recombinant human IL-12 protein synergistically enhances the production of IFN-γ (The Journal of Immunology, 1995, vol. 154, p. 5093-5102). It has been reported that an oncolytic vaccinia virus that expresses an immune-stimulating molecule may rapidly be cleared by strong immune responses. It is also stated that strong immune response could serve either as a foe or as an ally to the vaccinia virus-mediated cancer therapy (Molecular Therapy, 2005, vol. 11, No. 2, p. 180-195).

Citation List

Patent Literatures

[0006]

Patent Literature 1: WO2015/150809

Patent Literature 2: WO2015/076422

SUMMARY

Technical Problem

[0007]

An object of the present invention is to provide a recombinant vaccinia virus (in particular, oncolytic vaccinia virus), a pharmaceutical composition and a combination kit, for treating or preventing cancer.

Solution to Problem

[0008]

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.

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.

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 aspect, 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.
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 aspect, 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 aspect, 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 aspect, there is provided use of (1) a vaccinia virus comprising a polynucleotide encoding IL-7 and (2) a vaccinia virus comprising a polynucleotide

encoding IL-12 in the manufacture of a combination kit for preventing or treating cancer.

Also described is use of (1) a vaccinia virus comprising a polynucleotide encoding IL-7 and (2) a vaccinia virus comprising a polynucleotide encoding IL-12 for the manufacture of a combination kit for preventing or treating cancer.

[33] The use according to [32], 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,

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.

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.

3. 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 claim 1, wherein the vaccinia virus is deficient in the function of vaccinia virus growth factor (VGF).

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

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

7. The vaccinia virus according to claim 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 claim 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 claims 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 claims 1 and 4-9 and a pharmaceutically acceptable excipient.

11. The pharmaceutical composition according to claim 2 or the kit according to claim 3, wherein the one or both of the vaccinia viruses are deficient in the function of VGF.

12. The pharmaceutical composition according to claim 2 or the kit according to claim 3, wherein the one or both of vaccinia viruses are deficient in the function of O1L.

13. The pharmaceutical composition according to claim 2 or the kit according to claim 3, wherein the one or both of the vaccinia viruses are deficient in the functions of VGF and O1L.

14. The pharmaceutical composition according to claim 2 or the kit according to claim 3, wherein the one or both of the vaccinia viruses have a deletion in the SCR domains in the B5R extracellular region.

15. The pharmaceutical composition according to claim 2 or the kit according to claim 3, wherein the one or both of the vaccinia viruses are 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 claims 2 and 11-15 or the kit according to any one of

claims 3 and 11-15, wherein the one or both of the vaccinia virus are a LC16mO strain.

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

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

19. The pharmaceutical composition or kit according to claim 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. The vaccinia virus according to any one of claims 1 and 4-9, for use in preventing or treating cancer.

21. The vaccinia virus according to claim 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. Use of the vaccinia virus according to any one of claim 1 and 4-9 in the manufacture of a pharmaceutical composition for preventing or treating cancer.

23. The use according to claim 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. 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.

25. The vaccinia virus according to claim 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. 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.

27. 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.

28. 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.

29. The use according to any one of claims 26 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. Use of (1) a vaccinia virus comprising a polynucleotide encoding IL-7 and (2) a vaccinia virus comprising a polynucleotide encoding IL-12 in the manufacture of a combination kit for preventing or treating cancer.

31. The use according to claim 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.