mechanisms of action and factors that influence the efficacy of the viruses, there is still a need to identify pathways that determine the overall response to virotherapy. In clinical trials, oncolytic viruses have demonstrated a favorable safety profile and promising efficacy.

WO2014170389 relates to oncolytic adenoviral vectors alone or together with therapeutic compositions for therapeutic uses and therapeutic methods for cancer. For instance, a separate administration of adoptive cell therapeutic composition and oncolytic adenoviral vectors is disclosed. Adoptive cell therapiess are a potent approach for treating cancer but also for treating other diseases such as infections and graft versus host disease. Adoptive cell transfer is the passive transfer of *ex vivo* grown cells, most commonly immune-derived cells, into a host with the goal of transferring the immunologic functionality and characteristics of the transplant. WO2014170389 also discloses nucleic acid sequences of oncolytic adenoviral vectors.

WO2016146894 discloses an oncolytic adenoviral vector encoding a bispecific monoclonal antibody.

EP 3858369 relates to a cancer therapy by combination use of an oncolytic vaccinia virus and an immune checkpoint inhibitor. The virus encodes two interleukins, IL-7 and IL-12, and is administered with an immune checkpoint inhibitor to further improve its antitumoral effect.

There is still room for improving oncolytic viral treatments for cancer patients, especially in patients with a significant metastasis burden. Further characterization of pathways related to the activity of oncolytic viruses could reveal potential targets for improving the efficacy of virotherapy. Therefore, the efficacy of oncolytic viral vectors, either alone or together with other therapies, can still be improved. The present invention provides efficient tools and methods for cancer therapeutics by utilizing specific viral vectors, with e.g. adoptive cell therapies and/or immune checkpoint inhibitors.

SUMMARY

The aim of this disclosure is to overcome the limitations seen in the use of oncolytic adenoviruses in cancer treatments. Accordingly, an object of the present disclosure is to provide simple methods and tools for overcoming the problems of inefficient, unsafe and unpredictable cancer therapies. In examples of the disclosure, novel approaches and means for cancer therapy are thus provided. The objects of the disclosure are achieved by specific viral vectors, methods and arrangements, which are characterized by what is stated in the independent claims. The specific examples of the disclosure are disclosed in the dependent claims.

Specifically, the present disclosure provides an oncolytic adenoviral vector comprising a nucleic acid sequence encoding an interleukin 7 (IL-7) polypeptide as a transgene. In one aspect, the present disclosure provides an oncolytic adenoviral vector comprising a nucleic acid sequence encoding an interleukin 7 (IL-7) polypeptide or a variant thereof as a transgene, wherein a backbone of the oncolytic adenoviral vector is an adenovirus serotype 5 (Ad5) backbone with the fiber knob of adenovirus serotype 3 (Ad3). In another aspect, the present disclosure also provides a pharmaceutical composition comprising said oncolytic vector and at least one of the following: physiologically acceptable carriers, buffers, excipients, adjuvants, additives, antiseptics, preservatives, filling, stabilising and/or thickening agents. In a further aspect, the present disclosure provides a use of the oncolytic adenoviral vector as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer or tumor, preferably a solid tumor. In a further aspect, the present disclosure provides the oncolytic adenoviral vector as described herein or the pharmaceutical composition as described herein for use in therapy. A particular aim of the present disclosure is to provide said oncolytic viral vector or pharmaceutical composition for use in the treatment of cancer or tumor, preferably a solid tumor.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Ad5/3-E2F-d24-IL7 functionality *in vitro*. (A) A schematic presentation of chimeric 5/3 oncolytic adenovirus containing an E2F promoter; 24-base-pair deletion in E1A; human IL7 transgene inserted in the E3 region; and an Ad3 serotype knob in the Ad5 fiber. (B) Relative human cancer cell viability after addition of 1, 10, 100 or 1000 virus particles (VP)/cell at day 4 after infection in epithelial adenocarcinoma (A549) and rhabdomyosarcoma (RD). No major differences between Ad5/3-E2F-d24-IL7 and Ad5/3-E2F-d24 tumor cell killing ability were observed, thus indicating that the presence of the IL7 transgene does not reduce the oncolytic potency of Ad5/3-E2F-d24-IL7 in human cancer cells. Statistical significance compared to mock is represented as *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001. (C) Relative hamster cancer cell viability after addition of 100, 1000, 5000 or 10000 VP/cell at day 5 after infection in hamster lung cancer (HT100) and hamster leiomyosarcoma (DDT1-MF2) or, at day 8 after infection in hamster pancreatic cancer (HapT1). There were no major differences between Ad5/3-E2F-d24-IL7 and Ad5/3-E2F-d24 cell killing ability, thus indicating that presence of IL7 transgene does not reduce the oncolytic potency of Ad5/3-E2F-d24-IL7 in hamster cancer cells. Statistical significance compared to mock is represented as **p<0.01, ***p<0.001, and ****p<0.0001. (D) IL7 expression

was analysed from the transfected cancer cells. IL7 concentration was measured in cell supernatants harvested on day 3 after 1000 VP/cell infection (A549 and RD) or 10000 VP/cell infection (HT100 and DDT1-MF2). The analysis showed that Ad5/3-E2F-d24-hIL7 is able to induce the expression of IL7 in multiple cancer cell lines. (E) IL7 bioactivity measured after 1000 VP/cell infection of A549 cell line. The supernatant was filtered, diluted with growth media and applied on IL7-dependent murine cell line 2E8. Recombinant murine IL7 (rmIL7) and murine IL7 (rhIL7) were used as controls in 20 ng/ml. These data indicates that the IL-7 produced by cancer cells upon infection with Ad5/3-E2F-d24-IL7 is functional. *In vitro* data sets performed in triplicates and all data are shown as means±SEM.

CLAIMS

1. An oncolytic adenoviral vector comprising a nucleic acid sequence encoding an interleukin 7 (IL-7) polypeptide or a variant thereof as a transgene, wherein a backbone of the oncolytic adenoviral vector is an adenovirus serotype 5 (Ad5) backbone with the fiber knob of adenovirus serotype 3 (Ad3).

2. The oncolytic adenoviral vector according to claim 1, wherein said nucleic acid sequence encoding an interleukin 7 (IL-7) polypeptide or a variant thereof is in the place of a deleted nucleic acid sequence in the E3 region of said oncolytic adenoviral vector.

3. The oncolytic adenoviral vector according to claim 2, wherein the deletion of a nucleic acid sequence in the E3 region is a deletion of viral *gp19k* and *6.7k* reading frames.

4. The oncolytic adenoviral vector according to any one of claims 1-3, wherein the vector comprises a 24 bp deletion (Δ24) in the adenoviral E1 sequence of said oncolytic adenoviral vector.

5. The oncolytic adenoviral vector according to any one of claims 1-4, wherein the vector comprises Ad5/3-E2F-d24 backbone.

6. The oncolytic adenoviral vector according to claim 5, wherein the vector has the structure Ad5/3-E2F-d24-IL-7.

7. The oncolytic adenoviral vector according to any one of claims 1-6, wherein the vector comprises nucleic acid sequence encoding a further transgene.

8. The oncolytic adenoviral vector according to claim 7, wherein the further transgene is encoding a cytokine.

9. The oncolytic adenoviral vector according to claim 8, wherein the cytokine is selected from the list consisting of: TNFalpha, interferon alpha, interferon beta, interferon gamma, complement C5a, CD40L, IL-12, IL-23, IL-21, IL-15, IL-17, IL-18, IL-2, CCL1, CCL11, CCL12, CCL13, CCL14-1, CCL14-2, CCL14-3, CCL15-1, CCL15-2, CCL16, CCL17, CCL18, CCL19, CCL2, CCL20, CCL21, CCL22, CCL23-1, CCL23-2, CCL24, CCL25-1, CCL25-2, CCL26, CCL27, CCL28, CCL3, CCL3L1, CCL4, CCL4L1, CCL5 (=RANTES), CCL6, CCL7, CCL8, CCL9, CCR10, CCR2,

CCR5, CCR6, CCR7, CCR8, CCRL1, CCRL2, CX3CL1, CX3CR, CXCL1, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL9, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7 and XCL2.

10. The oncolytic adenoviral vector according to claim 9, wherein the cytokine is TNFalpha or IL-15.

11. A pharmaceutical composition comprising an oncolytic adenoviral vector according to any one of claims 1-10 and at least one of the following: physiologically acceptable carriers, buffers, excipients, adjuvants, additives, antiseptics, preservatives, filling, stabilising and/or thickening agents.

12. Use of the oncolytic adenoviral vector according to any one of claims 1-10 or the pharmaceutical composition according to claim 11 in the manufacture of a medicament for treating cancer or tumor, preferably a solid tumor.

13. The use according to claim 12, wherein the cancer or tumor 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, pheo-chromocytoma, prolactinoma, T-cell leukemia/lymphoma, neuroma, von Hippel-Lindau disease, Zollinger-Ellison syndrome, adrenal cancer, anal cancer, bile duct cancer, bladder cancer, ureter 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, esophagus cancer, gall bladder cancer, head cancer, eye cancer, neck cancer, kidney cancer, Wilms' tumor, Kaposi's sarcoma, prostate cancer, testicular cancer, Hodgkin's disease, non-Hodgkin's lymphoma, skin cancer, mesothelioma, multiple myeloma, ovarian cancer, endocrine pancreatic cancer, glucagonoma, 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.

14. The use according to claim 12 or 13 together with an adoptive cell therapeutic composition.

15. The use according to any of the claims 12-14 together with an immune checkpoint inhibitor.

16. The use according to claim 15, wherein said immune checkpoint inhibitor selectively binds to PD-L1 or PD1.

17. The use according to claim 16, wherein the immune checkpoint inhibitor selectively binding to PD-L1 or PD-1 is selected from the group consisting of: BMS-936559, LY3300054, atezolizumab, durvalumab, avelumab, envafolimab, cosibelimab, pembrolizumab, nivolumab, cemiplimab, sintilimab, tislelizumab, spartalizumab, toripalimab, dostarlimab, INCMGA00012 and AMP-514.

18. The use according to any one of claims 12-17 together with radiotherapy, monoclonal antibodies, chemotherapy, small molecular inhibitors, hormonal therapy or other anti-cancer drugs or interventions to a subject.

19. The use according to any one of claims 12-17 together with an immune checkpoint inhibitor, wherein said adenoviral vector has the structure Ad5/3-E2F-d24-IL-7, and wherein said immune checkpoint inhibitor selectively binds to PD-L1 or PD-1.

20. The oncolytic adenoviral vector according to any one of claims 1-10 or the pharmaceutical composition according to claim 11 for use in therapy.