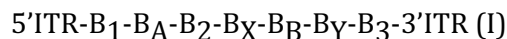


CLAIMS:

1. An oncolytic adenovirus comprising a sequence of formula **(I)**:



wherein:

B_1 is bond or comprises: E1A, E1B or E1A-E1B;

B_A comprises-E2B-L1-L2-L3-E2A-L4;

B_2 is a bond or comprises: E3;

B_X is a bond or a DNA sequence comprising: a restriction site, one or more transgenes or both;

B_B comprises L5;

B_Y is a DNA sequence comprising: a restriction site, one or more transgenes or both;

B_3 is a bond or comprises: E4;

wherein the adenovirus encodes a Bispecific T cell Engager (BiTE™) in position B_Y comprising at least two binding domains wherein :

one of the said domains is specific to a component of the T-cell receptor complex (TCR); and

one the binding domains of the BiTE™ is specific to a tumour stromal antigen expressed on fibroblasts, tumour-associated macrophages, dendritic cells, NK cells and/or T-cells which have infiltrated the stroma and

the adenovirus is Enadenotucirev (EnAd) or serotype 11 adenovirus (Ad11).

2. An oncolytic adenovirus according to claim 1, wherein the adenovirus is EnAd.
3. An oncolytic adenovirus according to claims 1 or 2, wherein the component of the TCR is CD3.
4. An oncolytic adenovirus according to claim 3, wherein the surface antigen is CD3.
5. An oncolytic adenovirus according to claim 4, wherein the surface antigen is selected from the group consisting of CD3ε, CD3γ and CD3δ.
6. An oncolytic adenovirus according to any one of claims 1 to 5, wherein, the tumour stromal antigen is selected from: fibroblast activation protein (FAP), TREM1, IGFBP7, FSP-1, platelet-derived growth factor-α receptor (PDGFR-α), platelet-derived growth factor-β receptor (PDGFR-β) and vimentin.
7. An oncolytic adenovirus according to claim 6, wherein the tumour stromal antigen is FAP.
8. An oncolytic adenovirus according to any one of claims 1 to 7, wherein the adenovirus is chimeric.
9. An oncolytic adenovirus according to any one of claims 1 to 8, wherein the adenovirus replication capable.
10. An oncolytic adenovirus according to claim 9, wherein the adenovirus is replication competent.
11. An oncolytic adenovirus according to any one of claims 1 to 8, wherein the adenovirus is replication deficient.
12. An oncolytic adenovirus according to any one of claims 1 to 11, wherein B_X comprises one or more transgenes or a transgene cassette.

13. An oncolytic adenovirus according to any one of claims 1 to 12, wherein the BiTE is encoded in position B_Y is under the control of the major late promoter.
14. An oncolytic adenovirus according to any one of claims 1 to 13, wherein the adenovirus further encodes a second BiTE.
15. An oncolytic adenovirus according to claim 14, wherein both BiTEs are encoded in position B_Y.
16. An oncolytic adenovirus according to claim 14, wherein a BiTE is encoded in position B_X.
17. An oncolytic adenovirus according to claim 16, wherein the encoded BiTE is under the control of an exogenous promoter.
18. An oncolytic adenovirus according to any one of claims 14 to 17, wherein the first BiTE molecule is specific to a tumour antigen, and the second BiTE molecule is specific to a tumour stromal antigen.
19. An oncolytic adenovirus according to any one of the claims 1 to 18, wherein the encoded BiTE binds to CD3 and comprises a VH domain comprising an amino acid sequence as set forth in SEQ ID NO: 8, or an amino acid sequence that is at least 95% identical thereto and a VL comprising an amino acid sequence as set forth in SEQ ID NO: 9 or a sequence at least 95% identical thereto.
20. An oncolytic adenovirus according to claim 19, wherein the encoded BiTE comprises an scFv comprising an amino acid sequence as set forth in SEQ ID NO: 7 or a sequence at least 95% identical thereto.
21. An oncolytic adenovirus according to any one of claims 1 to 20, wherein the encoded BiTE binds to FAP and comprises a VH domain comprising an amino acid sequence as set forth in SEQ ID NOs: 13, or an amino acid sequence that is at least 95% identical thereto and a VL comprising an amino acid sequence as set forth in SEQ ID NO: 12 or a sequence at least 95% identical thereto.
22. An oncolytic adenovirus according to claim 21, wherein the encoded BiTE comprises a scFv comprising an amino acid sequence as set forth in SEQ ID NO: 11 or 75 or a sequence at least 95% identical to any one of the same.
23. An oncolytic adenovirus according to any one of the claims 14 to 22, wherein the encoded BiTE binds to EpCAM and comprises a VH domain comprising an amino acid sequence as set forth in SEQ ID NOs: 18, or an amino acid sequence that is at least 95% identical thereto and a VL comprising an amino acid sequence as set forth in SEQ ID NO: 17 or a sequence at least 95% identical thereto.
24. An oncolytic adenovirus according to claim 23, wherein the encoded BiTE comprises an scFv comprising an amino acid sequence as set forth in SEQ ID NO: 16 or 73 or a sequence at least 95% identical to any one of the same.
25. An oncolytic adenovirus according to claims 1 or 14, wherein the adenovirus comprises a sequence shown in SEQ ID NO: 36, 37, 81, 82, 97, 98, 99 or 100
26. An oncolytic adenovirus according to claims 14 or 18 wherein the adenovirus comprises a sequence shown in SEQ ID NO: 34, 35, 79, 80 or 96.

27. An oncolytic denovirus according to any one of claims 1 to 26, wherein the adenovirus encodes 2, 3 or 4 further transgenes.
28. An oncolytic virus according to claim 27, wherein a different cleavage peptide is encoded between each of the transgenes.
29. An oncolytic adenovirus according to claims 27 or 28, wherein the further transgene(s) encodes a cytokine, chemokine and/or an immunomodulator.
30. An oncolytic adenovirus according to any one of claims 27 to 29, wherein all the further transgenes are in position B_y.
31. An oncolytic adenovirus according to any one of claims 27 to 30, wherein at least one further transgene encodes a cytokine.
32. An oncolytic adenovirus according to claim 31, wherein the cytokine is selected from the group consisting of MIP1 α , IL-1 α , IL-1 β , IL-6, IL-9, IL-12, IL-13, IL-17, IL-18, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-33, IL-35, IL-2, IL-4, IL-5, IL-7, IL-10, IL-15, IL-21, IL-25, IL-1RA, IFN α , IFN β , IFN γ , TNF α , lymphotoxin α (LTA), Flt3L, GM-CSF and IL-8.
33. An oncolytic adenovirus according to any one of claims 27 to 32, wherein at least one further transgene encodes a chemokine.
34. An oncolytic adenovirus according to claim 33, wherein the chemokine is selected from the group consisting of CCL2, CCL3, CCL5, CCL17, CCL20, CCL22, CXCL9, CXCL10, CXCL11, CXCL13, CXCL12, CCL2, CCL19 and CCL21.
35. A composition comprising an adenovirus according to any one of claims 1 to 34 and a diluent or carrier.
36. A composition according to claim 35, wherein the formulation comprises a second oncolytic virus.
37. A composition according to claim 36, wherein the second oncolytic virus is Ad11 or a derivative thereof.
38. A composition according to claims 36 or 37, wherein the second oncolytic virus is Enadenotucirev (EnAd).
39. An oncolytic adenovirus of any one of claims 1 to 34 or a composition according to any one of claims 35 to 38 for use in treatment.
40. Use of an oncolytic adenovirus of any one of claims 1 to 34 or a composition according to any one of claims 35 to 38 in the manufacture of a medicament for the treatment of cancer.