

VECTOR FOR CANCER TREATMENT

Field of Invention

The present invention relates to vectors which are capable of eliciting an inflating memory CD8+ T cell response. These vectors which elicit an inflating memory CD8+ T cell response are suitable for use in the treatment of cancer. The present invention also relates to methods for making the vectors and methods for inducing an inflating memory CD8+ T cell response.

Introduction

Anti-cancer strategies aiming to activate the CD8 T cell arm of immunity have shown remarkable efficacy. There is considerable overlap between the requirements for a good CD8 T cell response against a chronic infection with that against cancer – they have to be durable, functional, sustained and able to home to the correct site and resist exhaustion owing to prolonged TCR stimulation.

Epitope based cancer vaccines are one strategy that has been used to activate a T cell response to specific tumour associated antigens. Initially, peptide-based single epitope vaccines were used, however these provided poor clinical responses as they did not adequately active the innate immune system. To enhance the immune activation multi-peptide vaccines were developed, wherein multiple epitopes were administered together.

This approach of administering multiple epitopes has also been performed using adenoviral vectors. By using an adenoviral vector, which has the capacity to encode large transgenes, multiple epitopes can be encoded and delivered as a concatemer (Bei and Scardino., J Biomed Biotechnol 2010;2010:102758). Alternatively, full length antigens can be encoded and delivered. However, there is still a need to improve immune activation against cancer cells.

Summary

In one aspect, the present disclosure relates to a viral vector comprising a nucleotide sequence encoding a polypeptide comprising a single cancer specific CD8+ T cell epitope, wherein the single cancer specific CD8+ T cell epitope is not a viral immunogen associated with a virally driven cancer, wherein the polypeptide encoded by the nucleotide sequence consists of 8 to 15 amino acids, wherein the vector is an adenoviral vector, wherein the vector does not comprise a nucleic acid encoding any other cancer specific T cell epitopes other than the single cancer specific CD8+ T cell epitope, and wherein the viral vector induces an inflating memory CD8+ T cell response and inhibits tumor growth when administered to a subject.

In another aspect, disclosed herein is a composition, comprising at least two viral vectors wherein each of the at least two viral vectors is a viral vector disclosed herein and wherein each of the at least two viral vectors encodes a different single cancer specific CD8+ T cell epitope

- 5 In another aspect, disclosed herein is a pharmaceutical composition comprising the viral vector disclosed herein and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

In yet another aspect, disclosed herein is a host cell, comprising the viral vector disclosed herein, the composition disclosed herein, or the pharmaceutical composition disclosed herein.

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In yet another aspect, disclosed herein is the use of a viral vector disclosed herein, the composition disclosed herein, the pharmaceutical composition disclosed herein, or the host cell disclosed herein, in the manufacture of a medicament for the treatment of a cancer, in a subject in need thereof.

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In yet another aspect, disclosed herein is the use of a viral vector disclosed herein, the composition disclosed herein, the pharmaceutical composition disclosed herein, or the host cell disclosed herein, in the manufacture of a medicament for treating cancer by inducing an inflating memory CD8+ T cell response in a subject in need thereof.

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In yet another aspect, disclosed herein is the use of a viral vector disclosed herein, the composition disclosed herein, the pharmaceutical composition disclosed herein, or the host cell disclosed herein in the manufacture of a medicament for treating cancer by inducing an inflating memory CD8+ T cell response in a subject in need thereof wherein the inflating memory CD8+

- 25 T cell response comprises production of CD8+/CX3CR1+/KLRG-1+ T cells.

In yet another aspect, disclosed herein is a viral vector disclosed herein, the composition of claim disclosed herein, the pharmaceutical composition disclosed herein, or the host cell disclosed herein for use in therapy.

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In yet another aspect, disclosed herein is the use of a composition disclosed herein in the manufacture of a medicament for the treatment of a cancer, in a subject in need thereof wherein each of the at least two viral vectors are present in the medicament at a lower amount compared to a vector amount present in a medicament comprising a single vector of any one of claims 1-
35 14, thereby treating the cancer in the subject, optionally wherein the cancer is selected from colorectal cancer, prostate cancer, oesophageal cancer, liver cancer, renal cancer, lung cancer, breast cancer, pancreatic cancer, brain cancer, hepatocellular cancer, lymphoma, leukaemia, gastric cancer, cervical cancer, ovarian cancer, thyroid cancer, melanoma, carcinoma, head and neck cancer, skin cancer, nasopharyngeal

cancer, Epstein Barr driven cancers, Human Papilloma virus driven cancers, or soft tissue sarcoma.

5 The present disclosure arises from the surprising finding that a vector encoding a single cancer specific CD8+ and/or CD4+ T cell epitope, referred to herein as a minigene vector, can induce an inflating memory CD8+ T cell response. Memory inflation describes the longitudinal development of stable, expanded CD8+ T cell memory pools, wherein the cells have distinct phenotype and function. This inflating memory response results in a long-lived pool of epitope specific T cells which remain abundant and functional even beyond the acute phase of infection
10 (Klerner et al., Immunol Rev 2018 283(1):99-111). It is believed that the features of inflating memory cells, may result in an enhanced anti-tumour response.

The present inventors have developed a vaccine platform based on the replication-deficient AdHu5 adenoviral vector backbone in which only the CD8+ T cell epitope of interest is inserted.

CLAIMS

1. A viral vector comprising a nucleotide sequence encoding a polypeptide comprising a single cancer specific CD8+ T cell epitope, wherein the single cancer specific CD8+ T cell epitope is not a viral immunogen associated with a virally driven cancer, wherein the polypeptide encoded by the nucleotide sequence consists of 8 to 15 amino acids, wherein the vector is an adenoviral vector, wherein the vector does not comprise a nucleic acid encoding any other cancer specific T cell epitopes other than the single cancer specific CD8+ T cell epitope, and wherein the viral vector induces an inflating memory CD8+ T cell response and inhibits tumor growth when administered to a subject.
2. The viral vector according to claim 1, wherein the inflating memory CD8+ T cell response comprises production of CD8+/CX3CR1+/KLRG-1+/CD44+/CD62L- T cells.
3. The viral vector according to claim 1 or 2, wherein the nucleotide sequence encoding the cancer specific CD8+ T cell epitope consists of from 12 to 45 nucleotide base pairs in length optionally wherein the nucleotide sequence encoding the cancer specific CD8+ T cell epitope comprises from 24 to 45 nucleotide base pairs in length.
4. The viral vector according to any of claims 1 to 3, wherein the cancer specific CD8+ T cell epitope is a tumour associated antigen that is overexpressed in a cancer cell, or an antigen that is mutated in a cancer cell.
5. The viral vector according to any of claims 1 to 4, wherein the nucleotide sequence encoding the cancer specific CD8+ T cell epitope encodes a polypeptide comprising the cancer specific CD8+ T cell epitope, and wherein the polypeptide comprising the cancer specific CD8+ T cell epitope is not processed by antigen presenting cells.
6. The viral vector according to any of claims 1 to 5, wherein the inflating memory CD8+ T cell response comprises
 - a) production of CD8+/CX3CR1+/KLRG-1+ T cells that have sustained expression of Tbx21 and/or E2f2;
 - b) production of CD8+/CX3CR1+/KLRG-1+ T cells that have low expression of Eomes; and/or
 - c) production of: CD8+/CX3CR1+/KLRG-1+ T cells that have low expression of PD-1, Tim-3, and/or Lag-3.

7. The viral vector according to any of claims 1 to 6, wherein the inflating memory CD8⁺ T cell response is capable of controlling tumour growth in the subject greater than 50 days after the pharmaceutical composition is administered.

8. The viral vector according to any of claims 2 to 7, wherein

a) the CD8⁺/CX3CR1⁺/KLRG-1⁺ T cells form 2 percent to 20 percent of total circulating CD8⁺ T cells in the subject; and/or

b) the CD8⁺/CX3CR1⁺/KLRG-1⁺ T cells maintain a memory effector phenotype for at least 30 days.

9. The viral vector according to any of claims 1 to 8, wherein the T cell epitope is derived from a tumour associated antigen selected from the group consisting of TRP-1, CEA, TAG-72, 9D7, Ep-CAM, EphA3, telomerase, mesothelin, SAP-1 Melan-A/MART-1, tyrosinase, CLPP, cyclin-A1, cyclin-B1 MAGE-A1, MAGE-C1, MAGE-C2, SSX2, XAGE1b/GAGED2a, CD45, glypican-3, IGF2B3, kallikrein-4, KIF20A, lengsin, meloe, MUC5AC, survivin, PRAME, SSX-2, NY-ESO-1/LAGE1, gp70, MC1R, TRP-1/-2, β -catenin, BRCA1/2, CDK4, and foetal protein SIM1.

10. The viral vector according to any of claims 1 to 9, wherein the viral vector comprises a sequence as set forth in SEQ ID NO: 13 and a sequence as set forth in SEQ ID NO: 14.

11. The viral vector according to any of claims 1 to 10, wherein the viral vector further comprises a sequence as set forth in SEQ ID NO: 15 and a sequence as set forth in SEQ ID NO: 33.

12. The viral vector according to any of claims 1 to 11, wherein the cancer specific CD8⁺ T cell epitope is specific for colorectal cancer, prostate cancer, oesophageal cancer, liver cancer, renal cancer, lung cancer, breast cancer, , pancreatic cancer, brain cancer, hepatocellular cancer, lymphoma, leukaemia, gastric cancer, cervical cancer, ovarian cancer, thyroid cancer, melanoma, carcinoma, head and neck cancer, skin cancer, nasopharyngeal cancer, Epstein Barr driven cancers, Human Papilloma virus driven cancers or soft tissue sarcoma.

13. The viral vector according to any of claims 1 to 12, wherein the viral vector

a) is human serotype 5 (AdHu5);

b) is human serotype 2;

c) comprises a CMV promoter;

d) comprises a TATA box; and/or

e) lacks a sequence encoding the E1 and E3 proteins.

14. The viral vector according to any of claims 1 to 13, wherein the vector is a replication-deficient AdHu5 adenoviral vector.

15. A composition, comprising at least two viral vectors wherein each of the at least two viral vectors is a viral vector according to any of claims 1 to 14 and wherein each of the at least two viral vectors encodes a different single cancer specific CD8+ T cell epitope.

16. A pharmaceutical composition comprising the viral vector according to any of claims 1-14 and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

17. A host cell, comprising the viral vector according to any of claims 1 to 14, the composition of claim 15, or the pharmaceutical composition according to claim 16.

18. Use of a viral vector according to any of claims 1 to 14, the composition of claim 15, the pharmaceutical composition of claim 16, or the host cell of claim 17, in the manufacture of a medicament for the treatment of a cancer, in a subject in need thereof.

19. Use of a viral vector according to any of claims 1 to 14, the composition of claim 15, the pharmaceutical composition of claim 16, or the host cell of claim 17, in the manufacture of a medicament for treating cancer by inducing an inflating memory CD8+ T cell response in a subject in need thereof.

20. Use of a viral vector according to any of claims 1 to 14, the composition of claim 15, the pharmaceutical composition of claim 16, or the host cell of claim 17 in the manufacture of a medicament for treating cancer by inducing an inflating memory CD8+ T cell response in a subject in need thereof wherein the inflating memory CD8+ T cell response comprises production of CD8+/CX3CR1+/KLRG-1+ T cells.

21. Use of any one of claims 18 to 20, wherein,

a) the vector, the composition, the pharmaceutical composition or the host cell is to be administered as a single dose; or

b) the vector, the composition, the pharmaceutical composition or the host cell is to be administered as multiple doses.

22. The use of any of claims 18-21, wherein,

a) the vector, the composition, the pharmaceutical composition or the host cell is to be administered intravenously or intramuscularly;

b) the vector, the composition, the pharmaceutical composition or the host cell is to be administered prophylactically;

c) the vector, the composition, the pharmaceutical composition or the host cell is to be administered therapeutically;

d) the vector, the composition, the pharmaceutical composition or the host cell is to be administered in combination with a therapy or therapeutic agent; and/or

e) the vector, the composition, the pharmaceutical composition or the host cell is to be administered in combination with an immunomodulatory molecule either separately, sequentially or simultaneously.

23. Use of claim 22, wherein the immunomodulatory molecule is an immune checkpoint inhibitor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-L2, TIM3, LAG -3, B7-H3, B7-H4, B7-H6, A2aR, BTLA, GAL9 and IDO.

24. Use of claim 19 or 20, wherein the inflating memory CD8⁺ T cell response comprises production of

a) CD8⁺/CX3CR1⁺/KLRG-1⁺/CD44⁺ T cells;

b) CD8⁺/CX3CR1⁺/KLRG-1⁺/CD62L⁻ T cells; or

c) CD8⁺/CX3CR1⁺/KLRG-1⁺/CD44⁺/CD62L⁻ T cells.

25. Use of claim 19 or 20, wherein the inflating memory CD8⁺ T cell response

a) is capable of controlling tumour growth in the subject greater than 50 days after the pharmaceutical composition is administered; and/or

b) comprises production of CD8⁺/CX3CR1⁺/KLRG-1⁺ T cells that

i) have sustained expression of Tbx21 and/or E2f2;

ii) have low expression of Eomes;

iii) have low expression of PD-1, Tim-3, and/or Lag-3;

iv) form 2 percent to 20 percent of total circulating CD8⁺ T cells in the subject; and/or

v) maintain a memory effector phenotype for at least 30 days.

26. Use of claim 18, wherein the cancer is colorectal cancer, prostate cancer, oesophageal cancer, liver cancer, renal cancer, lung cancer, breast cancer, pancreatic cancer, brain cancer, hepatocellular cancer,

lymphoma, leukaemia, gastric cancer, cervical cancer, ovarian cancer, thyroid cancer, melanoma, carcinoma, head and neck cancer, skin cancer, nasopharyngeal cancer, Epstein Barr driven cancers, Human Papilloma virus driven cancers, or soft tissue sarcoma.

27. A viral vector according to any of claims 1 to 14, the composition of claim 15, the pharmaceutical composition of claim 16, or the host cell of claim 17 for use in therapy.

28. Use of a composition of claim 15 in the manufacture of a medicament for the treatment of a cancer, in a subject in need thereof wherein each of the at least two viral vectors are present in the medicament at a lower amount compared to a vector amount present in a medicament comprising a single vector of any one of claims 1-14, thereby treating the cancer in the subject, optionally wherein the cancer is selected from colorectal cancer, prostate cancer, oesophageal cancer, liver cancer, renal cancer, lung cancer, breast cancer, pancreatic cancer, brain cancer, hepatocellular cancer, lymphoma, leukaemia, gastric cancer, cervical cancer, ovarian cancer, thyroid cancer, melanoma, carcinoma, head and neck cancer, skin cancer, nasopharyngeal cancer, Epstein Barr driven cancers, Human Papilloma virus driven cancers, or soft tissue sarcoma.