

Claims

1. A replication capable group B oncolytic adenovirus selected from the group consisting of Ad11 and enadenotucirev (EnAd), wherein the virus comprises a transgene encoding an antibody or a binding fragment thereof for expression on the surface of a cancer cell, wherein said antibody or binding fragment is specific to a CD3 protein of a T-cell receptor complex (TCR), and the gene encoding said antibody or binding fragment is located between the stop codon and polyA recognition site of the adenoviral gene L5 and the stop codon and polyA recognition site of the gene E4, and the encoded antibody further comprises a transmembrane domain or a GPI anchor,
wherein the transgene encoding the anti-CD3 antibody or binding fragment is under the control of the endogenous major late promoter,
wherein the virus encodes at least one further transgene,
wherein the further transgene encodes a cytokine selected from the group comprising TNF superfamily, TGF beta superfamily, IL-1 family, IL-10 family, IL-17 family and interferon family, and said one or more further transgenes are between the E4 region and the fibre L5 under the control of the major late promoter, and
wherein the anti-CD3 antibody or binding fragment thereof and protein encoded by the further transgene are expressed independently anchored at the surface of the cancer cell,
wherein the virus does not encode a B7 protein or an active fragment thereof.
2. An adenovirus according to claim 1, wherein the virus is Ad11.
3. An adenovirus according to claim 1, wherein the virus is EnAd.
4. An adenovirus according to any one of claims 1 to 3, wherein the virus is replication competent.
5. An adenovirus according to any one of claims 1 to 4, wherein the transmembrane domain is selected from a sequence shown in SEQ ID NO: 10 to 14.
6. An adenovirus according to any one of claims 1 to 5, wherein the antibody or binding fragment is selected from the group comprising a full-length antibody, a Fab, modified Fab, Fab', modified Fab', F(ab')₂, Fv, single domain antibodies, scFv, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies, humabodies, disulfide stabilised forms of any one of the same and epitope-binding fragments thereof.
7. An adenovirus according to any one of claims 1 to 6, wherein the antibody binding fragment is a single chain Fv.
8. An adenovirus according to any one of claims 1 to 7, wherein the oncolytic virus encodes at least two further transgenes.

9. An adenovirus according to ~~any one of claims 1 to 8, wherein the at least one immunomodulator further transgene is encodes~~ a membrane-associated protein ligand for immune cell surface receptors selected from the group comprising CTLA-4, PD-1, HVEM, ILT-2, ILT-3, ILT-4, TIM-3, LAG-3, BTLA, LIGHT or CD160, CD16, CD25, CD33, CD332, CD127, CD31, CD43, CD44, CD162, CD301a, CD301b and Galectin-3, FLT-3, FLT-3 ligand, TLRs, TLR ligands, CCR7, CD1a, CD1c, CD11b, CD11c, CD83, CD123, CD172a, CD205, CD207, CD209, CD273, CD281, CD283, CD286, CD289, CD287, CXCR4, GITR Ligand, IFN- α 2, IL-12, IL-23, ILT1, ILT2, ILT3, ILT4, ILT5, ILT7, TSLP Receptor, CD141, CD303, CADM1, CLEC9a, XCR1 and CD304, OX40, OX40 ligand, CD27, CD28, CD30, CD40, CD40 ligand, CD70, CD137, GITR, 4-1BB, ICOS and ICOS ligand.
10. An adenovirus according to ~~any one of claims 1 to 98, wherein a second further transgene encodes a cytokine (including secreted or cell membrane associated molecules).~~
11. An adenovirus according to any one of claims 1 to -10, wherein the encoded cytokine is independently selected from TNF-alpha, IL-1, IL-8, IL-10, IL-17, interferon, LIGHT, TL1A, Siva, TRAIL, RANKL, TWEAK, APRIL, NGF, BDNF, NT-3, and EDA-A2.
12. An adenovirus according to any one of claims 1 to ~~4410~~10, wherein the encoded cytokine is independently selected from TNF-C, OX40l, CD154, FasL, CD70, CD153, 4-1BB ligand, and EDA-A.
13. An adenovirus according to ~~any one of claims 1 to 1210~~10, wherein the cytokine is independently selected from the group comprising IL-2, IFN-alpha, IFN-beta, IFN-gamma, Flt3 ligand, GM-CSF, IL-15, and IL-12.
14. An adenovirus according to ~~any one of claims 1 to 138~~13, wherein at least one further transgene encodes a chemokine.
15. An adenovirus according to claim 14, wherein the chemokine is independently selected from the group comprising MIP-1 alpha, RANTES, IL-8, CCL5, CCL17, CCL20, CCL22, CXCL9, CXCL10, CXCL11, CXCL13, CXCL12, CCL2, CCL19 and CCL21.
16. An adenovirus according to claim 15, wherein the chemokine encoded is MIP-1 alpha.
17. An adenovirus according to any one of claims 1 to 16, wherein the virus comprises transgenes encoding a cytokine and chemokine combination selected from i) MIP-1 α and Flt3, and ii) MIP-1 α and IFN α .
18. An adenovirus according to any one of claims 1 to 17, wherein the anti-CD3 antibody or binding fragment has at least the binding domain comprising a VH and a VL regions from muromonab-CD3 (OKT3), otelexizumab, teplizumab or visilizumab.
19. An adenovirus according to claim 18, wherein the virus comprises SEQ ID NO: 117.

20. An adenovirus according to any one of claims 1 to 19, wherein the virus encodes high efficiency self-cleavage 2A peptides with different DNA sequences to generate multiple proteins or peptides by post-translational modification of an encoded polypeptide.
21. A replication capable group B oncolytic adenovirus according to any one of claims 1 to 20, for use in treatment.

22. Use of a replication capable group B oncolytic adenovirus according to any one of claims 1 to 20, in the manufacture of a medicament for the treatment of cancer.