MODIFIED EXTRACELLULAR ENVELOPED VIRUS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No 62/916,035 filed Oct 16, 2019, which is incorporated by reference herein in its entirety.

INCORPORATION BY REFERENCE

[0002] All publications, patents, patent applications, and NCBI accession numbers mentionedin this specification are herein incorporated by reference to the same extent as if each individualpublication, patent, or patent application was specifically and individually indicated to be incorporated by reference, and as if set forth in their entireties. In the event of a conflict betweena term as used herein and the term as defined in the incorporated reference, the definition of this disclosure controls.

SUMMARY

[0002a] In one aspect, provided herein is an oncolytic vaccinia virus comprising a nucleic acid that codes for an A34R protein comprising at least two mutations that are in amino acid residues thcorresponding to positions Lys119 and Lys151 of the wild-type vaccinia virus A34R protein (SEQ ID NO: 4), and wherein the mutations are Lys119Glu and Lys151Glu, respectively.

[0002b] In another aspect, provided herein is use of the oncolytic vaccinia virus as described herein, in the manufacture of a medicament for the treatment of a cancer.

[0002c] In another aspect, provided herein is an oncolytic vaccinia virus as described herein for use in therapy.

[0003] One example provides a modified oncolytic poxvirus comprising a nucleic acid that codes for an A34R protein or a fragment thereof comprising at least two mutations, wherein the at least two mutations are in positions corresponding to positions Lys119 and Lys151 of a wild-type vaccinia virus A43R protein (SEQ ID NO. 4). In some examples, the mutation in the position corresponding to position Lys119 is Lys119Glu. In some examples, the mutation in the position corresponding to position Lys151 is Lys151Glu. In some examples, the at least two mutations in positions corresponding to positions Lys119 and Lys151 of the wild-type vaccinia virus A43R protein (SEQ ID NO. 4) are Lys119Glu and Lys151Glu, respectively.

[0004] One example provides a modified oncolytic poxvirus comprising a nucleic acid that codes for an A34R protein or a fragment thereof comprising at least two non- naturally occurring mutations that are in amino acid residues that are positively charged at pH 5, within the wild-type A34R protein (SEQ ID No. 4).

[0005] Another example provides a modified oncolytic poxvirus comprising a nucleic acid that codes for an A34R protein or a fragment thereof comprising at least two non- naturally occurring mutations that are not at position 110 of the wild-type A34R protein (SEQ ID No. 4).

[0006] Another example provides a modified oncolytic poxvirus comprising a nucleic acid that codes for an A34R protein or a fragment thereof comprising at least two non-

CLAIMS

1. An oncolytic vaccinia virus comprising a nucleic acid that codes for an A34R protein comprising at least two mutations that are in amino acid residues corresponding to positions Lys119 and Lys151 of the wild-type vaccinia virus A34R protein (SEQ ID NO: 4), and wherein the mutations are Lys119Glu and Lys151Glu, respectively.

2. The oncolytic vaccinia virus of claim 1, wherein the oncolytic vaccinia virus produces a greater amount of an extracellular enveloped virus form than an intracellular mature virus form, as compared to an otherwise identical oncolytic vaccinia virus that does not comprise the at least two mutations.

3. The oncolytic vaccinia virus of any of one of claims 1-2, further comprising anexogenous nucleic acid that codes for at least one of: a therapeutic protein or a diagnostic protein.

4. The oncolytic vaccinia virus of claim 3, wherein the exogenous nucleic acid can code for at least one of: a chemokine receptor, a membrane associated protein, a microbial protein that is capable of degrading hyaluronan, a microbial protein, SOCS3, PH-20, HMGB1, PIAS3, IL15, IL15-Rα, LIGHT, ITAC, fractalkine, CCL5, N1L, an immune checkpoint modulator, a metabolic modulating protein, or any combinations thereof.

5. The oncolytic vaccinia virus of claim 4, comprising the exogenous nucleic acid that codes for a chemokine receptor, wherein the chemokine receptor comprises at least one of CXCR4 and CCR2.

6. The oncolytic vaccinia virus of any one of claims 1-5, further comprising the mutation or deletion of viral gene A52R.

7. The oncolytic vaccinia virus of any one of claims 1-6, wherein the oncolytic virus is modified at a genome level.

8. Use of the oncolytic vaccinia virus of any one of claims 1-7, in the manufacture

of a medicament for the treatment of a cancer.

9. The use of claim 8, wherein a therapeutically effective amount of an oncolytic vaccinia virus according to any one of claims 1-7 is to be administered to a subject.

10. The use of claim 8 or 9, wherein the oncolytic vaccinia virus is to be administered via anintratumoral injection, an intravenous injection, or a combination thereof.

11. The use of any one of claims 8-10, wherein said medicament is to be administered in combination with a further therapy, wherein the further therapy comprises at least one of: a chemotherapy, a radiation therapy, an oncolytic viral therapy withan additional virus, treatment with an immunomodulatory protein, a CAR T cellular therapy, an anti-cancer agent, an immunomodulatory agent, or any combinations thereof.

12. The use of claim 11, wherein the further therapy comprises the immunomodulatory agent selected from the group consisting of: an anti-CD33 antibody or anantigen binding fragment thereof, an anti-CD11b antibody or an antigen binding fragment thereof, a COX2 inhibitor, a cytokine, a chemokine, an anti-CTLA4 antibody or an antigen binding fragment thereof, an anti-PD-1 antibody or an antigen binding fragment thereof, an anti-PD-L1 antibody or an antigen binding fragment thereof, and a TLR agonist.

13. An oncolytic vaccinia virus of any one of claims 1-12 for use in therapy.