

Claims

1. An Ad5 serotype adenovirus characterised by the modifications comprising:
 - a) at least one of I421G, T423N, E424S, E450Q or L426Y point mutation(s) in the hexon hypervariable region 7 (HVR7 mutation) wherein said mutation prevents virus binding with coagulation factor 10 (FX);
 - b) at least one of S408E or P409A point mutation(s) in the fiber knob region AB loop (KO1 mutation) wherein said mutation prevents virus binding with the coxsackie and adenovirus receptor (CAR); and
 - c) at least one of D342E or D342A point mutation(s) in the penton integrin binding motif Arg-Gly-Asp (RGD) wherein said mutation prevents virus binding with $\alpha_V\beta_3/\alpha_V\beta_5$ integrin.
2. The adenovirus according to claim 1 wherein said HVR7 mutation comprises or consists of at least one of the following point mutations: I421G, T423N, E424S, and L426Y.
3. The adenovirus according to any preceding claim wherein said KO1 mutation comprises or consists of S408E and P409A point mutations.
4. The adenovirus according to any preceding claim wherein said RGD mutation is D342E, to produce RGE.
5. The adenovirus according to any preceding claim wherein said adenovirus is further modified to include at least one cancer targetting modification or sequence that selectively targets tumour cells.
6. The adenovirus according to claim 5 wherein said adenovirus comprises at least one NGR (containing) peptide motif to bind aminopeptidase N wherein said NGR is in the HI loop of the adenoviral fiber protein; or at least one YSA (containing) peptide motif to bind to pan-cancer marker EphA2, wherein said YSA is in the chimeric fiber, or at least one cancer targeting antibody or at least one growth factor antibody or at least one matrix degrading enzyme.
7. The adenovirus according to claim 5 wherein said cancer targetting modification comprises insertion or expression of an $\alpha_V\beta_6$ integrin binding peptide or the A20 peptide sequence NAVPNLRGDLQVLAQKVART (SEQ ID NO: 1) into or by the virus.

8. The adenovirus according to claim 7 wherein said A20 peptide sequence is inserted into or expressed in the viral fiber knob HI loop.

9. The adenovirus according to any preceding claim wherein said adenovirus (Ad5.3D.A20) comprises:

a) at least one of I421G, T423N, E424S, E450Q or L426Y point mutation(s) in the hexon hypervariable region 7 (HVR7 mutation) wherein said mutation prevents virus binding with coagulation factor 10 (FX);

b) at least one of S408E or P409A point mutation(s) in the fiber knob region AB loop (KO1 mutation) wherein said mutation prevents virus binding with the coxsackie and adenovirus receptor (CAR);

c) at least one of D342E or D342A point mutation(s) in the penton integrin binding motif Arg-Gly-Asp (RGD) wherein said mutation prevents virus binding with $\alpha_v\beta_3/\alpha_v\beta_5$ integrin; and

d) insertion or expression of the A20 peptide sequence NAVPNLRGDLQVLAQKVART (SEQ ID NO: 1) in the viral fiber knob HI loop.

10. The adenovirus according to claim 8 wherein modified adenovirus (Ad5.3D.A20) comprises:

a) I421G, T423N, E424S and L426Y point mutations in the hexon hypervariable region 7 (HVR7 mutation) wherein said mutation prevents virus binding with coagulation factor 10 (FX);

b) S408E and P409A point mutations in the fiber knob region AB loop (KO1 mutation) wherein said mutation prevents virus binding with the coxsackie and adenovirus receptor (CAR);

c) D342E point mutation in the penton integrin binding motif Arg-Gly-Asp (RGD) to produce RGE mutation wherein said mutation prevents virus binding with $\alpha_v\beta_3/\alpha_v\beta_5$ integrin; and

d) insertion or expression of the A20 peptide sequence NAVPNLRGDLQVLAQKVART (SEQ ID NO: 1) in the viral fiber knob HI loop.

11. The adenovirus according to any preceding claim wherein the adenovirus is further modified to include at least one transgene encoding a therapeutic molecule or agent.

12. The adenovirus according to any preceding claim wherein said adenovirus is further modified to include a 24-base pair deletion d1922–947 (Δ 24 mutation) in the E1A gene to restrict viral replication to pRB-defective cells.
- 5 13. The adenovirus according to any preceding claim wherein said adenovirus is further modified to include a single adenine base addition at position 445 within the endoplasmic reticulum (ER) retention domain in E3/19K (T1 mutation) for enhanced oncolytic potency.
- 10 14. An adenovirus according to any preceding claim for use as a medicament.
15. An adenovirus according to any one of claims 1-13 for use in the treatment of cancer.
- 15 16. The adenovirus according to claim 15 wherein said cancer is selected from the group comprising: nasopharyngeal cancer, synovial cancer, hepatocellular cancer, renal cancer, cancer of connective tissues, melanoma, lung cancer, bowel cancer, colon cancer, rectal cancer, colorectal cancer, brain cancer, throat cancer, oral cancer, liver cancer, bone cancer, pancreatic cancer, choriocarcinoma, gastrinoma, pheochromocytoma, prolactinoma, T-cell leukemia/lymphoma, neuroma, von Hippel-Lindau disease, Zollinger-Ellison syndrome, adrenal cancer, anal cancer, bile duct cancer, bladder cancer, ureter cancer, brain cancer, oligodendroglioma, neuroblastoma, meningioma, spinal cord tumor, bone cancer, osteochondroma, chondrosarcoma, Ewing's sarcoma, cancer of unknown primary site, carcinoid, carcinoid of gastrointestinal tract, fibrosarcoma, breast cancer, Paget's disease, 20 cervical cancer, colorectal cancer, rectal cancer, esophagus cancer, gall bladder cancer, head cancer, eye cancer, neck cancer, kidney cancer, Wilms' tumor, liver cancer, Kaposi's sarcoma, prostate cancer, lung cancer, testicular cancer, Hodgkin's disease, non-Hodgkin's lymphoma, skin cancer, mesothelioma, multiple myeloma, ovarian cancer, endocrine pancreatic cancer, glucagonoma, pancreatic cancer, 25 parathyroid cancer, penis cancer, pituitary cancer, soft tissue sarcoma, retinoblastoma, small intestine cancer, stomach cancer, thymus cancer, thyroid cancer, trophoblastic cancer, hydatidiform mole, uterine cancer, endometrial cancer, vagina cancer, vulva cancer, acoustic neuroma, mycosis fungoides, insulinoma, carcinoid syndrome, somatostatinoma, gum cancer, heart cancer, lip cancer, 30 meninges cancer, mouth cancer, nerve cancer, palate cancer, parotid gland cancer,
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peritoneum cancer, pharynx cancer, cancer of the larynx, pleural cancer, salivary gland cancer, tongue cancer and tonsil cancer.

5 17. A pharmaceutical composition comprising the adenovirus according to any one of claims 1-13 and a pharmaceutically acceptable carrier, adjuvant, diluent or excipient.

18. A method for preparing a pharmaceutical composition comprising bringing the adenovirus according to any one of claims 1-13 in conjunction or association with a pharmaceutically or veterinary acceptable carrier or vehicle.

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