any subject matter in the Background section should be treated as part of the inventor's approach to the particular problem, which in and of itself may also be inventive.

SUMMARY

[0006a] In one aspect, the disclosure provides a modified oncolytic herpes virus genome, wherein the modified herpes virus genome comprises: 1) at least one miRNA target sequence operably linked to a first, or, to a first and a second copy of an ICP34.5 gene; and 2) mutations or modifications in at least one viral gene selected from the group consisting of ICP6, ICP0, ICP4, ICP27, ICP47, ICP24, and ICP56, wherein said at least one viral gene is modified by replacement of the native promoter with a CEA promoter or a CXCR4 promoter.

[0006b] In another aspect, the disclosure also provides an *in vitro* method for lysing tumor cells, comprising providing a therapeutically effective amount of recombinant herpes simplex virus according to the disclosure.

[0006c] In another aspect, the disclosure also provides a therapeutic composition comprising the recombinant herpes simplex virus according to the disclosure for use in therapy.

[0006d] In another aspect, the disclosure also provides a therapeutic composition comprising the recombinant herpes simplex virus according to the disclosure and a pharmaceutically acceptable carrier.

[0006e] In another aspect, the disclosure also provides a use of the recombinant herpes simplex virus according to the disclosure in the manufacture of a medicament for treating cancer in a subject suffering therefrom.

[0007] Briefly stated, the application relates to recombinant herpes simplex viruses (also referred to as "oHSV vectors") comprising at least one ICP34.5 gene having at least two miRNA target sequences in the 3' untranslated region of ICP34.5. In certain examples, the at least two miRNA target sequences are targets for the same miRNA. In other examples, the at least two miRNA target sequences are targets for an miRNA selected from the group consisting of mIR-122, miR-124, miR-124*, miR-127, miR-128, miR-129, miR-129*, miR-132, mIR-133a, mIR133b, miR-135b, miR-136, miR-136*, miR-137, miR-139-5p, miR-143, mIR-145, miR-154, miR-184, miR-188, miR-204, mIR216a, miR-299, miR-300-3p, miR-300-5p, miR-323, miR-329, miR-337, miR-335, miR-341, miR-369-3p, miR-369-5p, miR-376a, miR-

376a*, miR-376b-3p, miR-376b-5p, miR-376c, miR-377, miR-379, miR-379*, miR-382, miR-382*, miR-409-5p, miR-410, miR-411, miR-431, miR-433, miR-434, miR-451, miR-466b, miR-485, miR-495, miR-539, miR-541, miR-543*, miR-551b, miR-758, and miR-873. By

CLAIMS

What is claimed is:

1. A recombinant herpes simplex virus comprising a modified oncolytic herpes virus genome, wherein the modified herpes virus genome comprises: 1) at least one miRNA target sequence operably linked to a first, or, to a first and a second copy of an ICP34.5 gene; and 2) mutations or modifications in at least one viral gene selected from the group consisting of ICP6, ICP0, ICP4, ICP27, ICP47, ICP24, and ICP56, wherein said at least one viral gene is modified by replacement of the native promoter with a CEA promoter or a CXCR4 promoter.

2. The recombinant herpes simplex virus according to claim 1 wherein the miRNAs are selected from the group consisting of mIR-122, miR-124, miR-124*, miR-127, miR-128, miR-129, miR-129*, miR-132, mIR-133a, mIR133b, miR-135b, miR-136, miR-136*, miR-137, miR-139-5p, miR-143, mIR-145, miR-154, miR-184, miR-188, miR-204, mIR216a, miR-299, miR-300-3p, miR-300-5p, miR-323, miR-329, miR-337, miR-335, miR-341, miR-369-3p, miR-369-5p, miR-376a, miR-376a*, miR-376b-3p, miR-376b-5p, miR-376c, miR-377, miR-379, miR-379*, miR-382, miR-382*, miR-409-5p, miR-410, miR-411, miR-431, miR-433, miR-434, miR-451, miR-466b, miR-485, miR-495, miR-539, miR-541, miR-543*, miR-551b, miR-758, and miR-873.

3. The recombinant herpes simplex virus of claim 2 wherein the miRNA target sequence~~sites~~ comprise ~~five~~two or more copies of the binding sites for miR-124 and miR-143.

4. The recombinant herpes simplex virus of claim 1, wherein the oncolytic herpes virus is HSV-1.

5. The recombinant herpes simplex virus of claim 4, wherein the genome further comprises a fusogenic mutation in a gene encoding glycoprotein B (gB).

6. The recombinant herpes simplex virus of claim 5, wherein the gene encoding for glycoprotein B (gB) encodes a glycoproptein B variant that terminates after amino acid 876.

~~7. The recombinant herpes simplex virus of claim 1, wherein the modified oncolytic herpes virus genome comprises additional mutations or modifications in at least~~

~~one viral gene selected from the group consisting of ICP6, ICP0, ICP4, ICP27, ICP47, ICP24, and ICP56.~~

~~8. The recombinant herpes simplex virus of claim 7, wherein said at least one viral gene is modified by replacement of the native promoter.~~

~~9.~~7. The recombinant herpes simplex virus of claim 1, further comprising at least one nucleic acid encoding a non-viral protein selected from the group consisting of immunostimulatory factors and checkpoint blocking peptides, wherein the at least one nucleic acid is operably linked to a tumor-specific promoter.

~~10.~~8. The recombinant herpes simplex virus of claim ~~9~~7, wherein the non-viral protein is selected from the group consisting of IL12, IL15, IL15 receptor alpha subunit, OX40L, and a PD-L1 blocker.

9. The recombinant herpes simplex virus of claim 1, wherein the at least one viral gene is ICP4 or ICP27.

~~11.~~10. An *in vitro* method for lysing tumor cells, comprising providing a therapeutically effective amount of recombinant herpes simplex virus according to any one of claims 1 to ~~9~~.

~~12.~~11. A therapeutic composition comprising the recombinant herpes simplex virus according to any one of claims 1 to ~~9~~ for use in therapy.

~~13.~~12. A therapeutic composition comprising the recombinant herpes simplex virus according to any one of claims 1 to ~~9~~ and a pharmaceutically acceptable carrier.

~~14.~~13. Use of the recombinant herpes simplex virus according to any one of claims 1 to ~~9~~ in the manufacture of a medicament for treating cancer in a subject suffering therefrom.