As a result of considerable repetitive thinking and studies in the generation of vaccinia virus, the present inventors have generated vaccinia viruses comprising a polynucleotide encoding IL-7 or vaccinia viruses comprising a polynucleotide encoding IL-12, and vaccinia viruses comprising two polynucleotides, a polynucleotide encoding IL-7 and a polynucleotide encoding IL-12 (Example 2); and found that 1) a vaccinia virus comprising two polynucleotides, a polynucleotide encoding IL-7 and a polynucleotide encoding IL-12 and 2) a mixture of two vaccinia viruses, a vaccinia virus comprising a polynucleotide encoding IL-7 and a vaccinia virus comprising a polynucleotide encoding IL-12 exhibit a cytolytic effect on various human cancer cells (Example 3), thereby completing the present invention:

1) a vaccinia virus comprising two polynucleotides, a polynucleotide encoding IL-7 and a polynucleotide encoding IL-12 could exhibit a tumor regression effect in cancer-bearing humanized mouse models (Example 6), could achieve complete remission (Example 7), and could induce acquired immunity to maintain the antitumor effect (Example 8) in syngeneic cancer-bearing mouse models. Moreover, 2) a mixture of two vaccinia viruses, a vaccinia virus comprising a polynucleotide encoding IL-7 and a vaccinia virus comprising a polynucleotide encoding IL-12 could achieve complete remission (Example 7), and could induce

acquired immunity to maintain the antitumor effect (Example 8) in syngeneic cancer-bearing mouse models.

[0009]

More specifically, the present disclosure may encompass, as a substance or method useful in medicine or industry, the following include:

[1] In an aspect, there is provided a vaccinia virus comprising the following (1) and (2):

(1) a polynucleotide encoding interleukin-7 (IL-7); and

(2) a polynucleotide encoding interleukin-12 (IL-12),

wherein the vaccinia virus is oncolytic against human cancer cells,and wherein the vaccinia virus is deficient in the functions of VGF and O1L and having a deletion in the short consensus repeat (SCR) domains in the B5R extracellular region.

Also described is a vaccinia virus comprising the following (1) and (2):

(1) a polynucleotide encoding interleukin-7 (IL-7); and

(2) a polynucleotide encoding interleukin-12 (IL-12).

[2] In another aspect, there is provided a pharmaceutical composition comprising the following vaccinia viruses (1) and (2):

(1) a vaccinia virus comprising a polynucleotide encoding IL-7; and

(2) a vaccinia virus comprising a polynucleotide encoding IL-12,

wherein the vaccinia viruses are oncolytic against human

cancer cells, and wherein the vaccinia viruses are deficient in the functions of VGF and O1L and having a deletion in the SCR domains in the B5R extracellular region.

Also described is a pharmaceutical composition selected from the following (1) or (2):

(1) a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-12 to be used in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-7; or

(2) a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-7 to be used in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-12.

[3] In another example, there is provided a combination kit comprising the following vaccinia viruses (1) and (2):

(1) a vaccinia virus comprising a polynucleotide encoding IL-7; and

(2) a vaccinia virus comprising a polynucleotide encoding IL-12.

[4] The vaccinia virus according to [1], wherein the vaccinia virus is deficient in the function of vaccinia virus growth factor (VGF).

[5] The vaccinia virus according to [1], wherein the vaccinia virus is deficient in the function of O1L.

[6] The vaccinia virus according to [1], wherein the vaccinia virus is deficient in the functions of VGF and O1L.

[7] The vaccinia virus according to [1], wherein the vaccinia virus has a deletion in the short consensus repeat (SCR) domains in the B5R extracellular region.

[8] The vaccinia virus according to [1], wherein the vaccinia virus is deficient in the functions of VGF and O1L and has a deletion in the SCR domains in the B5R extracellular region.

[9] The vaccinia virus according to any one of [1] and [4]-[8], wherein the vaccinia virus is a LC16mO strain.

[10] A pharmaceutical composition comprising a vaccinia virus according to any one of [1] and [4]-[9] and a pharmaceutically acceptable excipient.

[11] The pharmaceutical composition according to [2] or the kit according to [3], wherein the vaccinia virus is deficient in the function of VGF.

[12] The pharmaceutical composition according to [2] or the kit according to [3], wherein the vaccinia virus is deficient in the function of O1L.

[13] The pharmaceutical composition according to [2] or the kit according to [3], wherein the vaccinia virus is deficient in the functions of VGF and O1L.

[14] The pharmaceutical composition according to [2] or the kit according to [3], wherein the vaccinia virus has a deletion in the SCR domains in the B5R extracellular region.

[15] The pharmaceutical composition according to [2] or the kit according to [3], wherein the vaccinia virus is

deficient in the functions of VGF and O1L and has a deletion in the SCR domains in the B5R extracellular region.

[16] The pharmaceutical composition according to any one of [2] and [11]-[15] or the kit according to any one of [3] and [11]-[15], wherein the vaccinia virus is a LC16mO strain.

[17] The pharmaceutical composition according to any one of [2] and [11]-[16] or the kit according to any one of [3] and [11]-[16], further comprising a pharmaceutically acceptable excipient.

[18] The pharmaceutical composition or kit according to any one of [10]-[17], for preventing or treating cancer.

[19] The pharmaceutical composition or kit according to [18], wherein the cancer is malignant melanoma, lung adenocarcinoma, lung cancer, small cell lung cancer, lung squamous carcinoma, kidney cancer, bladder cancer, head and neck cancer, breast cancer, esophageal cancer, glioblastoma, neuroblastoma, myeloma, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, mesothelioma, cervical cancer or gastric cancer.

[20] A method for preventing or treating cancer, comprising the step of administering the vaccinia virus according to any one of [1] and [4]-[9] to a subject in need of the prevention or treatment for cancer.

[21] The method according to [20], wherein the cancer is malignant melanoma, lung adenocarcinoma, lung cancer, small cell lung cancer, lung squamous carcinoma, kidney cancer,

bladder cancer, head and neck cancer, breast cancer, esophageal cancer, glioblastoma, neuroblastoma, myeloma, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, mesothelioma, cervical cancer or gastric cancer.

[22] In another aspect, there is provided the vaccinia virus according to any one of [1] and [4]-[9], for use in preventing or treating cancer.

[23] The vaccinia virus according to [22], wherein the cancer is malignant melanoma, lung adenocarcinoma, lung cancer, small cell lung cancer, lung squamous carcinoma, kidney cancer, bladder cancer, head and neck cancer, breast cancer, esophageal cancer, glioblastoma, neuroblastoma, myeloma, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, mesothelioma, cervical cancer or gastric cancer.

[24] In another aspect, there is provided the use of the vaccinia virus as described herein in the manufacture of a pharmaceutical composition for preventing or treating cancer.

Also described is the use of the vaccinia virus according to any one of [1] and [4]-[9] for the manufacture of a pharmaceutical composition for preventing or treating cancer.

[25] The use according to [24], wherein the cancer is malignant melanoma, lung adenocarcinoma, lung cancer, small cell lung cancer, lung squamous carcinoma, kidney cancer,

bladder cancer, head and neck cancer, breast cancer, esophageal cancer, glioblastoma, neuroblastoma, myeloma, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, mesothelioma, cervical cancer or gastric cancer.

[26] A method for preventing or treating cancer, comprising the step of administering

(1) a vaccinia virus comprising a polynucleotide encoding IL-7; and

(2) a vaccinia virus comprising a polynucleotide encoding IL-12 to a subject in need of the prevention or treatment for cancer.

[27] The method according to [26], wherein the cancer is malignant melanoma, lung adenocarcinoma, lung cancer, small cell lung cancer, lung squamous carcinoma, kidney cancer, bladder cancer, head and neck cancer, breast cancer, esophageal cancer, glioblastoma, neuroblastoma, myeloma, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, mesothelioma, cervical cancer or gastric cancer.

[28] In another aspect, the present disclosure provides a vaccinia virus selected from the following (1) and (2):

(1) a vaccinia virus comprising a polynucleotide encoding IL-7, for preventing or treating cancer in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-12; or

(2) a vaccinia virus comprising a polynucleotide encoding IL-12, for preventing or treating cancer in combination with a pharmaceutical composition comprising a vaccinia

virus comprising a polynucleotide encoding IL-7, wherein the vaccinia virus is oncolytic against human cancer cells, and wherein the vaccinia virus is deficient in the functions of VGF and O1L and having a deletion in the short consensus repeat (SCR) domains in the B5R extracellular region.

Also described is a vaccinia virus selected from the following (1) or (2):

(1) a vaccinia virus comprising a polynucleotide encoding IL-7, for preventing or treating cancer in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-12; or

(2) a vaccinia virus comprising a polynucleotide encoding IL-12, for preventing or treating cancer in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-7.

[29] The vaccinia virus according to [28], wherein the cancer is malignant melanoma, lung adenocarcinoma, lung cancer, small cell lung cancer, lung squamous carcinoma, kidney cancer, bladder cancer, head and neck cancer, breast cancer, esophageal cancer, glioblastoma, neuroblastoma, myeloma, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, mesothelioma, cervical cancer or gastric cancer.

[30] In another aspect, there is provided the use of a vaccinia virus selected from the following (1) or (2):

(1) use of a vaccinia virus comprising a polynucleotide encoding IL-7 in the manufacture of a pharmaceutical composition for preventing or treating cancer to be used in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-12; or

(2) use of a vaccinia virus comprising a polynucleotide encoding IL-12 in the manufacture of a pharmaceutical composition for preventing or treating cancer to be used in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-7.

Also described is the use of a vaccinia virus selected from the following (1) or (2):

(1) use of a vaccinia virus comprising a polynucleotide encoding IL-7 for the manufacture of a pharmaceutical composition for preventing or treating cancer to be used in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-12; or

(2) use of a vaccinia virus comprising a polynucleotide encoding IL-12 for the manufacture of a pharmaceutical composition for preventing or treating cancer to be used in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-7.

In yet another example, the present disclosure provides the use of a vaccinia virus comprising a polynucleotide encoding IL-7 in the manufacture of a medicament for use in combinatorial therapy for preventing or treating cancer, wherein said medicament is to be administered in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-12.

In a further example, the present disclosure provides the use of a vaccinia virus comprising a polynucleotide encoding IL-12 in the manufacture of a medicament for use in combinatorial therapy for preventing or treating cancer, wherein said medicament is to be administered in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-7.

[31] The use according to [30], wherein the cancer is malignant melanoma, lung adenocarcinoma, lung cancer, small cell lung cancer, lung squamous carcinoma, kidney cancer, bladder cancer, head and neck cancer, breast cancer, esophageal cancer, glioblastoma, neuroblastoma, myeloma, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, mesothelioma, cervical cancer or gastric cancer.

[32] In another example, there is provided use of (1) a vaccinia virus comprising a polynucleotide encoding IL-7 and (2) a vaccinia virus comprising a polynucleotide

What is claimed is:

1. A vaccinia virus comprising the following (1) and (2):

(1) a polynucleotide encoding interleukin-7 (IL-7); and

(2) a polynucleotide encoding interleukin-12 (IL-12),

wherein the vaccinia virus is oncolytic against human cancer cells,

and wherein the vaccinia virus is deficient in the functions of VGF and O1L and having a deletion in the short consensus repeat (SCR) domains in the B5R extracellular region.

2. A pharmaceutical composition comprising the following vaccinia viruses (1) and (2):

(1) a vaccinia virus comprising a polynucleotide encoding IL-7; and

(2) a vaccinia virus comprising a polynucleotide encoding IL-12,

wherein the vaccinia viruses are oncolytic against human cancer cells,

and wherein the vaccinia viruses are deficient in the functions of VGF and O1L and having a deletion in the SCR domains in the B5R extracellular region.

3. The vaccinia virus according to claim 1, wherein the vaccinia virus is a LC16mO strain.

4. A pharmaceutical composition comprising a vaccinia virus according to any one of claims 1 and 3 and a pharmaceutically acceptable excipient.

5. The pharmaceutical composition according to claim 2, wherein the one or both of the vaccinia virus are a LC16mO strain.

6. The pharmaceutical composition according to any one of claims 2 and 5, further comprising a pharmaceutically acceptable excipient.

7. The pharmaceutical composition according to any one of claims4-6, for treating cancer.

8. The pharmaceutical composition according to claim 7, wherein the cancer is malignant melanoma, lung adenocarcinoma, lung cancer, small cell lung cancer, lung squamous carcinoma, kidney cancer, bladder cancer, head and neck cancer, breast cancer, esophageal cancer, glioblastoma, neuroblastoma, myeloma, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, mesothelioma, cervical cancer or gastric cancer.

9. The vaccinia virus according to any one of claims 1 and 3, for use in treating cancer.

10. The vaccinia virus according to claim 9, wherein the cancer is malignant melanoma, lung adenocarcinoma, lung cancer, small cell lung cancer, lung squamous carcinoma, kidney cancer, bladder cancer, head and neck cancer, breast cancer, esophageal cancer, glioblastoma, neuroblastoma, myeloma, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, mesothelioma, cervical cancer or gastric cancer.

11. Use of the vaccinia virus according to any one of claim 1 and 3 in the manufacture of a pharmaceutical composition for treating cancer.

12. The use according to claim 11, wherein the cancer is malignant melanoma, lung adenocarcinoma, lung cancer, small cell lung cancer, lung squamous carcinoma, kidney cancer, bladder cancer, head and neck cancer, breast cancer, esophageal cancer, glioblastoma, neuroblastoma, myeloma, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, mesothelioma, cervical cancer or gastric cancer.

13. Use of a vaccinia virus selected from the following (1) or (2):

(1) use of a vaccinia virus comprising a polynucleotide encoding IL-7 in the manufacture of a pharmaceutical composition for treating cancer to be used in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-12; or
(2) use of a vaccinia virus comprising a polynucleotide encoding IL-12 in the manufacture of a pharmaceutical composition for treating cancer to be used in combination with a pharmaceutical composition comprising a vaccinia virus comprising a polynucleotide encoding IL-7,
wherein the vaccinia virus is oncolytic against human cancer cells,
and wherein the vaccinia virus is deficient in the functions of VGF and O1L and having a deletion in the short consensus repeat (SCR) domains in the B5R extracellular region.

14. The use according to claim 13, wherein the cancer is malignant melanoma, lung adenocarcinoma, lung cancer, small cell lung cancer, lung squamous carcinoma, kidney cancer, bladder cancer, head and neck cancer, breast cancer, esophageal cancer, glioblastoma, neuroblastoma, myeloma, ovarian cancer, colorectal cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, mesothelioma, cervical cancer or gastric cancer.