

# **ALLOGENEIC T-CELL-BASED HIV VACCINE TO INDUCE CELLULAR AND HUMORAL IMMUNITY**

## **CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to U.S. Provisional Application No. 62/862,432, filed June 17, 2019, which is hereby incorporated by reference in their entirety.

## **FIELD OF THE INVENTION**

[0002] Provided herein are methods for treating a patient with human immunodeficiency virus (HIV), comprising administering cellular compositions further comprising recombinant allogeneic cells, such as CD4<sup>+</sup> T cells. The present invention further directs to compositions and methods for making an allogeneic T-cell-based protective HIV vaccine that induces both cellular and humoral immunity.

## **BACKGROUND OF THE INVENTION**

[0003] Significant progress has been made against the HIV epidemic. However, currently there are still 1.7 million new infections per year and 770,000 deaths worldwide. Antiretroviral therapy (ART), which is the most successful method of treatment, can cost \$18,000 to \$40,000 per year. The total expended on HIV from 2000-2016 was \$562 billion dollars and is almost \$50 billion per year. Thus, a vaccine and cure are badly needed.

## **SUMMARY**

[0004] In one aspect, provided herein is a CD4<sup>+</sup> T-cell comprising a heterologous nucleic acid molecule comprising a nucleotide sequence encoding CD40L and CXCL13. In an example, provided herein is a cell comprising a heterologous nucleic acid molecule comprising a nucleotide sequence encoding CD40L and CXCL13.

[0005] In additional examples, the CD40L comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 4, and wherein the CXCL13 comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 3.

[0006] In further examples, the cell is a T cell.

[0007] In further examples, the cell is transduced or transfected with a second and/or third nucleic acid that encodes a heterologous protein.

[0008] In further examples, the second nucleic acid comprises human immunodeficiency virus (HIV) genome, and wherein the HIV genomic nucleic acid comprises a

mutation in the retroviral reverse transcriptase, and further wherein the HIV genomic nucleic acid does not encode a retroviral packaging signal, creating a disabled HIV genomic construct.

**[0009]** In certain examples, provided herein is a CD4<sup>+</sup> cell comprising one or more heterologous nucleic acid molecules encoding for CD40L and CXCL13.

**[0010]** In another aspect, the present disclosure provides a CD4<sup>+</sup> T-cell comprising one or more heterologous nucleic acid molecules encoding for an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 3, and/or an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 4, wherein the one or more heterologous nucleic acid molecules encode at least one human immunodeficiency virus (HIV) protein. In further examples, the CD40L comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 4, and wherein the CXCL13 comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 3.

**[0011]** In another aspect, provided herein is a CD4<sup>+</sup> cell comprising a heterologous CD40L protein and heterologous CXCL13 protein and further comprising at least one nucleic acid which encodes at least one human immunodeficiency virus (HIV) protein.

**[0012]** In further examples, the CD4<sup>+</sup> cell further comprises heterologous nucleic acid molecule comprising human immunodeficiency virus (HIV) genome, and wherein the HIV genomic nucleic acid comprises a mutation in the retroviral reverse transcriptase, and further wherein the HIV genomic nucleic acid does not encode a retroviral packaging signal, creating a disabled HIV genomic construct.

**[0012a]** In a further aspect, the disclosure provides the CD4<sup>+</sup> T-cells as described herein for use in therapy. In a further aspect, the disclosure provides a use of the CD4<sup>+</sup> T-cells as described herein in the manufacture of a pharmaceutical composition for treating HIV in a subject. In a further aspect, the disclosure provides a use of the CD4<sup>+</sup> T-cells as described herein in the manufacture of a pharmaceutical composition for increasing immune response against a HIV protein in a subject in need thereof.

**[0013]** In certain examples, provided herein is a method of treating HIV in a subject comprising administering to the subject a composition comprising administering an effective amount of any of the cells described herein above.

**[0014]** In certain examples, provided herein is a method for increasing immune response in a subject in need thereof, comprising administering an effective amount of any of the cells described herein above.

**[0015]** In additional examples, the cells are allogeneic to the subject.

- [0016] In additional examples, the cells are not HLA-matched with the patient.
- [0017] In additional examples, the dosage of cells ranges from about  $1-5 \times 10^6$ .
- [0018] In additional examples, the viral infection is caused by human immunodeficiency virus (HIV).

## **WHAT IS CLAIMED IS:**

1. A CD4<sup>+</sup> T-cell comprising a heterologous nucleic acid molecule comprising a nucleotide sequence encoding CD40L and CXCL13.
2. The CD4<sup>+</sup> T-cell of claim 1, wherein the CD40L comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 4, and wherein the CXCL13 comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 3.
3. The CD4<sup>+</sup> T-cell of claim 1, wherein the cell heterologously expresses CD40L and CXCL13.
4. The CD4<sup>+</sup> T-cell of claim 1, wherein the cell is an isolated CD4<sup>+</sup> T-cell.
5. The CD4<sup>+</sup> T-cell of claim 1, wherein the cell is transduced or transfected with a second and/or third nucleic acid that encodes a heterologous protein or target antigen.
6. The CD4<sup>+</sup> T-cell of claim 5, wherein the second nucleic acid comprises human immunodeficiency virus (HIV) genome, and wherein the HIV genomic nucleic acid comprises a mutation in the retroviral reverse transcriptase, and further wherein the HIV genomic nucleic acid does not encode a retroviral packaging signal, creating a disabled HIV genomic construct.
7. The CD4<sup>+</sup> T-cell of claim 5, wherein the target antigen is a HIV protein.
8. The CD4<sup>+</sup> T-cell of claim 7, wherein the HIV protein is one or more of HIV Tat (full length or isoforms of 72 and 101 amino acids in length), Rev, Pol, GP120, GP160, GP41, env, Gag, Gag-Pol, Nef, Vpr, Vpu, or Vif, or any combination thereof.
9. A CD4<sup>+</sup> T-cell comprising one or more heterologous nucleic acid molecules encoding for an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 3, and/or an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 4, wherein the one or more heterologous nucleic acid molecules encode at least one human immunodeficiency virus (HIV) protein.
10. The CD4<sup>+</sup> T-cell of claim 9, wherein the cell expresses CD40L.
11. The CD4<sup>+</sup> T-cell of claims 9 and 10, wherein the cell expresses CXCL13.
12. The CD4<sup>+</sup> T-cell of claim 9, wherein the cell expresses CD40L and CXCL13.
13. The CD4<sup>+</sup> T-cell of claim 9, wherein the cell is an isolated CD4<sup>+</sup> T-cell.
14. A CD4<sup>+</sup> T-cell comprising a heterologous CD40L protein and heterologous CXCL13 protein and further comprising at least one nucleic acid which encodes at least one human immunodeficiency virus (HIV) protein.

15. The CD4<sup>+</sup> T-cell of claim 14, further comprising heterologous nucleic acid molecule comprising human immunodeficiency virus (HIV) genome, and wherein the HIV nucleic acid comprises a mutation in the retroviral reverse transcriptase, and further wherein the HIV genomic nucleic acid does not encode a retroviral packaging signal, creating a disabled HIV genomic construct.

16. The CD4<sup>+</sup> T-cell of claim 14, wherein the HIV protein is one or more of HIV Tat (full length or isoforms of 72 and 101 amino acids in length), Rev, Pol, GP120, GP160, GP41, env, Gag, Gag-Pol, Nef, Vpr, Vpu, or Vif, or any combination thereof.

17. The CD4<sup>+</sup> T-cells of any one of claims 1-16 for use in therapy.

18. Use of the CD4<sup>+</sup> T-cells of any one of claims 1-16 in the manufacture of a pharmaceutical composition for treating HIV in a subject.

19. The use of claim 18, wherein the pharmaceutical composition is to be administered intravenously or by infusion.

20. The use of claim 18 or 19, wherein the cells are allogeneic to, or not HLA-matched to the subject.

21. The use of claim 18 or 19, wherein the cells are autologous to the subject.

22. The use of any one of claims 18-21, wherein, the dosage of cells in the pharmaceutical composition is from  $1 \times 10^6$  to  $5 \times 10^6$ .

23. Use of the CD4<sup>+</sup> T-cells of any one of claims 1-16 in the manufacture of a pharmaceutical composition for increasing immune response against a HIV protein in a subject in need thereof.

24. The use of claim 23, wherein the HIV protein is one or more of HIV Tat (full length or isoforms of 72 and 101 amino acids in length), Rev, Pol, GP120, GP160, GP41, env, Gag, Gag-Pol, Nef, Vpr, Vpu, or Vif, or any combination thereof.

25. The use of claim 23 or 24, wherein the cells are allogeneic to the subject.

26. The use of claim 23 or 24, wherein the cells are not HLA-matched with the patient.

27. The use of any of claims 23-26, wherein the dosage of cells ranges from  $1-5 \times 10^6$ .

28. The use of any of claims 23-27, wherein the immune response is against a viral infection, wherein the viral infection can be a human immunodeficiency virus (HIV) infection.

29. The use of any of claims 18-28, wherein the treatment or increasing the immune response is to be repeated periodically for time frames of from once every week, to once every 2 weeks, to once every 3 weeks, to once per month, to once every two months, to once every 3 months, to once every 4 months, to once every 5 months, to once every 6 months, or once every 7 months, or once every 8 months, or once every 9 months, or once every 10 months, or once every 11 months, or once annually as a maintenance treatment for as long as the subject exhibits improvement, decreased or undetectable viral titer, or stable/non-progressing disease.

30. The use of any of claims 18-29, wherein cellular and humoral immunity are to be induced in the subject.