg
145                 150                 155                 160

Leu Tyr Ser Gly Asn Leu Val Ala Ile Pro Ser Leu Lys Gln Glu Val
                165                 170                 175

Ala Val Gly Gln Ser Ala Ser Val Arg Val Pro Leu Tyr Asp Lys Glu
            180                 185                 190

Val Phe Pro Glu Gly Val Pro Gln Leu Arg Gln Phe Tyr Asn Ser Asp
        195                 200                 205

Leu Ser Arg Cys Met His Glu Ala Leu Tyr Thr Gly Leu Ala Gln Ala
    210                 215                 220

Leu Arg Val Arg Arg Val Gly Lys Leu Val Glu Leu Leu Glu Lys Gln
225                 230                 235                 240

Ser Leu Gln Asp Gln Ala Lys Val Ala Lys Val Ala Pro Leu Lys Glu
                245                 250                 255

Phe Pro Ala Ser Thr Ile Ser His Pro Asp Ser Gly Ala Leu Met Ile
            260                 265                 270

Val Asp Ser Ala Ala Cys Glu Leu Ala Val Ser Tyr Ala Pro Ala Met
        275                 280                 285

Leu Glu Ala Ser His Glu Thr Pro Ala Ser Leu Asn Tyr Asp Ser Trp
    290                 295                 300

Pro Leu Phe Ala Asp Cys Glu Gly Pro Glu Ala Arg Val Ala Ala Leu
305                 310                 315                 320

His Arg Tyr Asn Ala Ser Leu Ala Pro His Val Ser Thr Gln Ile Phe
                325                 330                 335

Ala Thr Asn Ser Val Leu Tyr Val Ser Gly Val Ser Lys Ser Thr Gly
            340                 345                 350

Gln Gly Lys Glu Ser Leu Phe Asn Ser Phe Tyr Met Thr His Gly Leu
        355                 360                 365

Gly Thr Leu Gln Glu Gly Thr Trp Asp Pro Cys Arg Arg Pro Cys Phe
    370                 375                 380

Ser Gly Trp Gly Gly Pro Asp Val Thr Gly Thr Asn Gly Pro Gly Asn
385                 390                 395                 400
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Tyr Ala Val Glu His Leu Val Tyr Ala Ala Ser Phe Ser Pro Asn Leu
                405                 410                 415

Leu Ala Arg Tyr Ala Tyr Tyr Leu Gln Phe Cys Gln Gly Gln Lys Ser
            420                 425                 430

Ser Leu Thr Pro Val Pro Glu Thr Gly Ser Tyr Val Ala Gly Ala Ala
        435                 440                 445

Ala Ser Pro Met Cys Ser Leu Cys Glu Gly Arg Ala Pro Ala Val Cys
    450                 455                 460

Leu Asn Thr Leu Phe Phe Arg Leu Arg Asp Arg Phe Pro Pro Val Met
465                 470                 475                 480

Ser Thr Gln Arg Arg Asp Pro Tyr Val Ile Ser Gly Ala Ser Gly Ser
                485                 490                 495

Tyr Asn Glu Thr Asp Phe Leu Gly Asn Phe Leu Asn Phe Ile Asp Lys
            500                 505                 510

Glu Asp Asp Gly Gln Arg Pro Asp Asp Glu Pro Arg Tyr Thr Tyr Trp
        515                 520                 525

Gln Leu Asn Gln Asn Leu Leu Glu Arg Leu Ser Arg Leu Gly Ile Asp
    530                 535                 540

Ala Glu Gly Lys Leu Glu Lys Glu Pro His Gly Pro Arg Asp Phe Val
545                 550                 555                 560

Lys Met Phe Lys Asp Val Asp Ala Ala Val Asp Ala Glu Val Val Gln
                565                 570                 575

Phe Met Asn Ser Met Ala Lys Asn Asn Ile Thr Tyr Lys Asp Leu Val
            580                 585                 590

Lys Ser Cys Tyr His Val Met Gln Tyr Ser Cys Asn Pro Phe Ala Gln
        595                 600                 605

Pro Ala Cys Pro Ile Phe Thr Gln Leu Phe Tyr Arg Ser Leu Leu Thr
    610                 615                 620

Ile Leu Gln Asp Ile Ser Leu Pro Ile Cys Met Cys Tyr Glu Asn Asp
625                 630                 635                 640

Asn Pro Gly Leu Gly Gln Ser Pro Pro Glu Trp Leu Lys Gly His Tyr
                645                 650                 655

Gln Thr Leu Cys Thr Asn Phe Arg Ser Leu Ala Ile Asp Lys Gly Val
            660                 665                 670

Leu Thr Ala Lys Glu Ala Lys Val Val His Gly Glu Pro Thr Cys Asp
        675                 680                 685

Leu Pro Asp Leu Asp Ala Ala Leu Gln Gly Arg Val Tyr Gly Arg Arg
    690                 695                 700

Leu Pro Val Arg Met Ser Lys Val Leu Met Leu Cys Pro Arg Asn Ile
705                 710                 715                 720

Lys Ile Lys Asn Arg Val Val Phe Thr Gly Glu Asn Ala Ala Leu Gln
                725                 730                 735

Asn Ser Phe Ile Lys Ser Thr Thr Arg Arg Glu Asn Tyr Ile Ile Asn
            740                 745                 750

Gly Pro Tyr Met Lys Phe Leu Asn Thr Tyr His Lys Thr Leu Phe Pro
        755                 760                 765

Asp Thr Lys Leu Ser Ser Leu Tyr Leu Trp His Asn Phe Ser Arg Arg
    770                 775                 780

Arg Ser Val Pro Val Pro Ser Gly Ala Ser Ala Glu Glu Tyr Ser Asp
785                 790                 795                 800

Leu Ala Leu Phe Val Asp Gly Gly Ser Arg Ala His Glu Glu Ser Asn
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                805                 810                 815

Val Ile Asp Val Val Pro Gly Asn Leu Val Thr Tyr Ala Lys Gln Arg
            820                 825                 830

Leu Asn Asn Ala Ile Leu Lys Ala Cys Gly Gln Thr Gln Phe Tyr Ile
        835                 840                 845

Ser Leu Ile Gln Gly Leu Val Pro Arg Thr Gln Ser Val Pro Ala Arg
    850                 855                 860

Asp Tyr Pro His Val Leu Gly Thr Arg Ala Val Glu Ser Ala Ala Ala
865                 870                 875                 880

Tyr Ala Glu Ala Thr Ser Ser Leu Thr Ala Thr Thr Val Val Cys Ala
                885                 890                 895

Ala Thr Asp Cys Leu Ser Gln Val Cys Lys Ala Arg Pro Val Val Thr
            900                 905                 910

Leu Pro Val Thr Ile Asn Lys Tyr Thr Gly Val Asn Gly Asn Asn Gln
        915                 920                 925

Ile Phe Gln Ala Gly Asn Leu Gly Tyr Phe Met Gly Arg Gly Val Asp
    930                 935                 940

Arg Asn Leu Leu Gln Ala Pro Gly Ala Gly Leu Arg Lys Gln Ala Gly
945                 950                 955                 960

Gly Ser Ser Met Arg Lys Lys Phe Val Phe Ala Thr Pro Thr Leu Gly
                965                 970                 975

Leu Thr Val Lys Arg Arg Thr Gln Ala Ala Thr Thr Tyr Glu Ile Glu
            980                 985                 990

Asn Ile Arg Ala Gly Leu Glu Ala  Ile Ile Ser Gln Lys  Gln Glu Glu
        995                 1000                1005

Asp Cys  Val Phe Asp Val Val  Cys Asn Leu Val Asp  Ala Met Gly
    1010                1015                1020

Glu Ala  Cys Ala Ser Leu Thr  Arg Asp Asp Ala Glu  Tyr Leu Leu
    1025                1030                1035

Gly Arg  Phe Ser Val Leu Ala  Asp Ser Val Leu Glu  Thr Leu Ala
    1040                1045                1050

Thr Ile  Ala Ser Ser Gly Ile  Glu Trp Thr Ala Glu  Ala Ala Arg
    1055                1060                1065

Asp Phe  Leu Glu Gly Val Trp  Gly Gly Pro Gly Ala  Ala Gln Asp
    1070                1075                1080

Asn Phe  Ile Ser Val Ala Glu  Pro Val Ser Thr Ala  Ser Gln Ala
    1085                1090                1095

Ser Ala  Gly Leu Leu Leu Gly  Gly Gly Gly Gln Gly  Ser Gly Gly
    1100                1105                1110

Arg Arg  Lys Arg Arg Leu Ala  Thr Val Leu Pro Gly  Leu Glu Val
    1115                1120                1125


<210> SEQ ID NO 26
<211> LENGTH: 1235
<212> TYPE: PRT
<213> ORGANISM: Human cytomegalovirus

<400> SEQUENCE: 26

Met Ser His Glu Glu Leu Thr Ala Leu Ala Pro Val Gly Pro Ala Ala
1               5                   10                  15

Phe Leu Tyr Phe Ser Arg Leu Asn Ala Glu Thr Gln Glu Ile Leu Ala
            20                  25                  30
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Thr Leu Ser Leu Cys Asp Arg Ser Ser Ser Val Val Ile Ala Pro Leu
        35                  40                  45

Leu Ala Gly Leu Thr Val Glu Ala Asp Phe Gly Val Ser Val Arg Thr
    50                  55                  60

Pro Val Leu Cys Tyr Asp Gly Gly Val Leu Thr Lys Val Thr Ser Phe
65                  70                  75                  80

Cys Pro Phe Ala Leu Tyr Phe His His Thr Gln Gly Ile Val Ala Phe
                85                  90                  95

Thr Glu Asp His Gly Asp Val His Arg Leu Cys Glu Asp Ala Arg Gln
            100                 105                 110

Lys Tyr Ala Leu Glu Ala Tyr Met Pro Glu Ala Asp Arg Val Pro Thr
        115                 120                 125

Asp Leu Ala Ala Leu Cys Ala Ala Val Gly Cys Gln Ala Ser Glu Thr
    130                 135                 140

Thr Val His Val Val Val Gly Asn Gly Leu Lys Glu Phe Leu Phe Ala
145                 150                 155                 160

Gly Gln Leu Ile Pro Cys Val Glu Glu Ala Thr Thr Val Arg Leu His
                165                 170                 175

Gly Gly Glu Ala Val Arg Val Pro Leu Tyr Pro Pro Thr Leu Phe Asn
            180                 185                 190

Ser Leu Gln Leu Asp Ala Glu Ala Asp Glu Val Ser Leu Asp Ala Arg
        195                 200                 205

Ser Ala Phe Val Glu Ala Arg Gly Leu Tyr Val Pro Ala Val Ser Glu
    210                 215                 220

Thr Leu Phe Tyr Tyr Val Tyr Thr Ser Trp Cys Gln Ser Leu Arg Phe
225                 230                 235                 240

Ser Glu Pro Arg Val Leu Ile Glu Ala Ala Leu Arg Gln Phe Val His
                245                 250                 255

Asp Ser Gln Gln Ser Val Lys Leu Ala Pro His Lys Arg Tyr Leu Gly
            260                 265                 270

Tyr Met Ser Gln Arg Leu Ser Ser Leu Glu Lys Asp His Leu Met Leu
        275                 280                 285

Ser Asp Ala Val Val Cys Glu Leu Ala Phe Ser Phe Ala Ser Val Phe
    290                 295                 300

Phe Asp Ser Ala Tyr Gln Pro Ala Glu Ser Met Leu Phe Ser Glu Trp
305                 310                 315                 320

Pro Leu Val Thr Asn Ala Thr Asp His Arg Asp Leu Ile Arg Ala Leu
                325                 330                 335

Thr Glu Leu Lys Leu His Leu Ser Thr His Val Ala Ala Leu Val Phe
            340                 345                 350

Ser Ala Asn Ser Val Leu Tyr Gln His Arg Leu Val Tyr Leu Gln Ser
        355                 360                 365

Ser Ala Arg His Pro Ser Ala Gly Gly Thr Ala Ser Gln Glu Thr Leu
    370                 375                 380

Leu Lys Ala Ile Gln Phe Thr Asn Gly Leu Ser Ala Ala Cys Glu Asp
385                 390                 395                 400

Val Tyr Asn Asp Ala Arg Lys Val Leu Lys Phe Gln Gly Ala Pro Leu
                405                 410                 415

Lys Asp Glu Arg Tyr Gly Pro Gln His Leu Ala Leu Val Cys Gly Thr
            420                 425                 430

Cys Pro Gln Leu Val Ser Gly Phe Val Trp Tyr Leu Asn Arg Val Ser
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        435                 440                 445

Val Tyr Asn Thr Gly Leu Ser Gly Ser Ser Thr Leu Thr Asn His Leu
    450                 455                 460

Val Gly Cys Ala Ala Gly Leu Cys Glu Ala Cys Gly Gly Thr Cys Cys
465                 470                 475                 480

His Thr Cys Tyr Gln Thr Ala Phe Val Arg Val Arg Thr Arg Leu Pro
                485                 490                 495

Val Val Pro Lys Gln Pro Lys Lys Glu Pro Cys Val Ile Thr Val Gln
            500                 505                 510

Ser Arg Phe Leu Asn Asp Val Asp Ile Leu Gly Ser Phe Gly Arg Arg
        515                 520                 525

Tyr Asn Val Asp Ala Lys Asp Gly Gly Leu Asp Gly Lys Gly Asp Asp
    530                 535                 540

Gly Val Pro Gly Gly Gly Ala Gly Gly Gly Gly Gly Arg Asp Val Ser
545                 550                 555                 560

Gly Gly Pro Ser Asp Gly Leu Gly Gly Gly Arg Gly Gly Gly Gly Gly
                565                 570                 575

Gly Asp Ser Gly Gly Met Met Gly Arg Gly Gly Arg Met Leu Gly Ala
            580                 585                 590

Ser Val Asp Arg Thr Tyr Arg Leu Asn Arg Ile Leu Asp Tyr Cys Arg
        595                 600                 605

Lys Met Arg Leu Ile Asp Pro Val Thr Gly Glu Asp Thr Phe Ser Ala
    610                 615                 620

His Gly Lys Ser Asp Phe Val Ala Val Phe Ser Ala Leu Asn Lys Phe
625                 630                 635                 640

Val Asp Asp Glu Ala Leu Gly Phe Val Ser Glu Val Arg Leu Lys Ser
                645                 650                 655

Ser Arg Asp Glu Val Ala Gly Ala Thr Gln Ala Phe Asn Leu Asp Leu
            660                 665                 670

Asn Pro Tyr Ala Val Ala Phe Gln Pro Leu Leu Ala Tyr Ala Tyr Phe
        675                 680                 685

Arg Ser Val Phe Tyr Val Ile Gln Asn Val Ala Leu Ile Thr Ala Thr
    690                 695                 700

Ser Tyr Ile Val Asp Asn Pro Leu Thr Thr Asn Leu Val Ser Lys Trp
705                 710                 715                 720

Met Thr Gln His Phe Gln Ser Ile His Gly Ala Phe Ser Thr Thr Ser
                725                 730                 735

Ser Arg Lys Gly Phe Leu Phe Thr Lys Gln Ile Lys Ser Ser Lys Asn
            740                 745                 750

Ser Asp His Asp Arg Leu Leu Asp Phe Arg Leu Tyr Ala Gln Gly Thr
        755                 760                 765

Tyr Ala Val Val Pro Met Glu Ile Lys Leu Ser Arg Leu Ser Val Pro
    770                 775                 780

Thr Leu Ile Met Val Arg Val Lys Asn Arg Pro Ile Tyr Arg Ala Gly
785                 790                 795                 800

Lys Gly Asn Ala Gly Ser Val Phe Phe Arg Arg Asp His Val Pro Arg
                805                 810                 815

Arg Asn Pro Ala Lys Gly Cys Leu Gly Phe Leu Leu Tyr Arg His His
            820                 825                 830

Glu Arg Leu Phe Pro Glu Cys Gly Leu Pro Cys Leu Gln Phe Trp Gln
        835                 840                 845
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Lys Val Cys Ser Asn Ala Leu Pro Lys Asn Val Pro Ile Gly Asp Met
    850                 855                 860

Gly Glu Phe Asn Ala Phe Val Lys Phe Leu Val Ala Val Thr Ala Asp
865                 870                 875                 880

Tyr Gln Glu His Asp Leu Leu Asp Val Ala Pro Asp Cys Val Leu Ser
                885                 890                 895

Tyr Val Glu Ser Arg Phe His Asn Lys Phe Leu Cys Tyr Tyr Gly Phe
            900                 905                 910

Lys Asp Tyr Ile Gly Ser Leu His Gly Leu Thr Thr Arg Leu Thr Thr
        915                 920                 925

Gln Asn His Ala Gln Phe Pro His Val Leu Gly Ala Ser Pro Arg Phe
    930                 935                 940

Ser Ser Pro Ala Glu Phe Ala Leu His Val Lys Gly Leu Lys Thr Ala
945                 950                 955                 960

Gly Val Pro Ala Pro Met Ala Ala Thr Val Ala Arg Glu Ser Leu Val
                965                 970                 975

Arg Ser Val Phe Glu His Arg Ser Leu Val Thr Val Pro Val Ser Val
            980                 985                 990

Glu Lys Tyr Ala Gly Ile Asn Asn  Ser Lys Glu Ile Tyr  Gln Phe Gly
        995                 1000                1005

Gln Ile  Gly Tyr Phe Ser Gly  Asn Gly Val Glu Arg  Ser Leu Asn
    1010                 1015                 1020

Val Ser  Ser Met Ser Gly Gln  Asp Tyr Arg Phe Met  Arg Gln Arg
    1025                 1030                 1035

Tyr Leu  Leu Ala Thr Arg Leu  Ala Asp Val Leu Ile  Lys Arg Ser
    1040                 1045                 1050

Arg Arg  Glu Asn Val Leu Phe  Asp Ala Asp Leu Ile  Lys Asn Arg
    1055                 1060                 1065

Val Met  Leu Ala Leu Asp Ala  Glu Asn Leu Asp Cys  Asp Pro Glu
    1070                 1075                 1080

Val Met  Ala Val Tyr Glu Ile  Leu Ser Val Arg Glu  Glu Ile Pro
    1085                 1090                 1095

Ala Ser  Asp Asp Val Leu Phe  Phe Val Asp Gly Cys  Glu Ala Leu
    1100                 1105                 1110

Ala Ala  Ser Leu Met Asp Lys  Phe Ala Ala Leu Gln  Glu Gln Gly
    1115                 1120                 1125

Val Glu  Asp Phe Ser Leu Glu  Asn Leu Arg Arg Val  Leu Asp Ala
    1130                 1135                 1140

Asp Ala  Gln Arg Leu Thr Asp  Ala Ala Gly Gly Glu  Val His Asp
    1145                 1150                 1155

Leu Ser  Ala Leu Phe Ala Pro  Ser Gly Val Gly Ala  Ala Ser Gly
    1160                 1165                 1170

Val Gly  Gly Gly Gly Leu Leu  Leu Gly Glu Ser Val  Ala Gly Asn
    1175                 1180                 1185

Ser Ile  Cys Phe Gly Val Pro  Gly Glu Thr Gly Gly  Gly Cys Phe
    1190                 1195                 1200

Leu Val  Asn Ala Gly Glu Asp  Glu Ala Gly Gly Val  Gly Gly Ser
    1205                 1210                 1215

Ser Gly  Gly Gly Gly Gly Ser  Gly Leu Leu Pro Ala  Lys Arg Ser
    1220                 1225                 1230
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Arg Leu
    1235

<210> SEQ ID NO 27
<211> LENGTH: 1191
<212> TYPE: PRT
<213> ORGANISM: Murine cytomegalovirus

<400> SEQUENCE: 27

Met Ala Asp Asp Asp Leu Ser Ser Leu Ala Pro Val Ala Pro Ala Val
1   5   10   15

Trp Met Phe Phe Leu Lys Lys Thr Arg Glu Leu Ala Asp Ile Val Ala
            20   25   30

Ala Met Ser Leu Cys Asp Lys Ala Thr Pro Val Val Ile Ala Pro Leu
        35   40   45

Leu Ile Asp Leu Thr Val Asp Arg Asp Phe Cys Gly Ala Val Arg Thr
    50   55   60

Pro Met Ser Thr Tyr Glu Gly Gly Val Leu Thr Lys Val Thr Ser Phe
65   70   75   80

Cys Pro Phe Ala Phe Phe Phe His Asn Thr Asp Glu Ile Leu Asp Val
                85   90   95

Val Glu Asp His Gly Asp Val Val His Leu Cys Asp Asp Ala Arg Arg
            100   105   110

Arg Phe Gly Val Gln Ala Phe Ser Pro Leu Ala Asn Arg Asp Arg Thr
        115   120   125

Asp Val Asp Val Leu Cys Asp Glu Leu Gly Ile Ala Pro Ala Glu Tyr
    130   135   140

Thr Gly His Val Val Cys Gly Asn Gly Leu Lys Glu Leu Leu Tyr Ala
145   150   155   160

Gly Gln Leu Ile Pro Cys Pro Glu Glu Ala Val Lys Val Gln Val Gly
                165   170   175

Ala Val Asp Gly Val Lys Val Pro Leu Tyr Pro Tyr Thr Leu Phe Ser
            180   185   190

Gly Gly Ala Asp Ala Ala His Ala Asp Gly Pro Ser Ala Ala Val Ala
        195   200   205

Cys Asp Asp Pro Trp Val Leu Glu His Gly Phe Tyr Asp Pro Ala Leu
    210   215   220

Ser Glu Ala Leu Phe Tyr Phe Met Phe Thr Ser Trp Gly Gln Ser Leu
225   230   235   240

Arg Val Cys Glu Thr Ser Arg Leu Ile Glu Ala Gly Leu Gln Gln Phe
                245   250   255

Val Glu Asp Thr Gln Gln Thr Val Lys Leu Thr Pro Phe Lys Lys Tyr
            260   265   270

His Gly Tyr Thr Ser Gln Lys Leu Thr Ala Val Glu Arg Asp Gln Leu
        275   280   285

Met Thr Val Asp Ala Val Cys Ser Glu Leu Ala Phe Ser Tyr Ala Ser
    290   295   300

Ile Tyr Leu Asp Ser Val Tyr Glu Phe Ser Thr Ala Ser Asn Phe Leu
305   310   315   320

Glu Trp Pro Leu Val Lys Asn Ala Lys Thr His Ala Asp Leu Leu Asp
                325   330   335

Asn Leu Arg Asp Phe Gln Leu His Leu Ala Lys His Ile Ala Ala Leu
            340   345   350

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Ile Phe Ser Ser Asn Ser Ile Leu Tyr Gln Thr Arg Ile Val Phe Val
        355                 360                 365

Pro Ser Ala Gly Lys Gly Ala Asn Ser Asn Pro Ser Ala Gln Asp Ser
    370                 375                 380

Leu Leu Lys Ser Ile Arg Phe Phe Asn Gly Leu Thr Gly Met Tyr Asp
385                 390                 395                 400

Asp Ile Leu Asn Asp Ala Lys Lys Thr Ile Arg Phe Glu Gly Ala Val
                405                 410                 415

Gly Arg Asp Glu Lys Tyr Ser Pro His His Leu Ala Tyr Phe Cys Gly
            420                 425                 430

Thr Ser Pro Gln Leu Phe Ser Thr Leu Met Trp Phe Phe Asn Arg Met
        435                 440                 445

Ser Ile Tyr Ser Thr Gly Val Thr Ser Gly Asp Thr Val Phe Ser His
    450                 455                 460

Ile Val Asn Ala Gly Ser Lys Leu Cys Gly Ala Cys Gly Gly Arg Cys
465                 470                 475                 480

Cys His Thr Cys Tyr Ala Thr Ser Phe Ile Arg Val Asn Thr Arg Leu
                485                 490                 495

Pro Gly Ile Pro Lys Gln Ile Lys Lys Glu Pro Val Val Val Thr Leu
            500                 505                 510

Leu Ser Arg Ala Phe Ala Asp Ala Asp Leu Leu Gly Asn Tyr Gly Lys
        515                 520                 525

Arg Tyr Gly Leu Glu Ser Arg Glu Ala Gly Asp Gly Gly Gly Gly Gly
    530                 535                 540

Ala Gly Gly Arg Thr Asp Glu Val Ala Ala Gly Pro Pro Ala Gly Gly
545                 550                 555                 560

Ala Ser Gly Leu Asn Phe Val Ser Val Asp Arg Met Lys Tyr Leu Gly
                565                 570                 575

Gln Val Leu Asp Tyr Cys Lys Lys Asn Ser Leu Ile Asp Ala Ile Thr
            580                 585                 590

Gly Glu Asp Ile Ile Asn Val Arg Thr Lys Arg Asp Phe Val Ala Thr
        595                 600                 605

Val Thr Ala Leu Asn Gln Thr Ile Asp Asp Ala Val Cys Arg Phe Ala
    610                 615                 620

Met Asp Val Arg Arg Ser Gly His Gly Arg Asp Glu Ile Ser Gly Ser
625                 630                 635                 640

Thr Gln Ser Phe Asn Leu Asp Leu Ser Pro Tyr Ala Thr Ala Phe Ser
                645                 650                 655

Pro Val Leu Ser Phe Gln Tyr Tyr Arg Thr Met Phe Ser Ile Ile Gln
            660                 665                 670

Asn Leu Ala Leu Ile Asn Ala Ala Ser Tyr Val Val Asp Asn Pro Leu
        675                 680                 685

Thr Thr Ala Gln Ile Ser Lys Trp Val Thr Leu His Phe Gln Ser Ile
    690                 695                 700

Cys Gly Ala Phe Gly Thr Thr Pro Leu Lys Lys Gly Phe Leu Asn Val
705                 710                 715                 720

Lys Asp Thr Lys Asn Leu Lys Ser Val Glu Phe Glu Arg Ile Met Asp
                725                 730                 735

Phe Arg Ser Phe Gln Glu Thr Gly Arg Tyr Arg Lys Ile Ser Thr Glu
            740                 745                 750
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```
Ile Lys Ser Cys Lys Met Ser Val Gln Ser Leu Lys Ser Cys Arg Ile
        755                 760                 765

Lys Asn Arg Pro Ile Ser Lys Thr Pro Gln Ser Ser Val Phe Phe Lys
    770                 775                 780

Lys Gly Ala Leu Gln Arg Lys Asn Pro Ile Lys Gly Cys Leu Ser Phe
785                 790                 795                 800

Leu Leu Phe Arg Cys His Glu Lys Leu Phe Pro Arg Cys Gly Leu Ser
                805                 810                 815

Cys Leu Glu Phe Trp Gln Arg Val Leu Gln Asn Ser Leu Pro Arg Ser
            820                 825                 830

Val Asn Val Gly Lys Val Glu Asp Phe Asp Asn Leu Val Arg Phe Leu
        835                 840                 845

Leu Thr Val Thr Asp Asp Tyr Asp Glu Ser Asp Val Val Asp Ile Gln
    850                 855                 860

Pro Asp Cys Leu Leu Ser Tyr Val Glu Asn Arg Phe His Asn Lys Phe
865                 870                 875                 880

Leu Tyr Met Phe Gly Phe Arg Asp Tyr Met Ser Thr Ile Gln Gly Met
                885                 890                 895

Ser Thr Arg Leu Thr Pro Gln Asn His Ser Gln Phe Pro Cys Leu Leu
            900                 905                 910

Lys Asp Ala Pro Lys Phe Ala Ser Ile Ala Glu Tyr Val Leu His Phe
        915                 920                 925

Lys Lys Met Lys Leu Asp Gly Val Lys Ala Pro Gln Val Ala Thr Ile
    930                 935                 940

Thr Arg Glu Pro Val Leu Lys Lys Leu Phe Asp Gly Arg Ser Leu Val
945                 950                 955                 960

Ser Val Ser Phe Ala Val Glu Lys Tyr Ser Ser Ser Met Gly Thr Arg
                965                 970                 975

Asp Val Phe Gln Phe Gly Gln Ile Gly Tyr Tyr Val Gly Ser Gly Val
            980                 985                 990

Asp Arg Ser Leu Asn Thr Gly Ser  Met Gly Thr Gln Asp  Tyr Arg Phe
        995                 1000                 1005

Met Arg  Tyr Arg Tyr Ile Ile  Ala Thr Lys Leu Val  Asp Val Leu
    1010                 1015                 1020

Ile Arg  Arg Ser Arg Arg Glu  Asn Val Met Tyr Asp  Arg Asp Val
    1025                 1030                 1035

Val Arg  Ser Arg Val Leu Ala  Ala Leu Asp Ser Thr  Gly Leu Asp
    1040                 1045                 1050

Val Asp  Pro Glu Leu Ala Ala  Ile Ala Glu Leu Met  Glu Gly Arg
    1055                 1060                 1065

Asp Glu  Gly Asp Ile Pro Glu  Ile Asp Asp Ile Leu  Phe Tyr Val
    1070                 1075                 1080

Asp Gln  Gln Glu Tyr Ile Ala  Arg Ser Met Tyr Arg  Lys Met Arg
    1085                 1090                 1095

Ser Leu  Ala Glu Arg Gly Val  Thr Asp Phe Ser Leu  Ala Ser Leu
    1100                 1105                 1110

Arg Glu  Ala Thr Ala Thr Asn  Ala Thr Ala Ala Gly  Ser Ala Ala
    1115                 1120                 1125

Gly Gly  Gly Gly Ser Ala Thr  Glu Gly Gly Gly Gly  Gly Ala Ala
    1130                 1135                 1140

Ala Asp  Glu Ser Gly Pro Met  Tyr Asp Phe Ser Ala  Leu Phe Ser
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    1145                1150                1155

Arg Arg  Asp Glu Ala Glu Asp  Val Asn Ala Gly Leu  Ile Asn Gly
    1160                1165                1170

Asp Asp  Val Arg Gly Asp Asp  Glu Phe Glu Leu Pro  Ser Lys Arg
    1175                1180                1185

Ser Arg  Leu
    1190


<210> SEQ ID NO 28
<211> LENGTH: 1131
<212> TYPE: PRT
<213> ORGANISM: Human herpesvirus

<400> SEQUENCE: 28

Met Ala Asp Asp Asn Glu Thr Val Val Ser Ala Pro Ile Cys Thr Ala
1               5                   10                  15

Ala Trp Leu Tyr Ile Leu Pro Lys Glu Gln Lys Leu Ile Glu Ile Leu
            20                  25                  30

Thr Thr Leu Ser Leu Met Glu Lys Arg Lys Ser Val Val Ile Ser Pro
        35                  40                  45

Leu Leu Leu Asn Leu Thr Val Glu Asn Asp Phe Phe Pro Thr Val Lys
    50                  55                  60

Thr Pro Ile Ile Asn Tyr Gly Gly Thr Val Ile Thr Lys Ile Thr Ser
65                  70                  75                  80

Phe Met Pro Val Cys Phe Phe Phe His Gly Thr Asp Val Phe Leu Lys
                85                  90                  95

Glu Ala Glu Asp His Gly Asn Leu Asp Lys Leu Cys Lys Gln Thr Arg
            100                 105                 110

Glu Lys Phe Asn Leu Gln Glu Phe Val Val Asn Gly Asn Arg Lys Pro
        115                 120                 125

Val Asp Ile Gly Lys Ile Cys Glu Ser Val Gly Arg Asn Ala Asp Asp
    130                 135                 140

Val Leu Cys His Ile Val Val Gly Asn Gly Phe Lys Glu Leu Leu Phe
145                 150                 155                 160

Ala Gly Leu Leu Ile Pro Cys Val Glu Glu Gln Ile Gln Val Gln Val
                165                 170                 175

Gly Glu Cys Leu Ala Ile Lys Ile Pro Leu Tyr Ser Ala Thr Leu Phe
            180                 185                 190

Glu Ser Glu Glu Thr Leu Cys Ile Asp Thr Cys Thr Glu Phe Ile Gln
        195                 200                 205

Glu Asn Gly Phe Tyr Ala Pro Gln Ile Ser Glu Val Leu Phe Tyr Leu
    210                 215                 220

Ile Phe Thr Ser Trp Gly Met Thr Leu Arg Phe Asn Asn Thr Leu Glu
225                 230                 235                 240

Leu Ile Lys Ala Gly Leu Lys Gln Phe Ile Gln Asp Thr Glu Gln Thr
                245                 250                 255

Val Lys Leu Ala Pro Asn Lys Thr Tyr His Gly Ile Pro Gly Gln Lys
            260                 265                 270

Leu Ser Pro Ile Glu Lys Asp His Leu Met Leu Val Asp Ala Val Ile
        275                 280                 285

Thr Glu Leu Thr Phe Ser Tyr Thr Ala Glu Tyr Leu Asp Ser Ile Tyr
    290                 295                 300
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Glu Asn Asn Gln Ile Met Asn Phe Ser Glu Trp Pro Ile Ile Lys Ser
305                 310                 315                 320

Ala Glu Thr His Glu Glu Lys Ile Val Glu Leu Lys Lys Leu Arg Leu
                325                 330                 335

His Leu Ser Ser His Val Ala Ala Leu Val Phe Ala Ala Asn Ser Ile
            340                 345                 350

Leu Tyr Ser Asn Lys Leu Ala Tyr Ile Ser Asn Thr Lys Gln Ala Phe
        355                 360                 365

Asn Ser Ala Ile Thr Gln Glu Thr Leu Leu Arg Ser Ile Gln Phe Cys
    370                 375                 380

Asn Ser Leu Ser Ser Leu Asn Glu Asp Phe Tyr Asn Asp Ala Arg Lys
385                 390                 395                 400

Leu Ile Lys Cys Asn Ser Ser Pro Cys Lys Glu Asp Lys Phe Ser Ala
                405                 410                 415

Phe His Leu Ala Tyr Ala Cys Ala Thr Cys Pro Gln Ile Leu Ser His
            420                 425                 430

Ile Ile Trp Asn Leu Asn Arg Met Ser Ile Tyr Asn Thr Asn Cys Gly
        435                 440                 445

Asn Ser Glu Ile Tyr Asn His Ile Val Asn Cys Ser Ser Asn Leu Cys
    450                 455                 460

Glu Phe Cys Glu Gly Lys Cys Cys His Ser Cys Ile Gly Thr Ala Leu
465                 470                 475                 480

Ile Arg Ile Asn Ser Arg Leu Pro Gln Ile Ser Lys Thr Thr Lys Lys
                485                 490                 495

Glu Pro Ile Val Met Thr Met Phe Ser Arg Phe Tyr Ala Asp Val Asp
            500                 505                 510

Val Leu Gly Ser Phe Gly Lys Lys Gly Val Asn Glu Ser Lys Asp Pro
        515                 520                 525

Met Lys Glu Ala Gln Thr Thr Pro Ser Leu Asp Arg Phe Lys Phe Leu
    530                 535                 540

Gly Met Ile His Asp Tyr Cys Lys Lys Asn Asn Leu Ile Asp Ala Ile
545                 550                 555                 560

Thr Gly Glu Asp Asn Leu Asn Phe Lys Ser Gln Asn Asp Phe Val Asn
                565                 570                 575

Met Ile Asn Asp Leu Ile Gln Cys Ile Glu Glu Ala Val Ser Lys Cys
            580                 585                 590

Ile Ser Glu Met Arg Lys Thr Gln Thr Ser Arg Glu Gln Ile Glu Asn
        595                 600                 605

Cys Leu Gln Ser Phe Asn Ile Asp Thr Thr Pro Leu Ser Leu Ala Phe
    610                 615                 620

Ser Pro Phe Phe Val Phe Thr Tyr Tyr Lys Val Ile Leu Ile Val Leu
625                 630                 635                 640

Gln Asn Leu Ala Leu Ile Ile Gly Thr Gly Tyr Val Val Asp Arg Pro
                645                 650                 655

Cys Thr Gly Asn Leu Ile Ser Lys Trp Leu Met Gln Gln Tyr Gln Ser
            660                 665                 670

Leu Tyr Gly Ala Phe Tyr Asn Ser His Phe Lys Lys Gly Phe Leu Asn
        675                 680                 685

Met Lys Thr Val Lys Ile Ala Ser Asn Val Asp Met Glu Gln Tyr Ile
    690                 695                 700

Asp Phe Asn Leu Phe Lys Ser Gly Lys Tyr Ala Lys Thr Ser Ile Gln
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705                 710                 715                 720

Ala Lys Leu Cys Arg Leu Ser Met Gln Cys Leu Lys Asp Phe Arg Val
                725                 730                 735

Lys Asn Arg Pro Phe Asn Lys Pro Asn Lys Asn Thr Gln Asn Asn Pro
            740                 745                 750

Phe Phe Lys Lys Val Lys Gln Lys Lys Asn Pro Leu Ser Gly Cys Leu
        755                 760                 765

Ser Phe Leu Leu Phe Lys Tyr His Glu Arg Leu Phe Pro Asn Leu Lys
    770                 775                 780

Ile Ser Cys Leu Glu Phe Trp Gln Arg Ile Leu Leu Asn Asn Met Pro
785                 790                 795                 800

Lys Thr Ile Asp Ile Gly Asn Val Glu Asp Met Arg Ser Phe Ile Lys
                805                 810                 815

Phe Thr Phe Arg Val Thr Asn Ser Tyr Asp Glu Ile Asp Leu Leu Asp
            820                 825                 830

Ile Gln Pro Glu Cys Leu Leu Ser Phe Ile Glu Tyr Tyr Phe His Asn
        835                 840                 845

Lys Leu Leu Ser Val Leu Gly Tyr Arg Asp Tyr Leu Thr Ser Leu His
    850                 855                 860

Ala Leu Thr Ser Lys Leu Val Pro Gln Asn Pro Met Leu Phe Pro Val
865                 870                 875                 880

Phe Leu Lys Glu His Pro Thr Phe Ser Ser Val Gln Glu Tyr Val Met
                885                 890                 895

His Val Lys Lys Leu Val Gly Asn Gly Leu Lys Glu Pro Met Thr Ala
            900                 905                 910

Ser Leu Thr Lys Glu Pro Asn Phe Gly Ser Ile Phe Thr Gly Arg Ser
        915                 920                 925

Ile Ile Thr Phe Gly Leu Met Ile Glu Lys Phe Val Ser Val Ala Ser
    930                 935                 940

Arg Asp Tyr Phe His Phe Gly Gln Leu Gly Trp Ile Ala Gly Ser Gly
945                 950                 955                 960

Val Asp Arg Asn Leu Asn Pro Pro Ser Ser Gly Leu Gln Asp Phe Arg
                965                 970                 975

Phe Met Arg Gln Lys Phe Val Ile Ala Thr Lys Leu Cys Asp Ile Ile
            980                 985                 990

Val Lys Lys Val Lys Arg Glu Ala  Ile Val Tyr Asp Val  Glu Val Ile
        995                 1000                1005

Arg Gly  Lys Val Leu Asn Ile  Ile Glu Ser Leu Ser  Asn Ser Val
    1010                1015                1020

Asn Pro  Glu Leu Leu Ile Leu  Ala Glu Val Met Lys  Asp Arg Asp
    1025                1030                1035

Ser Lys  Pro Thr Met Asp Asp  Met Leu Phe Tyr Val  Asp Gly Arg
    1040                1045                1050

Glu Pro  Leu Ala Lys Ser Val  Met Asn Lys Ile Gln  His Leu Thr
    1055                1060                1065

Asp Leu  Asn Val His Asp Phe  Ser Leu Ser Thr Leu  Leu Ser Val
    1070                1075                1080

Phe Glu  Glu Gln Val Glu Asp  Ser Ala Ala Ile Tyr  Asp Phe Ser
    1085                1090                1095

Glu Leu  Leu Val Glu Gly Asn  Glu Gln Gly Phe Gly  Ile Leu Lys
    1100                1105                1110
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Cys Glu  Glu Thr Glu His Glu  Asn Glu Glu Pro Ser  Leu Lys Lys
    1115                 1120                 1125

Ala Arg  Leu
    1130


<210> SEQ ID NO 29
<211> LENGTH: 1132
<212> TYPE: PRT
<213> ORGANISM: Kaposi's sarcoma-associated herpesvirus

<400> SEQUENCE: 29

Met Ala Leu Lys Gly Pro Gln Thr Leu Glu Glu Asn Ile Gly Ser Ala
1               5                   10                  15

Ala Pro Thr Gly Pro Cys Gly Tyr Leu Tyr Ala Tyr Leu Thr His Asn
            20                  25                  30

Phe Pro Ile Gly Glu Ala Ser Leu Leu Gly Asn Gly Tyr Pro Glu Ala
        35                  40                  45

Lys Val Phe Ser Leu Pro Leu Leu His Gly Leu Thr Val Glu Ser Asp
    50                  55                  60

Phe Pro Leu Asn Val Lys Ala Val His Lys Lys Ile Asp Ala Thr Thr
65                  70                  75                  80

Ala Ser Val Lys Leu Thr Ser Tyr His Arg Glu Ala Ile Val Phe His
                85                  90                  95

Asn Thr His Leu Phe Gln Pro Ile Phe Gln Gly Lys Gly Leu Glu Lys
            100                 105                 110

Leu Cys Arg Glu Ser Arg Glu Leu Phe Gly Phe Ser Thr Phe Val Glu
        115                 120                 125

Gln Gln His Lys Gly Thr Leu Trp Ser Pro Glu Ala Cys Pro Gln Leu
    130                 135                 140

Pro Cys Ala Asn Glu Ile Phe Met Ala Val Ile Val Thr Glu Gly Phe
145                 150                 155                 160

Lys Glu Arg Leu Tyr Gly Gly Lys Leu Val Pro Val Pro Ser Gln Thr
                165                 170                 175

Thr Pro Val His Ile Gly Glu His Gln Ala Phe Lys Ile Pro Leu Tyr
            180                 185                 190

Asp Glu Asp Leu Phe Gly Pro Ser Arg Ala Gln Glu Leu Cys Arg Phe
        195                 200                 205

Tyr Asn Pro Asp Ile Ser Arg Tyr Leu His Asp Ser Ile Phe Thr Gly
    210                 215                 220

Ile Ala Gln Ala Leu Arg Val Lys Asp Val Ser Thr Val Ile Gln Ala
225                 230                 235                 240

Ser Glu Arg Gln Phe Val His Asp Gln Tyr Lys Ile Pro Lys Leu Val
                245                 250                 255

Gln Ala Lys Asp Phe Pro Gln Cys Ala Ser Arg Gly Thr Asp Gly Ser
            260                 265                 270

Thr Leu Met Val Ile Asp Ser Leu Val Ala Glu Leu Gly Met Ser Tyr
        275                 280                 285

Gly Leu Ser Phe Ile Glu Gly Pro Gln Asp Ser Cys Glu Val Leu Asn
    290                 295                 300

Tyr Asp Thr Trp Pro Ile Phe Glu Asn Cys Glu Thr Pro Asp Ala Arg
305                 310                 315                 320

Leu Arg Ala Leu Glu Val Trp His Ala Glu Gln Ala Leu His Ile Gly
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                325                 330                 335

Ala Gln Leu Phe Ala Ala Asn Ser Val Leu Tyr Leu Thr Arg Val Ala
            340                 345                 350

Lys Leu Pro Gln Lys Asn Gln Arg Gly Asp Ala Asn Met Tyr Asn Ser
        355                 360                 365

Phe Tyr Leu Gln His Gly Leu Gly Tyr Leu Ser Glu Ala Thr Val Lys
    370                 375                 380

Glu Asn Gly Ala Ser Ala Phe Lys Gly Val Pro Val Ser Ala Leu Asp
385                 390                 395                 400

Gly Ser Ser Tyr Thr Leu Gln His Leu Ala Tyr Ala Ser Ser Phe Ser
                405                 410                 415

Pro His Leu Leu Ala Arg Met Cys Tyr Tyr Leu Gln Phe Leu Pro His
            420                 425                 430

His Lys Asn Thr Asn Ser Gln Ser Tyr Asn Val Val Asp Tyr Val Gly
        435                 440                 445

Thr Ala Ala Pro Ser Gln Met Cys Asp Leu Cys Gln Gly Gln Cys Pro
    450                 455                 460

Ala Val Cys Ile Asn Thr Leu Phe Tyr Arg Met Lys Asp Arg Phe Pro
465                 470                 475                 480

Pro Val Leu Ser Asn Val Lys Arg Asp Pro Tyr Val Ile Thr Gly Thr
                485                 490                 495

Ala Gly Thr Tyr Asn Asp Leu Glu Ile Leu Gly Asn Phe Ala Thr Phe
            500                 505                 510

Arg Glu Arg Glu Glu Glu Gly Asn Pro Val Glu Asp Ala Pro Lys Tyr
        515                 520                 525

Thr Tyr Trp Gln Leu Cys Gln Asn Ile Thr Glu Lys Leu Ala Ser Met
    530                 535                 540

Gly Ile Ser Glu Gly Gly Asp Ala Leu Arg Thr Leu Ile Val Asp Ile
545                 550                 555                 560

Pro Ser Phe Val Lys Val Phe Lys Gly Ile Asp Ser Thr Val Glu Ala
                565                 570                 575

Glu Leu Leu Lys Phe Ile Asn Cys Met Ile Lys Asn Asn Tyr Asn Phe
            580                 585                 590

Arg Glu Asn Ile Lys Ser Val His His Ile Leu Gln Phe Ala Cys Asn
        595                 600                 605

Val Tyr Trp Gln Ala Pro Cys Pro Val Phe Leu Thr Leu Tyr Tyr Lys
    610                 615                 620

Ser Leu Leu Thr Val Ile Gln Asp Ile Cys Leu Thr Ser Cys Met Met
625                 630                 635                 640

Tyr Glu Gln Asp Asn Pro Ala Val Gly Ile Val Pro Ser Glu Trp Leu
                645                 650                 655

Lys Met His Phe Gln Thr Met Trp Thr Asn Phe Lys Gly Ala Cys Phe
            660                 665                 670

Asp Lys Gly Ala Ile Thr Gly Gly Glu Leu Lys Ile Val His Gln Ser
        675                 680                 685

Met Phe Cys Asp Leu Phe Asp Thr Asp Ala Ala Ile Gly Gly Met Phe
    690                 695                 700

Ala Pro Ala Arg Met Gln Val Arg Ile Ala Arg Ala Met Leu Met Val
705                 710                 715                 720

Pro Lys Thr Ile Lys Ile Lys Asn Arg Ile Ile Phe Ser Asn Ser Thr
                725                 730                 735
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Gly Ala Glu Ser Ile Gln Ala Gly Phe Met Lys Pro Ala Ser Gln Arg
            740                 745                 750

Asp Ser Tyr Ile Val Gly Gly Pro Tyr Met Lys Phe Leu Asn Ala Leu
        755                 760                 765

His Lys Thr Leu Phe Pro Ser Thr Lys Thr Ser Ala Leu Tyr Leu Trp
    770                 775                 780

His Lys Ile Gly Gln Thr Thr Lys Asn Pro Ile Leu Pro Gly Val Ser
785                 790                 795                 800

Gly Glu His Leu Thr Glu Leu Cys Asn Tyr Val Lys Ala Ser Ser Gln
                805                 810                 815

Ala Phe Glu Glu Ile Asn Val Leu Asp Leu Val Pro Asp Thr Leu Thr
            820                 825                 830

Ser Tyr Ala Lys Ile Lys Leu Asn Ser Ser Ile Leu Arg Ala Cys Gly
        835                 840                 845

Gln Thr Gln Phe Tyr Ala Thr Thr Leu Ser Cys Leu Ser Pro Val Thr
    850                 855                 860

Gln Leu Val Pro Ala Glu Glu Tyr Pro His Val Leu Gly Pro Val Gly
865                 870                 875                 880

Leu Ser Ser Pro Asp Glu Tyr Arg Ala Lys Val Ala Gly Arg Ser Val
                885                 890                 895

Thr Ile Val Gln Ser Thr Leu Lys Gln Ala Val Ser Thr Asn Gly Arg
            900                 905                 910

Leu Arg Pro Ile Ile Thr Val Pro Leu Val Val Asn Lys Tyr Thr Gly
        915                 920                 925

Ser Asn Gly Asn Thr Asn Val Phe His Cys Ala Asn Leu Gly Tyr Phe
    930                 935                 940

Ser Gly Arg Gly Val Asp Arg Asn Leu Arg Pro Glu Ser Val Pro Phe
945                 950                 955                 960

Lys Lys Asn Asn Val Ser Ser Met Leu Arg Lys Arg His Val Ile Met
                965                 970                 975

Thr Pro Leu Val Asp Arg Leu Val Lys Arg Ile Val Gly Ile Asn Ser
            980                 985                 990

Gly Glu Phe Glu Ala Glu Ala Val  Lys Arg Ser Val Gln  Asn Val Leu
        995                 1000                 1005

Glu Asp  Arg Asp Asn Pro Asn  Leu Pro Lys Thr Val  Val Leu Glu
    1010                 1015                 1020

Leu Val  Lys His Leu Gly Ser  Ser Cys Ala Ser Leu  Thr Glu Glu
    1025                 1030                 1035

Asp Val  Ile Tyr Tyr Leu Gly  Pro Tyr Ala Val Leu  Gly Asp Glu
    1040                 1045                 1050

Val Leu  Ser Leu Leu Ser Thr  Val Gly Gln Ala Gly  Val Pro Trp
    1055                 1060                 1065

Thr Ala  Glu Gly Val Ala Ser  Val Ile Gln Asp Ile  Ile Asp Asp
    1070                 1075                 1080

Cys Glu  Leu Gln Phe Val Gly  Pro Glu Glu Pro Cys  Leu Ile Gln
    1085                 1090                 1095

Gly Gln  Ser Val Val Glu Glu  Leu Phe Pro Ser Pro  Gly Val Pro
    1100                 1105                 1110
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Ser Leu  Thr Val Gly Lys Lys  Arg Lys Ile Ala Ser  Leu Leu Ser
    1115                 1120                 1125

Asp Leu  Asp Leu
    1130
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1. A method of inhibiting herpes virus replication in a cell, the method comprising contacting the cell with an agent that inhibits a DDE recombinase, thereby inhibiting herpes virus replication in the cell.

2. A method of inhibiting herpes virus replication in a cell, the method comprising contacting the cell with an agent that reduces the biological activity of a herpes virus polypeptide having functional and/or structural homology to a human immunodeficiency virus (HIV) integrase, thereby inhibiting herpes virus replication in the cell.

3. The method of claim **2**, wherein the polypeptide is ICP8.

4. The method of claim **1**, wherein the agent is a small compound that inhibits Human Immunodeficiency Virus (HIV) integrase enzymatic activity.

5. The method of claim **1**, wherein the agent is selected from the group consisting of Raltegravir, 118-D-24, L-841411, elvitegrevir, MK-2048, XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50; or a derivative or analog thereof.

6. (canceled)

7. (canceled)

8. A method of treating or preventing a herpes virus infection in a subject, the method comprising administering to the subject an effective amount of an agent that inhibits a DDE recombinase, or administering to the subject an effective amount of an agent that reduces the biological activity of a herpes virus polypeptide having functional and/or structural homology to a human immunodeficiency virus (HIV) integrase, thereby treating or preventing a herpes virus infection in the subject.

9. (canceled)

10. The method of claim **8**, wherein the agent reduces herpes virus replication.

11. (canceled)

12. The method of claim **8**, wherein the agent is selected from the group consisting of Raltegravir, 118-D-24, L-841411, elvitegrevir, MK-2048, XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50; or a derivative or analog thereof.

13. (canceled)

14. (canceled)

15. The method of claim **8**, wherein the method further comprises identifying the subject as having or at risk of developing a herpes virus infection.

16. The method of claim **8**, wherein the method further comprises identifying the subject as testing negative for an HIV infection.

17. The method of claim **8**, the method further comprising, prior to the step of administration, the step of

diagnosing the subject as having a herpes virus infection.

18. The method of claim **17**, wherein the subject is identified as testing negative for an HIV infection.

19. The method of claim **17**, wherein the effective amount is sufficient to reduce viral replication by at least about 85% or more.

20. The method of claim **8**, wherein the subject is identified as having an acyclovir-resistant herpes virus infection.

21. (canceled)

22. (canceled)

23. (canceled)

24. (canceled)

25. The method of claim **1**, wherein the herpes virus is an alpaherpesvirus, a betaherpesvirus, or a gammaherpesvirus.

26. The method of claim **1**, wherein the herpes virus is selected from the group consisting of Herpes simplex virus Type 1 (HSV-1), Herpes simplex virus Type 2 (HSV-2), Epstein Barr virus (EBV), Cytomegalovirus (CMV), Varicella Zoster Virus (VZV), Herpes lymphotropic virus, Human herpes virus 6 (HHV-6), Human herpes virus 7 (HHV-7), Human herpes virus 8 (HHV-8), and Kaposi's sarcoma-associated herpes virus (KSHV).

27. The method of claim **1**, wherein the herpes virus is HSV-1 or HSV-2.

28. A pharmaceutical composition comprising an effective amount of an agent select from the group consisting of Raltegravir, 118-D-24, L-841411, elvitegrevir, MK-2048, XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50; or a derivative or analog thereof; or an agent that reduces the biological activity of a herpes virus polypeptide having functional and/or structural homology to a human immunodeficiency virus (HIV) integrase formulated for topical administration.

29. An immunogenic composition comprising an effective amount of an isolated herpes virus comprising an alteration in an ICP8 nucleic acid sequence, wherein the alteration decreases viral replication in a cell.

30. (canceled)

31. (canceled)

32. (canceled)

33. (canceled)

34. A method of inhibiting recombination mediated by ICP8 or an ICP8 homolog comprising contacting the ICP8 or ICP8 homolog with an agent selected from the group consisting of Raltegravir, 118-D-24, L-841411, elvitegrevir, MK-2048, XZ100, XZ99, XZ45, XZ15, XZ49, XZ48, and XZ50; or a derivative or analog thereof.

35. (canceled)

36. (canceled)

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