acute phase of viremia. Although RhCMV-protected macaques exhibited periodic low-level "blips" of viremia, $CD4^+$ memory T cell depletion was not observed, SIV-specific antibody responses did not develop, and subsequently, over time, viral nucleic acid became barely quantifiable while replication competent virus disappeared from the tissues of protected animals. These events did not occur in spontaneous SIV elite controllers and DNA prime/Ad5 boost vaccinated controllers (Hansen, S.G. *et al., Nature* 502, 100 (2013); incorporated by reference herein). Given the central role of RhCMV-induced $CD8^+$ T cells in mediating this protective effect in RhCMV/SIV-vaccinated macaques, defining the functional properties of these T cells is critical to understanding their mechanistic contribution to RhCMV/SIV vector-induced control of SIV replication. Understanding these properties can in turn lead to new uses for cytomegalovirus (CMV) vaccine vectors expressing heterologous antigens.

SUMMARY

Disclosed herein is a method of generating an immune response to at least one heterologous antigen in a subject. In one aspect, the present invention refers to a method of generating $CD8^+$ T cells that recognize MHC-E-peptide complexes, the method comprising (1) identifying a first $CD8^+$ T cell receptor (TCR) from a set of $CD8^+$ T cells, wherein a cytomegalovirus (CMV) vector had been administered to a subject in an effective amount for generating the set of $CD8^+$ T cells that recognize MHC-E/peptide complexes, wherein the first $CD8^+$ TCR recognizes a MHC-E/heterologous antigen-derived peptide complex; wherein the CMV vector comprises a. a first nucleic acid sequence encoding at least one heterologous antigen; b. a second nucleic acid sequence encoding at least one active UL40 protein, or an ortholog or homolog thereof; and c. a third nucleic acid sequence encoding at least one active US28 protein, or an ortholog or homolog thereof; wherein the CMV vector does not express an active UL128 protein, or an ortholog thereof, and does not express an active UL130 protein, or an ortholog thereof; (2) isolating one or more $CD8^+$T cells from the subject; and (3) transfecting the one or more $CD8^+$T cells with an expression vector, wherein the expression vector comprises a nucleic acid sequence encoding a second $CD8^+$ TCR and a promoter operably linked to the nucleic acid sequence encoding the second CD8+ TCR, wherein the second $CD8^+$ TCR comprises CDR3α and CDR3β of the first $CD8^+$ TCR, thereby generating one or more transfected $CD8^+$ T cells that recognize a MHC-E/heterologous antigen-derived peptide complex. In another aspect, the present invention refers to use of the transfected $CD8^+$ T cells generated according to the method disclosed herein in the manufacture of a medicament for treating cancer. In yet another aspect, the present invention refers to use of the transfected $CD8^+$ T cells generated according to the method as disclosed herein in the manufacture of a medicament for treating a pathogenic infection. In one example, there is described the use of the transfected $CD8^+$ T cells generated according to the method disclosed herein in the manufacture of a medicament for treating an autoimmune disease or disorder. In yet another aspect, the present invention refers to use of the transfected $CD8^+$ T cells generated according to the method disclosed herein in the manufacture of a medicament for inducing an autoimmune response to the host self-antigen or tissue-specific antigen. In another aspect, the present invention refers to a method of generating $CD8^+$ T cells that recognize MHC-E-peptide complexes, the method comprising: (1) identifying a first $CD8^+$ TCR from a set of $CD8^+$ T cells wherein a CMV vector had been administered in an amount effective for generating the set of $CD8^+$ T cells that recognize MHC-E/peptide complexes, wherein the first $CD8^+$ TCR recognizes a MHC-E/heterologous antigen-derived peptide complex; wherein the CMV vector comprises: a. a first nucleic acid sequence encoding at least one heterologous antigen; b. a second nucleic acid sequence encoding at least one active UL40 protein, or an ortholog or homolog thereof; and c. a third nucleic acid sequence encoding at least one active US28 protein, or an ortholog or homolog thereof; wherein the CMV vector does not express an active UL128 protein, or an ortholog thereof, and does not express an active UL130 protein, or an ortholog thereof; (2) isolating one or more $CD8^+$T cells from a second subject; and (3) transfecting the one or more $CD8^+$T cells with an expression vector, wherein the expression vector comprises a nucleic acid sequence encoding a second $CD8^+$ TCR

and a promoter operably linked to the nucleic acid sequence encoding the second $CD8^+$ TCR, wherein the second $CD8^+$ TCR comprises CDR3α and CDR3β of the first $CD8^+$ TCR, thereby generating one or more transfected $CD8^+$ T cells that recognize a MHC-E/heterologous antigen-derived peptide complex. In yet another aspect, the present invention refers to use of the transfected $CD8^+$ T cells generated according to the method disclosed herein in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to the second subject. In a further aspect, the present invention refers to use of the transfected $CD8^+$ T cells generated according to the method disclosed herein in the manufacture of a medicament for treating a pathogenic infection, wherein the medicament is to be administered to the second subject. In one example, there is described the use of the transfected $CD8^+$ T cells generated according to the method disclosed herein in the manufacture of a medicament to treat an autoimmune disease or disorder, wherein the medicament is to be administered to the second subject. In a further aspect, the present invention refers to use of the transfected $CD8^+$ T cells generated according to the method disclosed herein in the manufacture of a medicament for inducing an autoimmune response to the host self-antigen or tissue-specific antigen. In yet another aspect, the present invention refers to a $CD8^+$T cell generated by the method disclosed herein. In a further aspect, the present invention refers to use of the $CD8^+$ T cell as disclosed herein in the manufacture of a medicament for treating cancer. In another aspect, the present invention refers to use of the $CD8^+$T cell as disclosed herein in the manufacture of a medicament for treating a pathogenic infection. In one example, there is disclosed the use of the $CD8^+$T cell as disclosed herein in the manufacture of a medicament for treating an autoimmune disease or disorder. In another aspect, the present invention refers to use of the $CD8^+$ T cell as disclosed herein in the manufacture of a medicament for inducing an autoimmune response to a host self-antigen or tissue-specific antigen. The method involves administering to the subject an effective amount of a CMV vector. The CMV vector comprises a first nucleic acid that encodes the at least one heterologous antigen, a second nucleic acid sequence that encodes at least one active UL40 protein, or a homolog or ortholog thereof, and a third nucleic acid sequence that encodes at least one US28 protein, or a homolog or ortholog thereof. The CMV vector does not express an active UL128 protein, or an ortholog thereof, and does not express an active UL130 protein, or an ortholog thereof, and at least 10% of the $CD8^+$ T cells generated by the vector are restricted by MHC-E or a homolog thereof. In some examples, the third nucleic acid sequence encodes two through five active US28 proteins, or homologs or orthologs thereof. The heterologous antigen can be any antigen, including a pathogen-specific antigen derived from, for example, human immunodeficiency virus (HIV), simian immunodeficiency virus (SIV), herpes simplex virus, hepatitis B or C virus, papillomavirus, *Plasmodium* parasites, and *Mycobacterium tuberculosis.* In still further examples, the heterologous antigen can be a tumor antigen including, for example, a tumor antigen related to acute myelogenous leukemia,

CLAIMS

1. A method of generating $CD8^+$ T cells that recognize MHC-E-peptide complexes, the method comprising:

(1) identifying a first $CD8^+$ T cell receptor (TCR) from a set of $CD8^+$ T cells, wherein a cytomegalovirus (CMV) vector had been administered to a subject in an effective amount for generating the set of $CD8^+$ T cells that recognize MHC-E/peptide complexes, wherein the first $CD8^+$ TCR recognizes a MHC-E/heterologous antigen-derived peptide complex; wherein the CMV vector comprises:

a. a first nucleic acid sequence encoding at least one heterologous antigen;
b. a second nucleic acid sequence encoding at least one active UL40 protein, or an ortholog or homolog thereof; and
c. a third nucleic acid sequence encoding at least one active US28 protein, or an ortholog or homolog thereof;

wherein the CMV vector does not express an active UL128 protein, or an ortholog thereof, and does not express an active UL130 protein, or an ortholog thereof;

(2) isolating one or more $CD8^+$T cells from the subject; and

(3) transfecting the one or more $CD8^+$T cells with an expression vector, wherein the expression vector comprises a nucleic acid sequence encoding a second $CD8^+$ TCR and a promoter operably linked to the nucleic acid sequence encoding the second $CD8^+$ TCR, wherein the second $CD8^+$ TCR comprises CDR3α and CDR3β of the first $CD8^+$ TCR, thereby generating one or more transfected $CD8^+$ T cells that recognize a MHC-E/heterologous antigen-derived peptide complex.

2. The method of claim 1, wherein the first $CD8^+$ TCR is identified by DNA or RNA sequencing.

3. The method of claim 1 or 2, wherein the second $CD8^+$ TCR comprises CDR1α, CDR2α, CDR3α, CDR1β, CDR2β, and CDR3β of the first $CD8^+$ TCR.

4. The method of claim 3, wherein the nucleic acid sequence encoding the second $CD8^+$ TCR is identical to the nucleic acid sequence encoding the first $CD8^+$TCR.

5. The method of any one of claims 1-4, wherein the CMV vector had been administered to the subject intravenously, intramuscularly, intraperitoneally, or orally.

6. The method of any one of claims 1-5, wherein the subject has been previously exposed to CMV.

7. The method of any one of claims 1-6, wherein the subject is a human or nonhuman primate.

8. The method of any one of claims 1-7, wherein the at least one heterologous antigen of the CMV vector comprises a tumor antigen.

9. The method of claim 8, wherein the tumor antigen is related to a cancer selected from the group consisting of: acute myelogenous leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, non-Hodgkin's lymphoma, multiple myeloma, malignant melanoma, breast cancer, lung cancer, ovarian cancer, prostate cancer, pancreatic cancer, colon cancer, renal cell carcinoma (CC), and germ cell tumors.

10. Use of the transfected $CD8^+$ T cells generated according to the method of claim 8 or 9 in the manufacture of a medicament for treating cancer.

11. The method of any one of claims 1-7, wherein the at least one heterologous antigen of the CMV vector comprises a pathogen-specific antigen.

12. The method of claim 11, wherein the pathogen-specific antigen is derived from a pathogen selected from the group consisting of: human immunodeficiency virus, simian immunodeficiency virus, herpes simplex virus, hepatitis B virus, hepatitis C virus, papillomavirus, Plasmodium parasites, and Mycobacterium tuberculosis.

13. Use of the transfected $CD8^+$ T cells generated according to the method of claim 11 or 12 in the manufacture of a medicament for treating a pathogenic infection.

14. The method of any one of claims 1-7, wherein the at least one heterologous antigen of the CMV vector comprises a host self-antigen or a tissue-specific antigen.

15. The method of claim 14, wherein the host self-antigen is an antigen derived from the variable region of a TCR or an antigen derived from the variable region of a B cell receptor.

16. Use of the transfected $CD8^+$ T cells generated according to claim 14 or 15 in the manufacture of a medicament for inducing an autoimmune response to the host self-antigen or tissue-specific antigen.

17. A method of generating $CD8^+$ T cells that recognize MHC-E-peptide complexes, the method comprising:

(1) identifying a first $CD8^+$ TCR from a set of $CD8^+$ T cells wherein a CMV vector had been administered in an amount effective for generating the set of $CD8^+$ T cells that recognize MHC-E/peptide complexes, wherein the first $CD8^+$ TCR recognizes a MHC-E/heterologous antigen-derived peptide complex; wherein the CMV vector comprises:

a. a first nucleic acid sequence encoding at least one heterologous antigen;
b. a second nucleic acid sequence encoding at least one active UL40 protein, or an ortholog or homolog thereof; and
c. a third nucleic acid sequence encoding at least one active US28 protein, or an ortholog or homolog thereof;

wherein the CMV vector does not express an active UL128 protein, or an ortholog thereof, and does not express an active UL130 protein, or an ortholog thereof;

(2) isolating one or more $CD8^+$T cells from a second subject; and

(3) transfecting the one or more $CD8^+$T cells with an expression vector, wherein the expression vector comprises a nucleic acid sequence encoding a second $CD8^+$ TCR and a promoter operably linked to the nucleic acid sequence encoding the second $CD8^+$ TCR, wherein the second $CD8^+$ TCR comprises CDR3α and CDR3β of the first $CD8^+$ TCR, thereby generating one or more transfected $CD8^+$ T cells that recognize a MHC-E/heterologous antigen-derived peptide complex.

18. The method of claim 17, wherein the first $CD8^+$ TCR is identified by DNA or RNA sequencing.

19. The method of claim 17 or 18, wherein the first subject is a human or nonhuman primate.

20. The method of any one of claims 17-19, wherein the second subject is a human or nonhuman primate.

21. The method of any one of claims 17-20, wherein the first subject is a nonhuman primate and the second subject is a human, and wherein the second $CD8^+$ TCR is a chimeric nonhuman primate-human $CD8^+$ TCR comprising the non-human primate CDR3α and CDR3β of the first $CD8^+$ TCR.

22. The method of claim 21, wherein the second $CD8^+$ TCR comprises the non-human primate CDR1α, CDR2α, CDR3α, CDR1β, CDR2β, and CDR3β of the first $CD8^+$ TCR.

23. The method of any one of claims 17-20, wherein the second $CD8^+$ TCR comprises CDR1α, CDR2α, CDR3α, CDR1β, CDR2β, and CDR3β of the first $CD8^+$ TCR.

24. The method of claim 23, wherein the nucleic acid sequence encoding the second $CD8^+$ TCR is identical to the nucleic acid sequence encoding the first $CD8^+$TCR.

25. The method of any one of claims 17-20, wherein the second $CD8^+$ TCR is a chimeric $CD8^+$ TCR.

26. The method of claim 25, wherein the second $CD8^+$ TCR comprises CDR1α, CDR2α, CDR3α, CDR1β, CDR2β, and CDR3β of the first $CD8^+$ TCR.

27. The method of any one of claims 17-26, wherein the CMV vector had been administered to the first subject intravenously, intramuscularly, intraperitoneally, or orally.

28. The method of any one of claims 17-27, wherein the first subject has been previously exposed to CMV.

29. The method of any one of claims 17-28, wherein the at least one heterologous antigen comprises a tumor antigen.

30. The method of claim 29, wherein the tumor antigen is related to a cancer selected from the group consisting of: acute myelogenous leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, non-Hodgkin's lymphoma, multiple myeloma, malignant melanoma, breast cancer, lung cancer, ovarian cancer, prostate cancer, pancreatic cancer, colon cancer, renal cell carcinoma (RCC), and germ cell tumors.

31. Use of the transfected $CD8^+$ T cells generated according to claim 29 or 30 in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to the second subject.

32. The method of any one of claims 17-28, wherein the at least one heterologous antigen comprises a pathogen-specific antigen.

33. The method of claim 32, wherein the pathogen-specific antigen is derived from a pathogen selected from the group consisting of: human immunodeficiency virus, simian immunodeficiency virus, herpes simplex virus, hepatitis B virus, hepatitis C virus, papillomavirus, Plasmodium parasites, and Mycobacterium tuberculosis.

34. Use of the transfected $CD8^+$ T cells generated according to the method of claim 32 or 33 in the manufacture of a medicament for treating a pathogenic infection, wherein the medicament is to be administered to the second subject.

35. The method of any one of claims 17-28, wherein the at least one heterologous antigen comprises a host self-antigen or a tissue-specific antigen.

36. The method of claim 35, wherein the host self-antigen is an antigen derived from the variable region of a TCR or an antigen derived from the variable region of a B cell receptor.

37. Use of the transfected $CD8^+$ T cells generated according to the method of claim 35 or 36 in the manufacture of a medicament for inducing an autoimmune response to the host self-antigen or tissue-specific antigen.

38. A $CD8^+$T cell generated by the method of any one of claims 1-9, 11-12, 14-15, 17-30, 32-33, 35-36.

39. The $CD8^+$ T cell of claim 38, wherein the at least one heterologous antigen of the CMV vector comprises a tumor antigen.

40. The $CD8^+$ T cell of claim 39, wherein the tumor antigen is related to a cancer selected from the group consisting of: acute myelogenous leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, non-Hodgkin's lymphoma, multiple myeloma, malignant melanoma, breast cancer, lung cancer, ovarian cancer, prostate cancer, pancreatic cancer, colon cancer, renal cell carcinoma (RCC), and germ cell tumors.

41. The $CD8^+$ T cell of claim 38, wherein the at least one heterologous antigen of the CMV vector comprises a pathogen-specific antigen

42. The $CD8^+$ T cell of claim 41, wherein the pathogen-specific antigen is derived from a pathogen selected from the group consisting of: human immunodeficiency virus, simian immunodeficiency virus, herpes simplex virus, hepatitis B virus, hepatitis C virus, papillomavirus, Plasmodium parasites, and Mycobacterium tuberculosis.

43. The $CD8^+$ T cell of claim 38, wherein the at least one heterologous antigen of the CMV vector comprises a host self-antigen or a tissue-specific antigen.

44. The $CD8^+$ T cell of claim 43, wherein the host self-antigen is an antigen derived from the variable region of a TCR or an antigen derived from the variable region of a B cell receptor.

45. Use of the $CD8^+$ T cell of claim 39 or 40 in the manufacture of a medicament for treating cancer.

46. Use of the $CD8^+$T cell of claim 41 or 42 in the manufacture of a medicament for treating a pathogenic infection.

47. Use of the $CD8^+$ T cell of claim 43 or 44 in the manufacture of a medicament for inducing an autoimmune response to a host self-antigen or tissue-specific antigen.