SUMMARY

[4a] In one aspect, the present disclosure refers to a non-natural herpes simplex virus ("HSV"), wherein the virus comprises: i. a first polynucleotide encoding an amino acid sequence as shown by SEQ ID NO: 13, ii.a second polynucleotide encoding an amino acid sequence as shown by SEQ ID NO: 21, iii. a third polynucleotide encoding an amino acid sequence as shown by SEQ ID NO: 36, iv. a fourth polynucleotide encoding an amino acid sequence as shown by SEQ ID NO: 28, and v. a fifth polynucleotide encoding an amino acid sequence as shown by SEQ ID NO: 2.

[4b] In another aspect, the present disclosure refers to a composition comprising the non-natural HSV as described herein and a carrier and optionally wherein the carrier is a pharmaceutically available carrier.

[4c] In another aspect, the present disclosure refers to a cell infected with the non-natural HSV as described herein, or the composition as described herein, optionally a lymphocyte.

[4d] In another aspect, the present disclosure refers to a method to infect a cell, comprising contacting the cell with the non-natural HSV as described herein or the composition as described herein, optionally wherein the cell is a lymphocyte; and/or wherein the cell has been infected with an Epstein-Barr virus ("EBV").

[4e] In another aspect, the present disclosure refers to a method to prepare a viral vector comprising introducing a transgene into the non-natural HSV as described herein.

[4f] In another aspect, the present disclosure refers to an *in vitro* method for inhibiting the growth or metastasis of cancer cell, comprising contacting the cell with an effective amount of the non-natural HSV as described herein or the composition as described herein.

[4g] In yet another aspect, the present disclosure refers to a use of the non-natural HSV as described herein or the composition as described herein in the manufacture of a

medicament for treating cancer in a subject, wherein an effective amount of the non-natural HSV as described herein or the composition as described herein is to be administered to the

subject, and optionally wherein the cancer is of the type, or the cancer cell is selected from a cell of the type: pancreatic cancer, renal cancer, small cell lung cancer, brain cancer, neural cancer, bone cancer, lymphoma, myeloma, colon cancer, uterine cancer, breast cancer, leukemia, liver cancer, prostate cancer, skin cancer, or melanoma; and/or wherein the HSV or the pharmaceutical composition is to be administered by injection, infusion, instillation, and/or inhalation; and/or wherein the administration comprises a therapy of the group of: a first line therapy, a second line therapy, a third line therapy, a fourth line therapy, or a fifth line therapy; and/or an effective amount of an anticancer therapy is to be further administered to the subject.

[4h] In yet another aspect, the present disclosure refers to an *in vitro* method for inducing cell lysis, comprising contacting the cell with the non-natural HSV as described herein or the composition as described herein.

[4i] In yet another aspect, the present disclosure refers to a kit comprising the HSV as described herein or the composition as described herein, and instructions for use.

[4j] In yet another aspect, the present disclosure refers to a method of producing the HSV as described herein, comprising

(a) introducing to a host cell a polynucleotide encoding a viral genome of the HSV;

(b) growing the host cell; and

(c) isolating an HSV particle produced by the host cell.

[4k] In yet another aspect, the present disclosure refers to the non-natural HSV as described herein or the composition as described herein for use in therapy.

[5] The present disclosure provides a non-natural herpes simplex virus ("HSV"), wherein the virus comprises, alternatively consists essentially of, or yet further consists of a mutation in one or more of: (a) a glycoprotein E ("gE")-encoding gene, (b) an Infected Cell Protein 0 ("ICP0")-encoding gene, (c) a DNA packaging terminase subunit 1-encoding gene, (d) an ICP8-encoding gene, or (e) an ICP34.5-encoding gene.

[6] In another example, the present disclosure provides a composition or a pharmaceutical composition that comprises, alternatively consists essentially of, or yet further consists of the

non-natural HSV of this disclosure. In another example, provided in this disclosure is a method to infect a cell, comprising, or alternatively consisting essentially of, or yet further consisting of contacting the cell with the non-natural HSV or a composition or pharmaceutical composition containing the non-natural HSV.

[7] In one example, the present disclosure provides a method of preparing the non-natural HSV of this disclosure comprising, or alternatively consisting essentially of, or yet further consisting of mutating a gene in a non-natural HSV viral particle or introducing into the non-natural HSV a transgene. In another example, the method of producing the non-natural HSV vector, comprises, or alternatively consists essentially of, or yet further consists of: (a) introducing to a host cell a 17TermA HSV vector and an rRp450 HSV vector; (b) growing the host cell for at least 3 passages; and (c) isolating a HSV particle produced by the host cell.

[8] Also provided is a method for inhibiting the growth or metastasis of a cancer cell or a metastatic cancer cell, the method comprising, or consisting essentially of, or yet further consisting of, contacting the cell with an effective amount of the non-natural HSV vector or a composition or a pharmaceutical composition containing the non-natural HSV vector as described herein. The contacting is *in vitro* or *in vivo*. In one example, the contacting is *in vivo* by administration of the non-natural HSV or a composition or a pharmaceutical composition to a subject. *In vitro*, the method is practiced by placing the non-natural HSV in contact with the cell. The *in vitro* method can be used to test for new therapies or as a personalized assay to determine if the therapy is suitable for the cancer to be treated. Additional cancer therapies

WHAT IS CLAIMED IS:

1. A non-natural herpes simplex virus ("HSV"), wherein the virus comprises:

i. a first polynucleotide encoding an amino acid sequence as shown by SEQ ID NO: 13,

ii. a second polynucleotide encoding an amino acid sequence as shown by SEQ ID NO: 21,

iii. a third polynucleotide encoding an amino acid sequence as shown by SEQ ID NO: 36,

iv. a fourth polynucleotide encoding an amino acid sequence as shown by SEQ ID NO: 28,

and

v. a fifth polynucleotide encoding an amino acid sequence as shown by SEQ ID NO: 2.

2. A composition comprising the non-natural HSV of claim 1 and a carrier and optionally wherein the carrier is a pharmaceutically available carrier.

3. The composition of claim 2 and a cryopreservative that facilitates the freezing and thawing of the non-natural HSV without loss of significant virulence.

4. A cell infected with the non-natural HSV of claim 1 or the composition of claim 2, optionally a lymphocyte.

5. A method to infect a cell, comprising contacting the cell with the non-natural HSV of claim 1 or the composition of claim 2, optionally wherein the cell is a lymphocyte; and/or wherein the cell has been infected with an Epstein-Barr virus ("EBV").

6. A method to prepare a viral vector comprising introducing a transgene into the non-natural HSV of claim 1.

7. An *in vitro* method for inhibiting the growth or metastasis of a cancer cell, comprising contacting the cell with an effective amount of the non-natural HSV of claim 1 or the composition of claim 2.

8. Use of the non-natural HSV of claim 1 or the composition of claim 2 in the manufacture of a medicament for treating cancer in a subject, wherein an effective amount of the non-natural HSV of claim 1 or the composition of claim 2 is to be administered to the subject, and optionally wherein the cancer is of the type, or the cancer cell is selected from a cell of the type: pancreatic cancer, renal cancer, small cell lung cancer, brain cancer, neural cancer, bone cancer, lymphoma, myeloma, colon cancer, uterine cancer, breast cancer, leukemia, liver cancer, prostate cancer, skin cancer, or melanoma; and/or wherein the HSV or the pharmaceutical composition is to be administered by injection, infusion, instillation, and/or inhalation; and/or wherein the administration comprises a therapy of the group of: a first line therapy, a second line therapy, a third line therapy, a fourth line therapy, or a fifth line therapy; and/or an effective amount of an anticancer therapy is to be further administered to the subject.

9. An *in vitro* method for inducing cell lysis, comprising contacting the cell with the non-natural HSV of claim 1 or the composition of claim 2.

10. A kit comprising the HSV of claim 1 or the composition of claim 2, and instructions for use.

11. A method of producing the HSV of claim 1, comprising
(a) introducing to a host cell a polynucleotide encoding a viral genome of the HSV;
(b) growing the host cell; and
(c) isolating an HSV particle produced by the host cell.

12. The non-natural HSV of claim 1 or the composition of claim 2 for use in therapy.