

Treatment and Prevention of Alloreactivity using Virus-Specific Immune Cells Expressing Chimeric Antigen Receptors

This application claims priority from US 63/015,769 filed 27 April 2020, the contents and elements of which are herein incorporated by reference for all purposes.

Technical Field

5 The present invention relates to molecular and cell biology, and also relates to methods of medical treatment and prophylaxis.

Background

10 Despite the success of autologous chimeric antigen receptor (CAR) T cells in hematologic malignancies, barriers to more widespread use of this potentially curative therapy exist. Manufacture failure, disease progression prior to infusion, and exorbitant cost prove prohibitive for many. There is an urgent need for an immediately available CAR T cell option.

15 “Off-the-shelf” T cell products derived from healthy donors that can rapidly be administered, would improve accessibility and reduce the cost of adoptive cellular immunotherapy. However, the development of “off-the-shelf” CAR T cell therapies has been hindered by two major pitfalls: potential for polyclonally activated CAR T cells from unrelated donors to cause graft versus host disease (GVHD), and rejection of allogeneic CAR T cells by recipient alloreactive T cells.

Summary

20 In a first aspectexample, the present disclosure provides a virus-specific immune cell, comprising a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).

30 In some embodimentexamples, the signalling domain comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:26.

In some exampleembodiments, the transmembrane domain is derived from the transmembrane domain of CD28.

35 In some exampleembodiments, the transmembrane domain comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:20.

40 In some exampleembodiments, the antigen-binding domain comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:14, and an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:15.

In some example embodiments, the antigen-binding domain comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:18.

In some example embodiments, the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD3ζ.

In some example embodiments, the signalling domain comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:25.

In some example embodiments, the CAR additionally comprises a hinge region provided between the antigen-binding domain and the transmembrane domain.

In some example embodiments, the hinge region comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:33.

In some example embodiments, the CAR comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:35 or 36.

In some example embodiments, the virus-specific immune cell comprises a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30, or nucleic acid encoding a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30.

The present disclosure also provides a virus-specific immune cell, comprising: a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain comprising an immunoreceptor tyrosine-based activation motif (ITAM);

wherein the virus-specific immune cell comprises a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30, or nucleic acid encoding a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30.

In some example embodiments, the virus-specific immune cell comprises more than one non-identical CAR, or nucleic acid encoding more than one non-identical CAR.

In some example embodiments, the target antigen other than CD30 is a cancer cell antigen.

In some example embodiments, the target antigen other than CD30 is selected from CD19, CD20, CD22, ROR1R, CD4, CD7, CD38, BCMA, Mesothelin, EGFR, GPC3, MUC1, HER2, GD2, CEA, EpCAM, LeY and PSCA.

In some example embodiments, the target antigen other than CD30 is CD19.

In some example embodiments, the virus-specific immune cell is a virus-specific T cell.

In some example embodiments, the virus-specific immune cell is specific for Epstein-Barr virus (EBV).

5 The present disclosure also provides a method for producing a virus-specific immune cell, comprising:
modifying a virus-specific immune cell to comprise a chimeric antigen receptor (CAR) or nucleic
acid encoding a CAR, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically
to CD30, (ii) a transmembrane domain, and (iii) a signalling domain, wherein the signalling domain
comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino
10 acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).

In some example embodiments, the signalling domain comprises an amino acid sequence having at least
80% amino acid sequence identity to SEQ ID NO:26.

15 In some example embodiments, the transmembrane domain is derived from the transmembrane domain
of CD28.

In some example embodiments, the transmembrane domain comprises an amino acid sequence having
at least 80% amino acid sequence identity to SEQ ID NO:20.

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In some example embodiments, the antigen-binding domain comprises an amino acid sequence having
at least 80% amino acid sequence identity to SEQ ID NO:14, and an amino acid sequence having at least
80% amino acid sequence identity to SEQ ID NO:15.

25 In some example embodiments, the antigen-binding domain comprises an amino acid sequence having
at least 80% amino acid sequence identity to SEQ ID NO:18.

In some example embodiments, the signalling domain comprises: (a) an amino acid sequence derived
from the intracellular domain of CD3 ζ .

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In some example embodiments, the signalling domain comprises an amino acid sequence having at least
80% amino acid sequence identity to SEQ ID NO:25.

35 In some example embodiments, the CAR additionally comprises a hinge region provided between the
antigen-binding domain and the transmembrane domain.

In some example embodiments, the hinge region comprises an amino acid sequence having at least
80% amino acid sequence identity to SEQ ID NO:33.

40 In some example embodiments, the CAR comprises an amino acid sequence having at least 80% amino
acid sequence identity to SEQ ID NO:35 or 36.

In some example embodiments, the virus-specific immune cell comprises a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30, or nucleic acid encoding a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30.

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The present invention disclosure also provides a method for producing a virus-specific immune cell, comprising:

modifying a virus-specific immune cell to comprise a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain comprising an immunoreceptor tyrosine-based activation motif (ITAM);

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wherein the virus-specific immune cell comprises a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30, or nucleic acid encoding a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30.

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In some example embodiments, the method further comprises:

modifying a virus-specific immune cell to comprise a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR, wherein the CAR comprises an antigen-binding domain which binds specifically to a target antigen other than CD30.

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In some example embodiments, the virus-specific immune cell comprises more than one non-identical CAR, or nucleic acid encoding more than one non-identical CAR.

In some example embodiments, the target antigen other than CD30 is a cancer cell antigen.

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In some example embodiments, the target antigen other than CD30 is selected from CD19, CD20, CD22, ROR1R, CD4, CD7, CD38, BCMA, Mesothelin, EGFR, GPC3, MUC1, HER2, GD2, CEA, EpCAM, LeY and PSCA.

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In some example embodiments, the target antigen other than CD30 is CD19.

In some example embodiments, the virus-specific immune cell is a virus-specific T cell.

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In some example embodiments, the virus-specific immune cell is specific for Epstein-Barr virus (EBV).

The present disclosure also provides a virus-specific immune cell obtained or obtainable by the method according to the present disclosure.

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The present disclosure also provides a pharmaceutical composition comprising a virus-specific immune cell according to the present disclosure and a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

The present disclosure also provides a virus-specific immune cell or a pharmaceutical composition according to the present disclosure, for use in a method of medical treatment or prophylaxis.

The present disclosure also provides a virus-specific immune cell or a pharmaceutical composition according to the present disclosure, for use in a method of treating or preventing a cancer.

- 5 The present disclosure also provides the use of a virus-specific immune cell or a pharmaceutical composition according to the present disclosure, in the manufacture of a medicament for treating or preventing a cancer.

- 10 The present disclosure also provides a method of treating or preventing a cancer comprising administering to a subject a therapeutically or prophylactically effective quantity of virus-specific immune cells or a pharmaceutical composition according to the present disclosure.

- 15 In some examples, the cancer is selected from the group consisting of: a CD30-positive cancer, an EBV-associated cancer, a hematological cancer, a myeloid hematologic malignancy, a hematopoietic malignancy, a lymphoblastic hematologic malignancy, myelodysplastic syndrome, leukemia, T cell leukemia, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, B cell non-Hodgkin's lymphoma, diffuse large B cell lymphoma, primary mediastinal B cell lymphoma, EBV-associated lymphoma, EBV-positive B cell lymphoma, EBV-positive diffuse large B cell lymphoma, EBV-positive lymphoma associated with X-linked lymphoproliferative disorder, EBV-positive lymphoma associated with HIV infection/AIDS, oral hairy leukoplakia, Burkitt's lymphoma, post-transplant lymphoproliferative disease, central nervous system lymphoma, anaplastic large cell lymphoma, T cell lymphoma, ALK-positive anaplastic T cell lymphoma, ALK-negative anaplastic T cell lymphoma, peripheral T cell lymphoma, cutaneous T cell lymphoma, NK-T cell lymphoma, extra-nodal NK-T cell lymphoma, thymoma, multiple myeloma, a solid cancer, epithelial cell cancer, gastric cancer, gastric carcinoma, gastric adenocarcinoma, gastrointestinal adenocarcinoma, liver cancer, hepatocellular carcinoma, cholangiocarcinoma, head and neck cancer, head and neck squamous cell carcinoma, oral cavity cancer, oropharyngeal cancer, oropharyngeal carcinoma, oral cancer, laryngeal cancer, nasopharyngeal carcinoma, oesophageal cancer, colorectal cancer, colorectal carcinoma, colon cancer, colon carcinoma, cervical carcinoma, prostate cancer, lung cancer, non-small cell lung cancer, small cell lung cancer, lung adenocarcinoma, squamous lung cell carcinoma, bladder cancer, urothelial carcinoma, skin cancer, melanoma, advanced melanoma, renal cell cancer, renal cell carcinoma, ovarian cancer, ovarian carcinoma, mesothelioma, breast cancer, brain cancer, glioblastoma, prostate cancer, pancreatic cancer, mastocytosis, advanced systemic mastocytosis, germ cell tumor or testicular embryonal carcinoma.

- 35 The present disclosure also provides a virus-specific immune cell or a pharmaceutical composition according to the present disclosure, for use in a method of treating or preventing a disease or condition characterised by an alloreactive immune response.

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5 The present disclosure also provides the use of a virus-specific immune cell or a pharmaceutical composition according to the present disclosure, in the manufacture of a medicament for treating or preventing a disease or condition characterised by an alloreactive immune response. In one aspect, the present disclosure refers to use of a virus-specific immune cell comprising a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR in the manufacture of a medicament for use in treating or preventing a disease or condition characterised by an alloreactive immune response, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).

15 The present disclosure also provides a method of treating or preventing a disease or condition characterised by an alloreactive immune response, comprising administering to a subject a therapeutically or prophylactically effective quantity of virus-specific immune cells or a pharmaceutical composition according to the present disclosure.

In some example embodiments, the disease or condition characterised by an alloreactive immune response is a disease or condition associated with allotransplantation.

20 In some example embodiments, the disease or condition is graft versus host disease (GVHD).

In some example embodiments, the disease or condition is graft rejection.

25 In some example embodiments, the method comprises administering a therapeutically or prophylactically effective quantity of the virus-specific immune cells or pharmaceutical composition to a donor subject for an allotransplant prior to harvesting the allotransplant.

30 In some example embodiments, the method comprises administering a therapeutically or prophylactically effective quantity of the virus-specific immune cells or pharmaceutical composition to a recipient subject for an allotransplant.

In some example embodiments, the method comprises contacting an allotransplant with a therapeutically or prophylactically effective quantity of the virus-specific immune cells or composition.

35 The present disclosure also provides a virus-specific immune cell or a pharmaceutical composition according to the present disclosure, for use in a method of treating or preventing a disease or condition by allotransplantation.

40 The present disclosure also provides the use of a virus-specific immune cell or a pharmaceutical composition according to the present disclosure, in the manufacture of a medicament for treating or preventing a disease or condition by allotransplantation. In one aspect, the present disclosure refers to use of a virus-specific immune cell comprising a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR in the manufacture of a medicament for use in treating or preventing a disease or condition by allotransplantation, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).

50 The present disclosure also provides a method of treating or preventing a disease or condition by allotransplantation, comprising administering to a subject a therapeutically or prophylactically effective quantity of virus-specific immune cells or a pharmaceutical composition according to the present disclosure.

In some example embodiments, the method comprises administering a therapeutically or prophylactically effective quantity of the virus-specific immune cells or pharmaceutical composition to a donor subject for an allotransplant prior to harvesting the allotransplant.

5 In some example embodiments, the method comprises administering a therapeutically or prophylactically effective quantity of the virus-specific immune cells or pharmaceutical composition to a recipient subject for an allotransplant.

10 In some example embodiments, the method comprises contacting an allotransplant with a therapeutically or prophylactically effective quantity of the virus-specific immune cells or composition.

In some example embodiments, the allotransplantation comprises adoptive transfer of allogeneic immune cells.

15 In some example embodiments, the disease or condition is a T cell dysfunctional disorder, a cancer or an infectious disease.

The present disclosure also provides a method of killing alloreactive immune cells, comprising contacting alloreactive immune cells with a virus-specific immune cell or a pharmaceutical composition according to

20 the present disclosure. In one aspect, the present disclosure refers to a method of killing alloreactive immune cells, comprising contacting alloreactive immune cells *in vitro* with a virus-specific immune cell comprising a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR for use in a method of treating or preventing a disease or condition characterised by an alloreactive immune response, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane
25 domain, and (iii) a signalling domain, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).

Description

30 The inventors developed a CAR-modified virus specific T cell (CAR-VST) approach for the elimination of hematologic malignancies without causing GVHD, and avoiding allorejection.

The present disclosure provides a strategy to eliminate alloreactive T cells in order to protect allogeneic tissues including off-the-shelf cellular therapies from graft rejection, or to treat GVHD.

35 CD30 has been identified as a marker of alloreactive T cells, and so the inventors targeted them by engineering therapeutic T cells to express a chimeric antigen receptor (CAR) directed against CD30 (CD30.CAR). CD30.CAR expressing VSTs can be employed in methods using allogeneic therapies, for reducing alloreactive immune responses in the recipient subject.

40 Administering allogeneic T cells into HLA-mismatched recipients carries the risk of alloreactive immune responses such as GVHD since a proportion of the T cells will inherently possess alloreactivity. The inventors used virus specific T cells (VSTs) as the platform cells for expressing the CD30.CAR since they have been shown to rarely cause GVHD in allogeneic recipients, which is likely a result of their restricted
45 TCR repertoire. In particular, Epstein-Barr Virus-specific T cells (EBVSTs) have been administered to more than 300 allogeneic recipients without any evidence of GVHD.

Claims:

~~1. A virus-specific immune cell comprising a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR for use in a method of treating or preventing a disease or condition characterised by an alloreactive immune response, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).~~

21. Use of a virus-specific immune cell comprising a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR in the manufacture of a medicament for use in treating or preventing a disease or condition characterised by an alloreactive immune response, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).

~~3. A method of treating or preventing a disease or condition characterised by an alloreactive immune response, comprising administering to a subject a therapeutically or prophylactically effective quantity of virus-specific immune cells comprising a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).~~

42. The virus-specific immune cell for use according to claim 1, the use according to claim 21, or the method according to claim 3, wherein the disease or condition characterised by an alloreactive immune response is a disease or condition associated with allotransplantation.

53. The virus-specific immune cell for use, the use, or the method according to any one of claims 1 to 4 or claim 2, wherein the disease or condition is graft versus host disease (GVHD).

64. The virus-specific immune cell for use, the use, or the method according to any one of claims 1 to 43, wherein the disease or condition is graft rejection.

75. The virus-specific immune cell for use, the use, or the method according to any one of claims 1 to 64, wherein the method comprises administering a therapeutically or prophylactically effective quantity of the virus-specific immune cells is to be administered to a donor subject for an allotransplant prior to harvesting the allotransplant.

~~86. The virus-specific immune cell for use, the use, or the method~~ according to any one of claims 1 to ~~75~~, wherein ~~the method comprises administering~~ a therapeutically or prophylactically effective quantity of the virus-specific immune cells is to be administered to a recipient subject for an allotransplant.

~~97. The virus-specific immune cell for use, the use, or the method~~ according to any one of claims 1 to ~~86~~, wherein ~~the method comprises contacting~~ an allotransplant is to be contacted with a therapeutically or prophylactically effective quantity of the virus-specific immune cells.

~~10. A virus-specific immune cell comprising a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR for use in a method of treating or preventing a disease or condition by allotransplantation, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).~~

~~118. Use of a virus-specific immune cell comprising a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR in the manufacture of a medicament for use in treating or preventing a disease or condition by allotransplantation, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).~~

~~12. A method of treating or preventing a disease or condition by allotransplantation, comprising administering to a subject a therapeutically or prophylactically effective quantity of virus-specific immune cells comprising a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).~~

~~139. The virus-specific immune cell for use according to claim 10, the use according to claim 118, or the method according to claim 12,~~ wherein ~~the method comprises administering~~ a therapeutically or prophylactically effective quantity of the virus-specific immune cells is to be administered to a donor subject for an allotransplant prior to harvesting the allotransplant.

~~1410. The virus-specific immune cell for use, the use, or the method~~ according to ~~any one of claims 10-8 to 13 or claim 9,~~ wherein ~~the method comprises administering~~ a therapeutically or prophylactically effective quantity of the virus-specific immune cells is to be administered to a recipient subject for an allotransplant.

1511. The ~~virus-specific immune cell for use, the use, or the method~~ according to any one of claims ~~10-8~~ to ~~1410~~, wherein ~~the method comprises contacting~~ an allotransplant is to be contacted with a therapeutically or prophylactically effective quantity of the virus-specific immune cells.
- 5 1612. The ~~virus-specific immune cell for use, the use, or the method~~ according to any one of claims ~~10-8~~ to ~~1510~~, wherein the allotransplantation comprises adoptive transfer of allogeneic immune cells.
1713. The ~~virus-specific immune cell for use, the use, or the method~~ according to any one of claims ~~10-8~~ to ~~1610~~, wherein the disease or condition is a T cell dysfunctional disorder, a cancer or an infectious
10 disease.
1814. A method of killing alloreactive immune cells, comprising contacting alloreactive immune cells in vitro with a virus-specific immune cell comprising a chimeric antigen receptor (CAR) or nucleic acid encoding a CAR for use in a method of treating or preventing a disease or condition characterised by an
15 alloreactive immune response, wherein the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD28, and (b) an amino acid sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).
- 20 1915. The ~~virus-specific immune cell for use, the use, or the method~~ according to any one of claims 1 to ~~1814~~, wherein the signalling domain comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:26.
2016. The ~~virus-specific immune cell for use, the use, or the method~~ according to any one of claims 1 to
25 ~~1915~~, wherein the transmembrane domain is derived from the transmembrane domain of CD28.
2117. The ~~virus-specific immune cell for use, the use, or the method~~ according to any one of claims 1 to ~~2016~~, wherein the transmembrane domain comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:20.
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2218. The ~~virus-specific immune cell for use, the use, or the method~~ according to any one of claims 1 to ~~2117~~, wherein the antigen-binding domain comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:14, and an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:15.
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2319. The ~~virus-specific immune cell for use, the use, or the method~~ according to any one of claims 1 to ~~2218~~, wherein the antigen-binding domain comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:18.

2420. The ~~virus-specific immune cell for use, the~~ use, or the method according to any one of claims 1 to 2319, wherein the signalling domain comprises: (a) an amino acid sequence derived from the intracellular domain of CD3ζ.
- 5 2521. The ~~virus-specific immune cell for use, the~~ use, or the method according to any one of claims 1 to 2420, wherein the signalling domain comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:25.
- 10 2622. The ~~virus-specific immune cell for use, the~~ use, or the method according to any one of claims 1 to 2521, wherein the CAR additionally comprises a hinge region provided between the antigen-binding domain and the transmembrane domain.
- 15 2723. The ~~virus-specific immune cell for use, the~~ use, or the method according to claim 2622, wherein the hinge region comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:33.
- 20 2824. The ~~virus-specific immune cell for use, the~~ use, or the method according to any one of claims 1 to 2723, wherein the CAR comprises an amino acid sequence having at least 80% amino acid sequence identity to SEQ ID NO:35 or 36.
- 25 2925. The ~~virus-specific immune cell for use, the~~ use, or the method according to any one of claims 1 to 2824, wherein the virus-specific immune cell comprises a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30, or nucleic acid encoding a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30.
- 30 3026. The ~~virus-specific immune cell for use, the~~ use, or the method according to any one of claims 1 to 2925, wherein:
the CAR comprises: (i) an antigen-binding domain which binds specifically to CD30, (ii) a transmembrane domain, and (iii) a signalling domain comprising an immunoreceptor tyrosine-based activation motif (ITAM); and
wherein the virus-specific immune cell comprises a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30, or nucleic acid encoding a CAR comprising an antigen-binding domain which binds specifically to a target antigen other than CD30.
- 35 3127. The ~~virus-specific immune cell for use, the~~ use, or the method according to claim 29-25 or claim 3026, wherein the virus-specific immune cell comprises more than one non-identical CAR, or nucleic acid encoding more than one non-identical CAR.
- 40 3228. The ~~virus-specific immune cell for use, the~~ use, or the method according to any one of claims 29-25 to 3127, wherein the target antigen other than CD30 is a cancer cell antigen.

3329. The ~~virus-specific immune cell for use, the~~ use, or the method according to any one of claims 29-25 to 3228, wherein the target antigen other than CD30 is selected from CD19, CD20, CD22, ROR1R, CD4, CD7, CD38, BCMA, Mesothelin, EGFR, GPC3, MUC1, HER2, GD2, CEA, EpCAM, LeY and PSCA.

5 3430. The ~~virus-specific immune cell for use, the~~ use, or the method according to any one of claims 29-25 to 3329, wherein the target antigen other than CD30 is CD19.

10 3531. The ~~virus-specific immune cell for use, the~~ use, or the method according to any one of claims 1 to 3430, wherein the virus-specific immune cell is a virus-specific T cell.

3632. The ~~virus-specific immune cell for use, the~~ uses, or the method according to any one of claims 1 to 3531, wherein the virus-specific immune cell is specific for Epstein-Barr virus (EBV).