

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⁺ 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-certain embodiments~~, provided herein is a cell comprising a heterologous nucleic acid molecule comprising a nucleotide sequence encoding CD40L and CXCL13.

[0005] In additional ~~embodimentexamples~~, 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 ~~embodimentexamples~~, the cell is a T cell.

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

[0008] In further ~~embodimentexamples~~, 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 embodimentexamples, provided herein is a CD4+ cell comprising one or more heterologous nucleic acid molecules encoding for CD40L and CXCL13.

[0010] In another aspect, the present disclosure provides a CD4+ 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. In further embodimentexamples, 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 ~~certain embodiments~~ another aspect, provided herein is a CD4+ cell comprising a heterologous CD40L protein and heterologous CXCL13 protein.

[0012] In further embodimentexamples, the CD4+ 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 cells as described herein for use in therapy. In a further aspect, the disclosure provides a use of the 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 cells as described herein in the manufacture of a pharmaceutical composition for increasing immune response in a subject in need thereof.

[0013] In certain embodimentexamples, 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 embodimentexamples, 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 embodimentexamples, the cells are allogeneic to the subject.

[0016] In additional embodimentexamples, the cells are not HLA-matched with the patient.

[0017] In additional embodiment examples, the dosage of cells ranges from about 1-5 x 10⁶.

[0018] In additional embodiment examples, the viral infection is caused by human immunodeficiency virus (HIV).

[0019] In additional embodiment examples, graft versus host disease (GVHD) is decreased or eliminated, while graft versus virus (GVV) is increased in the subject.

[0020] In additional embodiment examples, the treatment or increasing the immune response is 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.

[0021] In additional embodiment examples, cellular and humoral immunity are induced in the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] **FIG. 1A** illustrates a non-limiting vector map for making human and macaque constructs.

[0023] **FIG. 1B** illustrates a non-limiting vector map for making human and macaque constructs.

[0024] **FIG. 2** illustrates a scheme for using embodiments provided herein macaques.

[0025] **FIG. 3** illustrates a scheme for using embodiments provided herein.

[0026] **FIG. 4** illustrates a scheme for using embodiments provided herein

[0027] **FIG. 5** illustrates data showing enhanced cytotoxicity of immune cell compositions provided herein.

[0028] **FIG. 6** illustrates increases in NK cells after vaccination of PBMCs with cells provided for herein.

[0029] **FIG. 7** illustrates increases in NKT cells after vaccination of PBMCs with cells provided for herein.

[0030] **FIG. 8** illustrates increases in NK cell activation after vaccination of PBMCs with cells provided for herein.

[0031] **FIG. 9** illustrates increases in NK cell activation humoral response after vaccination of PBMCs with cells provided for herein.

[0032] **FIG. 10** illustrates increases in B cell activation after vaccination of PBMCs with cells provided for herein.

[0033] **FIG. 11** illustrates increases in T cell activation after vaccination of PBMCs with cells provided for herein.

[0034] **FIG. 12** illustrates increases in T cell activation after vaccination of PBMCs with cells provided for herein.

[0035] **FIG. 13** illustrates increases in CD8 T cell activation after vaccination of PBMCs with cells provided for herein.

WHAT IS CLAIMED IS:

1. A cell comprising a heterologous nucleic acid molecule comprising a nucleotide sequence encoding CD40L and CXCL13.
2. The 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 cell of claim 1, wherein the cell heterologously expresses CD40L and CXCL13.
4. The cell of claim 1, wherein the cell is an isolated cell.
5. The cell of claim 1, wherein the cell is a T cell, such as a CD4⁺ T cell.
6. The 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.
7. The cell of claim 6, 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.
8. The cell of claim 6, wherein the target antigen is a HIV protein.
9. The cell of claim 8, 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.
10. The cell of any one of claims 1-9, wherein the cell is a CD4⁺ T cell.
11. A CD4⁺ 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.
12. The CD4⁺ T-cell of claim 11, wherein the cell expresses CD40L.
13. The CD4⁺ T-cell of claims 11 and 12, wherein the cell expresses CXCL13.
14. The CD4⁺ T-cell of claim 11, wherein the cell expresses CD40L and CXCL13.
15. The CD4⁺ T-cell of claim 11, wherein the cell is an isolated CD4⁺ T-cell.
16. A CD4⁺ T-cell comprising a heterologous CD40L protein and heterologous CXCL13 protein.

17. The CD4+ T-cell of claim 16, further comprising 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.

18. The CD4+ T-cell of claim 16, further comprising a heterologous nucleic acid molecule encoding a target antigen.

19. The CD4+ T-cell of claim 18, wherein the target antigen is a HIV protein.

20. The CD4+ T-cell of claim 19, 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.

21. The cells of any one of claims 1-20 for use in therapy.

~~2122. A method of treating HIV in a subject comprising administering to the subject a composition comprising administering an effective amount of any Use~~ of the cells of any one of claims 1-20 in the manufacture of a pharmaceutical composition for treating HIV in a subject.

~~22. The method of claim 22, wherein the composition is a pharmaceutical composition.~~

23. The ~~method-use~~ of claim 2122, wherein the pharmaceutical composition is to be administered intravenously or by infusion.

24. The ~~usemethod~~ of ~~any one of~~ claims 2122 or-23, wherein the cells are allogeneic to, or not HLA-matched to the subject.

25. The ~~usemethod~~ of any one of claims 2122-23, wherein the cells are autologous to the subject.

26. The ~~usemethod~~ of any one of claims 2122-25, wherein, the dosage of cells in the pharmaceutical composition is from about 1×10^6 to about 5×10^6 .

~~27. A method for increasing immune response in a subject in need thereof, comprising administering an effective amount of any Use~~ of the cells of any one of claims 1-20 in the manufacture of a pharmaceutical composition for increasing immune response in a subject in need thereof.

28. The ~~usemethod~~ of claim 27, wherein the increased immune response is against a target antigen.

29. The ~~usemethod~~ of claim 28, wherein the target antigen is a HIV protein.

30. The ~~usemethod~~ of claim 29, 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.

31. The ~~usemethod~~ of any of claims 27-29, wherein the cells are allogeneic to the subject.

32. The ~~usemethod~~ of any of claims 27-29, wherein the cells are not HLA-matched with the patient.

33. The ~~usemethod~~ of any of claims 27-32, wherein the dosage of cells ranges from about $1-5 \times 10^6$.

34. The ~~usemethod~~ of any of claims 27-33, wherein the immune response is against a viral infection, wherein the viral infection can be a human immunodeficiency virus (HIV) infection.

35. The ~~usemethod~~ of any of claims 22-34, 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.

36. The ~~usemethod~~ of any of claims 22-35, wherein cellular and humoral immunity are to be induced in the subject.