

Anti-viral immunity has been considered restrictive for virotherapy approaches including oncolytic adenoviruses. One embodiment of anti-viral immunity is anti-viral T-cells. However, the present disclosure surprisingly reveals that when an oncolytic adenovirus is used for production of a BiTE at the tumor, anti-viral T-cells can be retargeted against the tumor. This effect amplifies during treatment, as replication of the oncolytic virus results in further anti-viral T-cells, which then are also targeted towards the tumor through the BiTE produced by the virus (Figure 7).

In one embodiment, the present disclosure relates to enhancement of T-cell therapy with an oncolytic adenovirus coding for a BiTE. Oncolytic adenovirus is the optimal platform for using a BiTE for enhancing T-cell therapy, because of the unexpected synergy between the anti-immunosuppressive effects of oncolysis and BiTE expression at the tumor.

The present specification describes construction of recombinant adenoviral vectors, methods related to the adenoviral vectors, and their different uses. Furthermore, the adenoviral vectors of the present disclosure coding for T-cell engagers may be combined with adoptive cell therapeutics for cancer treatment.

Advantages of the present disclosure are achieved by a method of treating malignancy, comprising administering an effective amount of an adenoviral vector of the present disclosure (e.g. alone or together with TILs) to a patient afflicted with cancer to cause regression or stabilization of the cancer.

The present disclosure relates to an oncolytic adenoviral vector comprising

a deletion of a nucleic acid sequence in the E3 region, and
a nucleic acid sequence encoding a bispecific monoclonal antibody in the place of the deleted nucleic acid sequence in E3 region.

In one aspect, there is provided an oncolytic adenoviral vector comprising

a deletion of a nucleic acid sequence in the E3 region, and
a nucleic acid sequence encoding a bispecific monoclonal antibody in the place of the deleted nucleic acid sequence in E3 region,

wherein the bispecific monoclonal antibody comprises a single chain variable fragment (scFv) specific for a cell surface molecule on an immunological effector cell and a scFv specific for a tumor antigen, wherein the backbone of the vector is adenovirus serotype 5 (Ad5) nucleic acid backbone and the vector further comprises an Ad3 fiber knob.

CLAIMS

1. An oncolytic adenoviral vector comprising
a deletion of a nucleic acid sequence in the E3 region, and
5 a nucleic acid sequence encoding a bispecific monoclonal antibody
in the place of the deleted nucleic acid sequence in E3 region, wherein the
bispecific monoclonal antibody comprises a single chain variable fragment
(scFv) specific for a cell surface molecule on an immunological effector cell
and a scFv specific for a tumor antigen, wherein the backbone of the vector is
10 adenovirus serotype 5 (Ad5) nucleic acid backbone and the vector further
comprises an Ad3 fiber knob.
2. The oncolytic adenoviral vector according to claim 1, wherein the
vector further comprises E2F1 promoter for tumor specific expression of E1A.
3. The oncolytic adenoviral vector according to any one of the previ-
15 ous claims, wherein the vector further comprises a 24 bp deletion (D24) in the
Rb binding constant region 2 of adenoviral E1.
4. The oncolytic adenoviral vector according to any one of the previ-
ous claims, wherein the deletion of a nucleic acid sequence in the E3 region is
a deletion of viral *gp19k* and *6.7k* reading frames.
- 20 5. The oncolytic adenoviral vector according to any one of the previ-
ous claims, wherein the vector comprises:
 - 1) E2F1 promoter for tumor specific expression of E1A
 - 2) a 24 bp deletion (D24) in the Rb binding constant region 2 of ad-
enoviral E1;
 - 25 3) a nucleic acid sequence deletion of viral *gp19k* and *6.7k* reading
frames; and
 - 4) a nucleic acid sequence encoding a bipartite molecule comprising
a single chain variable fragment (scFv) specific for a cell surface molecule and
a scFv specific for a tumor antigen in the place of the deleted nucleic acid se-
30 quence as defined in point 3).

6. The oncolytic adenoviral vector according to any one of the previous claims, wherein the effector cells are T lymphocytes.

7. The oncolytic adenoviral vector according to any one of the previous claims, wherein the tumor antigen is selected from Table 1 or from the group consisting of mesothelin, EpCAM1 and MUC1.

8. The oncolytic adenoviral vector according to any one of the previous claims, wherein the cell surface molecule is selected from CD3, CD8 and CD4.

9. The oncolytic adenoviral vector according to any one of the previous claims, wherein the tumor antigen is mesothelin and the cell surface molecule is CD3; the tumor antigen is EpCAM1 and the cell surface molecule is CD3; or the tumor antigen is MUC1 and the cell surface molecule is CD3.

10. The oncolytic adenoviral vector according to any one of the previous claims, wherein the oncolytic adenoviral vector codes for two or more transgenes.

11. The oncolytic adenoviral vector according to any one of the previous claims, further comprising IL-2, TNFalpha or CD40L transgene.

12. A pharmaceutical composition comprising an oncolytic adenoviral vector according to any one of claims 1-11.

13. An oncolytic adenoviral vector according to any one of claims 1-11 for use in treatment of cancer.

14. An oncolytic adenoviral vector for use according to claim 13 together with an adoptive cell therapeutic composition, wherein the administration(s) of the oncolytic adenoviral vector and the adoptive cell therapeutic composition to a subject is(are) to be conducted simultaneously or consecutively, in any order.

15. Use of an oncolytic adenoviral vector according to any one of claims 1-11 in the manufacture of a medicament for treating cancer in a subject.

16. The use according to claim 15, wherein the medicament is to be administered with an adoptive cell therapeutic composition to the subject.

17. The use of the oncolytic adenoviral vector for use according to claim 14 or 16, wherein the adoptive cell therapeutic composition comprises a cell type selected from a group consisting of a tumor infiltrating lymphocyte (TIL), T-cell receptor modified lymphocytes and chimeric antigen receptor modified lymphocytes.

18. The use or the oncolytic adenoviral vector for use according to any one of claims 14 or 16-17, wherein the adoptive cell therapeutic composition comprises a cell type selected from a group consisting of T-cells, CD8+ cells, CD4+ cells, NK-cells, delta-gamma T-cells, regulatory T-cells, and peripheral blood mononuclear cells.

19. The use or the oncolytic adenoviral vector for use according to any one of claims 14 or 16-18, wherein the adoptive cell therapeutic composition comprises T-cells.

20. The use or the oncolytic adenoviral vector for use according to any one of claims 13-19, wherein the cancer is selected from a group consisting of 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, neuroroma, 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, 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, oral cancer, skin cancer, mesothelioma, multiple myeloma, ovarian cancer, endocrine pancreatic cancer, glucagonoma, pancreatic cancer, 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, meninges cancer, mouth cancer, nerve cancer, palate cancer, parotid gland cancer, peritoneum cancer, pharynx cancer, pleural cancer, salivary gland cancer, tongue cancer and tonsil cancer.

21. The use according to any one of claims 16-20, wherein the administration(s) of oncolytic viral vectors and an adoptive cell therapeutic composition to a subject is(are) to be conducted simultaneously or consecutively, in any order.

5 22. The use or the oncolytic adenoviral vector for use according to any one of claims 13-21, wherein the medicament or oncolytic adenoviral vector is to be administered with concurrent or sequential radiotherapy, monoclonal antibodies, chemotherapy or other anti-cancer drugs or interventions to a subject.

10 23. The oncolytic adenoviral vector according to any one of claims 1-11 for use in increasing the efficacy of adoptive cell therapy in a subject.

 24. Use of an oncolytic adenoviral vector according to any one of claims 1-11 in the manufacture of a medicament for increasing the efficacy of adoptive cell therapy in a subject in need thereof, wherein the subject has been
15 administered or is to be administered with adoptive cell therapy.