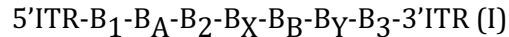


CLAIMS:

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 bond or 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 first Bispecific T cell Engager (BiTE™) comprising at least two binding domains, Bd1 and Bd2, wherein at least one of the said domains is specific to a component of the T-cell receptor complex (TCR), and
- a second BiTE comprising at least two binding domains, Bd3 and Bd4, and at least one of said binding domains is specific to a component of the T-cell receptor complex (TCR);

wherein both BiTEs™ are encoded in position B_Y ; 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 T-cell receptor complex (TCR), is CD3.
4. An oncolytic adenovirus according to claim 3, wherein the component of the T-cell receptor complex (TCR) is selected from CD3 ϵ , CD3 γ and CD3 δ .
5. An oncolytic adenovirus according to any one of claims 1 to 4, wherein Bd2 in said first BiTE and Bd4 in said second BiTE bind the same antigen of interest.
6. An oncolytic adenovirus according to any one of claims 1 to 4, wherein the Bd2 in said first BiTE and Bd4 in said second BiTE bind different antigens of interest.

7. An oncolytic adenovirus according to any one of claims 1 to 6, wherein one of the binding domains is specific to a tumour antigen.
8. An oncolytic adenovirus according to claim 7, wherein the tumour antigen is selected from the group consisting of CEA, MUC-1, EpCAM, HER receptors HER1, HER2, HER3, HER4, PEM, A33, G250, carbohydrate antigens Le^y, Le^x, Le^b, PSMA, TAG-72, STEAP1, CD166, CD24, CD44, E-cadherin, SPARC, ErbB2 and ErbB3.
9. An oncolytic adenovirus according to claims 7 or 8, wherein one of the binding domains is specific to EpCAM.
10. An oncolytic adenovirus according to any one of claims 1 to 9, wherein one of the binding domains is specific to a tumour stromal antigen.
11. An oncolytic adenovirus according to claim 10, wherein the tumour stromal antigen is selected from the group consisting of 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.
12. An oncolytic adenovirus according to claim 10 or 11, wherein one of the binding domains is specific to FAP.
13. An oncolytic adenovirus according to any one of claims 10 to 12, wherein the stromal antigen is an antigen is selected from a myeloid derived suppressor cell antigen, a tumor associated macrophage, and combinations thereof.
14. An oncolytic adenovirus according to claim 13, wherein the antigen is selected from CD163, CD206, CD68, CD11c, CD11b, CD14, CSF1 Receptor, CD15, CD33, CD66b and a combination of two or more of the same.
15. An oncolytic adenovirus according to any one of claims 1 to 14, wherein the adenovirus is chimeric.
16. An oncolytic adenovirus according to any one of claims 1 to 15, wherein the adenovirus replication capable.
17. An oncolytic adenovirus according to claim 16, wherein the adenovirus is replication competent.
18. An oncolytic adenovirus according to any one of claims 1 to 15, wherein the adenovirus is replication deficient.
19. An oncolytic adenovirus according to any one of claims 1 to 18, wherein a transgene or transgene cassette is under the control of an endogenous promoter, the major late promoter.

20. An oncolytic adenovirus according to any one of claims 1 to 19, wherein a binding domain in the first BiTE is specific to a tumour antigen, and a binding domain in the second BiTE is specific to a tumour stromal antigen.
21. An oncolytic adenovirus according to any one of the claims 1 to 20, wherein an encoded BiTE 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.
22. An oncolytic adenovirus according to claim 21, 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.
23. An oncolytic adenovirus according to any one of the claims 1 to 22, wherein the encoded BiTE comprises a VH domain comprising an amino acid sequence as set forth in SEQ ID NOs: 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: 7 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: 7 or a sequence at least 95% identical thereto.
25. An oncolytic adenovirus according to any one of the claims 1 to 24, wherein the encoded BiTE comprises a VH domain comprising an amino acid sequence as set forth in SEQ ID NO: 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.
26. An oncolytic adenovirus according to claim 25, wherein the encoded BiTE comprises an scFv comprising an amino acid sequence as set forth in SEQ ID NO: 11, 74, 75 or a sequence at least 95% identical to any one of the same.
27. An oncolytic adenovirus according to any one of the claims 1 to 26, wherein the encoded BiTE comprises a VH domain comprising an amino acid sequence as set forth in SEQ ID NO: 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.
28. An oncolytic adenovirus according to claim 25, wherein the encoded BiTE comprises an scFv comprising an amino acid sequence as set forth in SEQ ID NOs: 16, 72, 73 or a sequence at least 95% identical to any one of the same.

29. An oncolytic adenovirus according to any one of claims 1 to 28, wherein the adenovirus comprises a sequence shown in SEQ ID NO: 120.
30. An oncolytic adenovirus according to any one of claims 1 to 29, wherein the adenovirus encodes at least one further transgene.
31. An oncolytic adenovirus according to claim 30, wherein the further transgene(s) encodes a cytokine, chemokine and/or an immunomodulator.
32. An oncolytic adenovirus according to claim 31, wherein the further transgene(s) is encoded in position B_γ.
33. An oncolytic adenoviruses according to any one of claims 30 to 32, wherein at least one further transgene encodes a cytokine.
34. An oncolytic adenovirus according to claim 33, 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.
35. An oncolytic adenovirus according to any one of claims 30 to 34, wherein at least one further transgene encodes a chemokine.
36. An oncolytic adenovirus according to claim 35, 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.
37. A composition comprising an adenovirus according to any one of claims 1 to 36, and a diluent or carrier.
38. A composition according to claim 37, wherein the formulation comprises a second oncolytic virus.
39. A composition according to claim 38, wherein the second oncolytic virus is Ad1 or a derivative thereof.
40. A composition according to claim 39, wherein the second oncolytic virus is Enadenotucirev (EnAd).