

Dimeric Antigen Receptors (DAR) that Bind BCMA

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/896,190, filed on September 5, 2019, to U.S. Provisional Patent Application No. 62/896,990, filed September 6, 2019, to U.S. Provisional Patent Application No. 62/910,341, filed October 3, 2019, to U.S. Provisional Patent Application No. 62/943,069, filed December 3, 2019, and to U.S. Provisional Patent Application No. 63/030,145, filed May 26, 2020, the entire contents of each of which are expressly incorporated herein by reference.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on July 24, 2020, is named 2020-07-24_01223-0012-00PCT_Sequence_Listing_ST25.txt and is 167,936 bytes in size.

TECHNICAL FIELD

[0003] The present disclosure provides dimeric antigen receptors (DAR) protein constructs that bind specifically to a target antigen, nucleic acids that encode the dimeric antigen receptors, vectors comprising the nucleic acids, and host cells harboring the vectors.

BACKGROUND AND SUMMARY

[0003a] In one aspect, provided herein is a nucleic acid encoding a precursor polypeptide, the precursor polypeptide comprising:

- a. a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a heavy chain leader sequence, (ii) an antibody heavy chain variable region, (iii) an antibody heavy chain constant region, (iv) an optional hinge region, (v) a transmembrane region, (vi) an intracellular region, (vii) a self-cleaving sequence, (viii) a light chain leader sequence, (ix) an antibody light chain variable region, and (x) an antibody light chain constant region, wherein the self-cleaving sequence permits cleaving the of the precursor polypeptide into a first and second polypeptide chain; or

b. a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a light chain leader sequence (ii) an antibody light chain variable region, (iii) an antibody light chain constant region, (iv) an optional hinge region, (v) a transmembrane region, (vi) an intracellular region, (vii) a self-cleaving sequence, (viii) a heavy chain leader sequence, (ix) an antibody heavy chain variable region, and (x) an antibody heavy chain constant region, wherein the self-cleaving sequence permits cleaving the of the precursor polypeptide into a first and second polypeptide chain.

[0003b] In another aspect, provided herein is an expression vector comprising the nucleic acid as disclosed herein operably linked to a promoter.

[0003c] In another aspect, provided herein is a host cell, or a population of host cells, harboring the nucleic acid as disclosed herein operably linked to a promoter, optionally wherein the nucleic acid is present in an expression vector.

[0003d] In another aspect, provided herein is a pharmaceutical composition comprising the population of host cells as disclosed herein and a pharmaceutically-acceptable excipient.]

[0003e] In another aspect, provided herein is use of the population of host cells as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject having a disease, disorder or condition associated with detrimental expression of a tumor antigen in the subject.

[0003f] In another aspect, provided herein is a polypeptide encoded by the nucleic acid as disclosed herein.

[0003g] In another aspect, provided herein is the population of host cells as disclosed herein or the pharmaceutical composition as disclosed herein for use in therapy.

[0004] Chimeric antigen receptors (CARs) have been developed to target antigens associated, in particular, with cancer. The first-generation CAR was engineered to contain a signaling domain (TCR ζ) that delivers an activation stimulus (signal 1) only (Geiger et al., *J. Immunol.* 162(10): 5931-5939, 1999; Haynes et al., *J. Immunol.* 166(1): 182-187, 2001) (Hombach et al. *Cancer Res.* 61(5): 1976-1982, 2001; Hombach et al., *J. Immunol.* 167(11): 6123-6131, 2001; Maher et al., *Nat. Biotechnol.* 20(1): 70-75, 2002). T cells grafted with the first-generation CARs alone exhibited limited anti-tumor efficacy due to suboptimal activation (Beecham et al., *J. Immunother.* 23(6): 631-642, 2000). The second-generation CAR, immunoglobulin-CD28-T cell receptor (IgCD28TCR), incorporated a costimulatory CD28 (signal 2) into the first-generation receptor (Gerstmayer et al., *J. Immunol.* 158(10): 4584-4590, 1997; Emtage et al., *Clin. Cancer Res.* 14(24): 8112-8122, 2008; Lo, Ma et al.,

Clin. Cancer Res. 16(10): 2769-2780, 2010) that resulted in CAR-T cells with a greater anti-tumor capacity (Finney et al., *J. Immunol.* 161(6): 2791-2797, 1998; Hombach et al., *Cancer Res.* 61(5): 1976-1982, 2001; Maher et al., *Nat. Biotechnol.* 20(1): 70-75, 2002). Various CAR variants have been developed by replacing the signal domains of TCR ζ or CD28 with molecules with similar functions, such as FcR γ , 4-1BB and OX40 (Eshhar et al., *Proc. Natl. Acad. Sci. U S A* 90(2): 720-724, 1993). TCR CAR-T cells against various tumor antigens have been developed (Ma et al., *Cancer Gene Ther.* 11(4): 297-306, 2004; Ma et al., *Prostate* 61(1): 12-25, 2004; Lo et al., *Clin. Cancer Res.* 16(10): 2769-2780, 2010; Kong et al., *Clin. Cancer Res.* 18(21): 5949-5960, 2012; Ma et al., *Prostate* 74(3): 286-296, 2014; Katz et al., *Clin. Cancer Res.* 21(14): 3149-3159, 2015; Junghans et al., 2016 *The Prostate*, 76(14):1257-1270).

[0005] Adoptive immunotherapy by infusion of T cells engineered with chimeric antigen receptors (CARs) for redirected tumoricidal activity represents a potentially highly specific modality for the treatment of metastatic cancer. CAR-T cells targeting CD19, a molecule expressed on B cells, have shown success in treatment of B cell malignancies and have received FDA approval, with some trials showing a response rate of up to 70%, including sustained complete responses. Nonetheless, CAR-T cells may show nonspecific activation, which may result in potentially serious adverse events through inappropriate immune activity.

[0006] Thus, there remains a need in the art to harness the powerful efficacy of CAR treatments with increased specificity.

[0007] Antigen receptors comprising both an antibody heavy chain binding region and an antibody light chain binding region in separate polypeptide chains and their use in directed cell therapy are disclosed herein in an effort to meet this need and/or provide other benefits, or at least provide the public with a useful choice. In some [embodiment examples](#), the present disclosure provides dimeric antigen receptors (DAR) comprising first and second polypeptide chains, e.g., that form a Fab fragment joined to transmembrane and intracellular regions, and cells expressing such DARs. In some [embodiment examples](#), T cells expressing DARs can show target-specific expansion and cytotoxicity, e.g., in comparison to T cells expressing a traditional CAR. [Embodiment Examples](#) according to this disclosure are set forth in the claims and the detailed description.

were cultured in RPMI1640 medium (ATCC) supplemented with 10% fetal bovine serum (Sigma).

[00330] EXAMPLE 5: Transfection efficiency and expression levels of DAR-expressing T cells

[00331] Transfection and expression levels of either anti-BCMA chimeric antigen receptor (CAR) or anti-BCMA dimeric antigen receptor (DAR) from transgenic T cells were compared using flow cytometry.

[00332] The transfection efficiency of transgenic T cells (Donor 1) expressing various BCMA (bb2121 or 2C5) CAR or DAR constructs are similar to each other (**Figures 5A and B at day 11; Figure 37 at day 13**). The cell expansion level of cells expressing BCMA-2C5 CAR (83X) was nearly twice that of BCMA-bb2121 CAR (42X). The cell expansion level of cells expressing BCMA-2C5 DAR V3b (72X) was higher compared to cells expressing BCMA-2C5 DAR V2c (57X) and V3a (56X) (**Figure 5B**). The transfection efficiency of transgenic T cells expressing BCMA bb2121 DAR was less than 10% (data not shown).

[00333] The transfection efficiency of transgenic T cells (Donor 2) expressing BCMA-2C5 CAR or DAR constructs varied, where T cells expressing BCMA-2C5 CAR exhibited higher efficiency (62%) compared to T cells expressing BCMA-2C5 V2a (27%) or V3a (17%). The cell expansion level of cells expressing BCMA-2C5 CAR (72X) was higher compared to cells expressing BCMA-2C5 DAR V2c (15X) or V3a (49X) (**Figure 4214**).

[00334] EXAMPLE 6: *In vitro* cytotoxicity assays

[00335] Two to three weeks after preparing the CAR, DAR and control T cells, cells were subjected to nutrient starvation overnight with IL-2. The cells were co-cultured with the target cell mixture of BCMA positive RPMI-8226/GFP cells or BCMA negative K562/RPE cells. The ratio of effector to target cell ranged from 0.16:1 to 5:1. After overnight incubation, the cells were subjected to flow cytometry to measure the GFP cell population to determine the specific target cell killing by anti-BCMA CAR or DAR T cells.

[00336] Transgenic cells (Donor 1) expressing BCMA-2C5 CAR (**Line F**) exhibited a higher level of cell killing compared to BCMA-2C5 DAR V3b (Line E), DAR V3a (**Line D**) and DAR V3a (**Line B**). Transgenic cells expressing BCMA bb2121 CAR (**Line C**) exhibited a higher level of cell killing compared to BCMA-2C5 DAR V3a (**Line B**) (**Figure 6**).

[00337] Transgenic cells (Donor 2) expressing BCMA-2C5 DAR V2a (**Line D**) exhibited a higher level of cell killing compared to cells expressing BCMA-2C5 DAR V3a (**Line C**) or CAR (**Line B**) (**Figure 1312**). ~~See also Figure 40.~~

[00338] **EXAMPLE 7: *In vitro* cytokine secretion assays**

[00339] Two to three weeks after preparing the CAR, DAR and control T cells, the cells were subjected to nutrient starvation overnight with IL-2. The cells were co-cultured with BCMA-negative K562, or BCMA-positive U266 or RPMI8226 cells. The ratio of the effector to target cell was 2:1. After 40 hours incubation, the cells were centrifuged to collect the supernatant for detecting cytokine IFN-gamma (ELISA MAX Delux Set, from BioLegend, catalog No. 430104) or GM-CSF (Human Gm-CSF Uncoated ELISA kit from Invitrogen/Thermo Fisher, catalog No. 88-8337) according to the manufacturer's instructions.

[00340] The results in **Figure 7A** indicate that T cells (Donor 1) expressing BCMA-2C5 DAR V3a or V3b secrete higher levels of IFN-gamma when co-cultured with RPMI8226 cells compared to BCMA-bb2121 CAR, BCMA-2C5 CAR, or BCMA-2C5 DAR V2c.

[00341] The results in **Figure 7B** indicate that T cells (Donor 1) expressing BCMA-2C5 DAR V3a or V3b secrete much higher levels of GM-CSF when co-cultured with RPMI8226 cells compared to BCMA-bb2121 CAR, BCMA-2C5 CAR, or BCMA-2C5 DAR V2c.

[00342] **EXAMPLE 8: *In vitro* expansion of co-cultured transgenic cells**

[00343] Two to three weeks after preparing the CAR, DAR and control T cells, the cells were subjected to nutrient starvation overnight with IL-2. The cells were co-cultured with BCMA-negative K562, or BCMA-positive U266 or RPMI8226 cells. The level of cell expansion was measured using flow cytometry.

[00344] The negative control cells showed little or no expansion (**Figures 8A and 10A**). The transgenic cells (Donor 1) expressing BCMA bb2121 CAR showed higher expansion levels when co-cultured with RPMI8226 or U266 cells compared to co-culture with K562 cells (**Figures 8B and 10B**). The transgenic cells expressing BCMA-2C5 CAR unexpectedly showed high levels of expansion when co-cultured with RPMI8226, U266 and K562 cells (**Figure 8C**) indicating non-specific response. The transgenic cells expressing BCMA-2C5 DAR V2c showed higher expansion levels when co-cultured with RPMI8226 or U266 cells compared to co-culture with K562 cells (**Figure 8D**).

[00345] The fold-change in cell expansion of the co-cultured transgenic cells from Figures 8A-D is shown in the bar graph of **Figure 9**. The transgenic cells (Donor 1) expressing BCMA bb2121 CAR have a higher fold-change in cell expansion when co-cultured with

RPMI8226 or U266 cells, compared to transgenic cells expressing BCMA-2C5 DAR V2a. The transgenic cells expressing BCMA-2C5 CAR have a very low fold-change in cell expansion.

[00346] The transgenic cells (Donor 1) expressing BCMA-2C5 DAR V2c showed higher expansion levels when co-cultured with RPMI8226 or U266 cells compared to co-culture with K562 cells (**Figure 10C and 44B10D**). The transgenic cells expressing BCMA-2C5 DAR V2a (**Figure 44A10C**) or BCMA-2C5 DAR V3a (**Figure 10D10E**) or BCMA-2C5 DAR V3b (**Figure 10E10F**) showed even higher expansion levels when co-cultured with RPMI8226 or U266 cells compared to co-culture with K562 cells.

[00347] The fold-change in cell expansion of the co-cultured transgenic cells from Figures 10A-E10B and 10D-10F is shown in the bar graph of **Figure 11**. The transgenic cells (Donor 1) expressing BCMA bb2121 CAR have a higher fold-change in cell expansion when co-cultured with RPMI8226 cells, compared to transgenic cells expressing BCMA-2C5 DAR V2c, V3a and V3b. The transgenic cells expressing BCMA-2C5 DAR V3a have a higher fold-change in cell expansion when co-cultured with U266 cells, compared to transgenic cells expressing BCMA bb2121 CAR, or BCMA-2C5 DAR V2c or DAR V3b.

[00348] The negative control cells (TCR-minus and ATC) showed little or no expansion when co-cultured with K562, RPMI8226 or Raji cells (**Figures 14A-16A and B**). The transgenic cells (Donor 2) expressing BCMA-2C5 CAR unexpectedly showed high levels of expansion when co-cultured with K562, RPMI8226 or Raji cells (**Figure 14E16C**) indicating non-specific response. The transgenic cells expressing BCMA-2C5 DAR V2a showed higher expansion levels when co-cultured with Raji cells compared to co-culture with K562 or RPMI8226 cells (**Figure 14D16D**). The transgenic cells expressing BCMA-2C5 DAR V3a showed higher expansion levels when co-cultured with Raji cells compared to co-culture with K562 or RPMI8226 cells (**Figure 14E16E**).

[00349] The fold-change in cell expansion of the co-cultured transgenic cells from Figures 14A-E16C-E is shown in the bar graph of **Figure 1517**. The transgenic cells (Donor 2) expressing BCMA-2C5 DAR V2a and V3a have a similar higher fold-change in cell expansion when co-cultured with Raji cells, compared to transgenic cells expressing BCMA-2C5 DAR V2a and V3a when co-cultured with K562 or RPMI8226 cells.

[00350] **Example 9: Detecting memory T cells and central memory T cells**

[00351] The anti-BCMA-2C5 DAR T cells (from Donor 2 cells) were washed with DPBS 5% human serum albumin, then stained with anti-CD3-BV421 antibody (SK7, BioLegend)

WHAT IS CLAIMED:

1. A nucleic acid encoding a precursor polypeptide, the precursor polypeptide comprising:

- a. a plurality of regions ordered from the amino terminus to the carboxyl terminus:
(i) a heavy chain leader sequence, (ii) an antibody heavy chain variable region,
(iii) an antibody heavy chain constant region, (iv) an optional hinge region, (v) a
transmembrane region, (vi) an intracellular region, (vii) a self-cleaving sequence,
(viii) a light chain leader sequence, (ix) an antibody light chain variable region,
and (x) an antibody light chain constant region, wherein the self-cleaving
sequence permits cleaving the of the precursor polypeptide into a first and second
polypeptide chain; or
- b. a plurality of regions ordered from the amino terminus to the carboxyl terminus:
(i) a light chain leader sequence (ii) an antibody light chain variable region, (iii)
an antibody light chain constant region, (iv) an optional hinge region, (v) a
transmembrane region, (vi) an intracellular region, (vii) a self-cleaving sequence,
(viii) a heavy chain leader sequence, (ix) an antibody heavy chain variable region,
and (x) an antibody heavy chain constant region, wherein the self-cleaving
sequence permits cleaving the of the precursor polypeptide into a first and second
polypeptide chain.

~~2. — A precursor polypeptide comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a light chain leader sequence (ii) an antibody light chain variable region, (iii) an antibody light chain constant region, (iv) an optional hinge region, (v) a transmembrane region, (vi) an intracellular region, (vii) a self-cleaving sequence, (viii) a heavy chain leader sequence, (ix) an antibody heavy chain variable region, and (x) an antibody heavy chain constant region, wherein the self-cleaving sequence permits cleaving the of the precursor polypeptide into a first and second polypeptide chain.~~

~~3.2.~~ The precursor polypeptidenucleic acid of claim 1 ~~or 2~~, wherein the antibody heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 6, 12, 14, 16, 18, 20, 22, 24, 26, or 28.

4.3. The ~~precursor polypeptidenucleic acid~~ of ~~any one of claims 1-3~~ claim 1 or 2, wherein the antibody heavy chain constant region comprises:

- a) a human IgG, IgA, IgD, IgE, or IgM CH1 domain;
- b) a human IgG1, IgG2, IgG3, or IgG4 CH1 domain;
- c) a human IgG1 domain;
- d) an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:7 or 29; or
- e) the amino acid sequence of SEQ ID NO:7 or 29.

5.4. The ~~precursor polypeptidenucleic acid~~ of any one of claims 1-~~4~~3, wherein the antibody light chain variable region comprises the amino acid sequence of SEQ ID NO: 8, 9, 10, 13, 15, 17, 19, 21, 23, 25, 27 or 30.

6.5. The ~~precursor polypeptidenucleic acid~~ of any one of claims 1-~~5~~4, wherein the antibody light chain constant region comprises:

- a) a human Ig kappa constant domain;
- b) a human Ig lambda constant domain;
- c) an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:11 or 31; or
- d) the amino acid sequence of SEQ ID NO:11 or 31.

7.6. The ~~precursor polypeptidenucleic acid~~ of any one of claims 1-~~6~~5, wherein the hinge region comprises a hinge sequence from an antibody selected from a group consisting of IgG, IgA, IgM, IgE and IgD.

8.7. The ~~precursor polypeptidenucleic acid~~ of any one of claims 1-~~6~~5, wherein the hinge comprises a CD8 α and/or CD28 hinge region.

9.8. The ~~precursor polypeptidenucleic acid~~ of any one of claims 1-~~6~~5, wherein the hinge region comprises a CPPC or SPPC amino acid sequence.

10.9. The ~~precursor polypeptidenucleic acid~~ of any one of claims 1-~~6~~5, wherein the hinge region comprises the amino acid sequence of SEQ ID NO:34, 35 or 36.

11.10. The precursor polypeptidenucleic acid of any one of claims 1-~~109~~, wherein the transmembrane region comprises a transmembrane sequence from CD8 α , CD8 β , 4-1BB/CD137, CD28, CD34, CD4, Fc ϵ RI γ , CD16, OX40/CD134, CD3 ζ , CD3 ϵ , CD3 γ , CD3 δ , TCR α , TCR β , TCR ζ , CD32, CD64, CD64, CD45, CD5, CD9, CD22, CD33, CD37, CD64, CD80, CD86, CD137, CD154, LFA-1 T cell co-receptor, CD2 T cell co-receptor/adhesion molecule, CD40, CD40L/CD154, VEGFR2, FAS, and FGFR2B.

12.11. The precursor polypeptidenucleic acid of any one of claims 1-~~110~~, wherein the transmembrane region comprises the amino acid sequence of SEQ ID NO: 37, 38, 39 or 40.

13.12. The precursor polypeptidenucleic acid of any one of claims 1-~~121~~, wherein the intracellular region comprises one intracellular sequence or comprises 2-5 intracellular sequences in any order and any combination of intracellular sequences selected from a group consisting of 4-1BB, CD3zeta having ITAM 1, 2 and 3, CD3zeta having ITAM 1, CD3zeta having ITAM 3, CD28, CD27, OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, GITR (TNFRSF18), DR3 (TNFRSF25), TNFR2 and/or CD226.

14.13. The precursor polypeptidenucleic acid of any one of claims 1-~~121~~, wherein the intracellular region comprises:

- i) a CD3zeta having ITAM 1, 2 and 3 which comprises the amino acid sequence of SEQ ID NO:44,
- ii) a CD3zeta ITAM 1 which comprises the amino acid sequence of SEQ ID NO:45,
- iii) a CD3zeta ITAM 2 which comprises the amino acid sequence of SEQ ID NO:46,
- or
- iv) a CD3zeta having ITAM 3 which comprises the amino acid sequence of SEQ ID NO:47.

15.14. The precursor polypeptidenucleic acid of any one of claims 1-~~121~~, wherein the intracellular region comprises:

- i) intracellular sequences from CD28 and from CD3zeta having ITAM 1, 2 and 3, comprising the amino acid sequence of SEQ ID NO:48 or 50, or

- ii) intracellular sequences from 4-1BB and from CD3zeta having ITAM 1, 2 and 3, comprising the amino acid sequence of SEQ ID NO:49, or
- iii) intracellular sequences from CD28, from 4-1BB and from CD3zeta having ITAM 1, 2 and 3, comprising the amino acid sequence of SEQ ID NO:51 or 88, or
- iv) intracellular sequences from 4-1BB and from CD3zeta having ITAM 3, comprising the amino acid sequence of SEQ ID NO:52, or
- v) intracellular sequences from CD28 (SEQ ID NO:42) and from CD3zeta having ITAM 3 (SEQ ID NO:47), or
- vi) intracellular sequences from CD28, from 4-1BB and from CD3zeta having ITAM 3, comprising the amino acid sequence of SEQ ID NO:53 or 89.

~~16.15.~~ The ~~precursor molecule~~nucleic acid of claim 1, ~~comprising wherein the precursor polypeptide comprises~~ the amino acid sequence of SEQ ID NO:63, 66, 69, 72, 75, 78, 81 or 84.

~~17.16.~~ The ~~precursor molecule~~nucleic acid of claim ~~21~~, ~~comprising wherein the precursor polypeptide comprises~~ the orientation and amino acid sequences shown in Figures 4A and B.

~~18.17.~~ The ~~precursor molecule~~nucleic acid of any one of the preceding claims, wherein the self-cleaving sequence is other than a T2A sequence, e.g., the self-cleaving sequence is a P2A, E2A, or F2A sequence.

~~19.— A dimeric antigen receptor (DAR) construct, comprising:~~

- ~~a) a first polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) an antibody heavy chain variable region, (ii) an antibody heavy chain constant region, (iii) an optional hinge region, (iv) a transmembrane region, and (v) an intracellular region;~~
- ~~b) a second polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) an antibody light chain variable region, and (ii) an antibody light chain constant region;~~

~~wherein the antibody heavy chain constant region and the antibody light chain constant region form a dimerization domain for formation of the dimeric antigen receptor (DAR), and~~

~~wherein the antibody heavy chain variable region and the antibody light chain variable region form an antigen binding domain.~~

20. — ~~A dimeric antigen receptor (DAR) construct, comprising:~~

~~a) a first polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) an antibody light chain variable region, (ii) an antibody light chain constant region, (iii) an optional hinge region, (iv) a transmembrane region, and (v) an intracellular region;~~

~~b) a second polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) an antibody heavy chain variable region, and (ii) an antibody heavy chain constant region,~~

~~wherein the antibody heavy chain constant region and the antibody light chain constant region form a dimerization domain for formation of the dimeric antigen receptor (DAR), and~~

~~wherein the antibody heavy chain variable region and the antibody light chain variable region form an antigen binding domain.~~

21. — ~~The dimeric antigen receptor (DAR) construct of claim 18 or 19, wherein the antibody heavy chain constant region and the antibody light chain constant region dimerize via one or two disulfide bonds.~~

22. — ~~The dimeric antigen receptor construct of any one of claims 18-20, wherein the hinge region comprises a hinge sequence from an antibody selected from a group consisting of IgG, IgA, IgM, IgE and IgD.~~

23. — ~~The dimeric antigen receptor construct of any one of claims 18-20, wherein the hinge comprises a CD8 α and/or a CD28 hinge region.~~

24. ~~The dimeric antigen receptor construct of any one of claims 18-20, wherein the hinge region comprises a CPPC or SPPC amino acid sequence.~~
25. ~~The dimeric antigen receptor construct of any one of claims 18-23, wherein the transmembrane region comprises a transmembrane sequence from CD8 α , CD8 β , 4-1BB/CD137, CD28, CD34, CD4, Fc ϵ RI γ , CD16, OX40/CD134, CD3 ζ , CD3 ϵ , CD3 γ , CD3 δ , TCR α , TCR β , TCR ζ , CD32, CD64, CD64, CD45, CD5, CD9, CD22, CD33, CD37, CD64, CD80, CD86, CD137, CD154, LFA-1 T cell co-receptor, CD2 T cell co-receptor/adhesion molecule, CD40, CD40L/CD154, VEGFR2, FAS, and FGFR2B.~~
26. ~~The dimeric antigen receptor construct of any one of claims 18-24, wherein the intracellular region comprises one intracellular sequence or comprises 2-5 intracellular sequences in any order and any combination of intracellular sequences selected from a group consisting of 4-1BB, CD3zeta, CD28, CD27, OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, GITR (TNFRSF18), DR3 (TNFRSF25), TNFR2 and/or CD226.~~
27. ~~The dimeric antigen receptor (DAR) construct of any one of claims 18-25, wherein the antigen binding domain binds a BMCA (B-cell maturation antigen) protein.~~
28. ~~The dimeric antigen receptor (DAR) construct of claim 27, wherein the BMCA (B-cell maturation antigen) protein comprises the amino acid sequence of SEQ ID NO:1, 2 or 3.~~
29. ~~The dimeric antigen receptor (DAR) construct of claim 27, wherein the antibody heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 6, 12, 14, 16, 18, 20, 22, 24, 26, or 28.~~
30. ~~The dimeric antigen receptor (DAR) construct of claim 27, wherein the antibody heavy chain constant region comprises the amino acid sequence of SEQ ID NO:7 or 29.~~

31. ~~The dimeric antigen receptor (DAR) construct of claim 27, wherein the antibody light chain variable region comprises the amino acid sequence of SEQ ID NO: 8, 9, 10, 13, 15, 17, 19, 21, 23, 25, 27 or 30.~~

32. ~~The dimeric antigen receptor (DAR) construct of claim 27, wherein the antibody light chain constant region comprises the amino acid sequence of 11 or 31.~~

33. ~~The dimeric antigen receptor (DAR) construct of claim 27, wherein the hinge region comprises the amino acid sequence of SEQ ID NO:34, 35 or 36.~~

34. ~~The dimeric antigen receptor (DAR) construct of claim 27, wherein the transmembrane region comprises the amino acid sequence of SEQ ID NO:37, 38, 39 or 40.~~

35. ~~The dimeric antigen receptor of claim 27, wherein the intracellular region comprises:~~
~~i) a CD3zeta having ITAM 1, 2 and 3 comprising the amino acid sequence of SEQ ID NO:44,~~
~~ii) a CD3zeta ITAM 1 comprising the amino acid sequence of SEQ ID NO:45,~~
~~iii) a CD3zeta ITAM 2 comprising the amino acid sequence of SEQ ID NO:46, or~~
~~iv) a CD3zeta having ITAM 3 comprising the amino acid sequence of SEQ ID NO:47.~~

36. ~~The dimeric antigen receptor of claim 27, wherein the intracellular region comprises:~~
~~i) intracellular sequences from CD28 and from CD3zeta having ITAM 1, 2 and 3, comprising the amino acid sequence of SEQ ID NO:48 or 50, or~~
~~ii) intracellular sequences from 4-1BB and from CD3zeta having ITAM 1, 2 and 3, comprising the amino acid sequence of SEQ ID NO:49, or~~
~~iii) intracellular sequences from CD28, from 4-1BB and from CD3zeta having ITAM 1, 2 and 3, comprising the amino acid sequence of SEQ ID NO:51 or 88, or~~
~~iv) intracellular sequences from 4-1BB and from CD3zeta having ITAM 3, comprising the amino acid sequence of SEQ ID NO:52, or~~
~~v) intracellular sequences from CD28 (SEQ ID NO:42) and from CD3zeta having ITAM 3 (SEQ ID NO:47), or~~

~~vi) intracellular sequences from CD28, from 4-1BB and from CD3zeta having ITAM 3, comprising the amino acid sequence of SEQ ID NO:53 or 89.~~

~~37. The dimeric antigen receptor (DAR) construct of claim 27, wherein the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:64, 67, 70, 73, 76, 79, 82 or 85.~~

~~38. The dimeric antigen receptor (DAR) construct of claim 27, wherein the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:65, 68, 71, 74, 77, 80, 83, or 86.~~

~~39. The precursor polypeptide of any one of claims 1-18, wherein upon cleavage of the self-cleaving sequence, the heavy chain variable region and the light chain variable region are capable of forming an antigen-binding domain that binds a BMCA (B-cell maturation antigen) protein, optionally wherein the BMCA (B-cell maturation antigen) protein comprises the amino acid sequence of SEQ ID NO:1, 2 or 3.~~

~~40. The dimeric antigen receptor (DAR) construct of claim 27, wherein~~

~~a) the first polypeptide chain comprises a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6, 12, 14, 16, 18, 20, 22, 24, 26, or 28; (ii) an antibody heavy chain constant region; (iii) a hinge region comprising a CD8 and CD28 hinge region; (iv) a CD28 transmembrane region; and (v) an intracellular region comprising a CD28 co-stimulatory sequence and CD3zeta-ITAM 1, 2 and 3 intracellular sequences; and wherein~~

~~b) the second polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 8, 9, 10, 13, 15, 17, 19, 21, 23, 25, 27 or 30; and (ii) an antibody light chain constant region, wherein the antibody heavy chain constant region and the antibody light chain constant region form a dimerization domain, and~~

wherein the antibody heavy chain variable region and the antibody light chain variable region form an antigen-binding domain that binds a BCMA protein; optionally wherein the dimeric antigen receptor (DAR) construct is a DAR-V1 construct.

41.—The dimeric antigen receptor (DAR) construct of claim 27, wherein

- a) the first polypeptide chain comprises a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6, 12, 14, 16, 18, 20, 22, 24, 26, or 28; (ii) an antibody heavy chain constant region; (iii) a hinge region comprising a CD28 hinge region; (iv) a CD28 transmembrane region; and (v) an intracellular region comprising a 4-1BB co-stimulatory sequence and CD3zeta ITAM 1, 2 and 3 intracellular sequences; and wherein
- b) the second polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 8, 9, 10, 13, 15, 17, 19, 21, 23, 25, 27 or 30; and (ii) an antibody light chain constant region, wherein the antibody heavy chain constant region and the antibody light chain constant region form a dimerization domain, and wherein the antibody heavy chain variable region and the antibody light chain variable region form an antigen-binding domain that binds a BCMA protein; optionally wherein the dimeric antigen receptor (DAR) construct is a DAR-V2a construct.

42.—The dimeric antigen receptor (DAR) construct of claim 27, wherein

- a) the first polypeptide chain comprises a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6, 12, 14, 16, 18, 20, 22, 24, 26, or 28; (ii) an antibody heavy chain constant region; (iii) a hinge region; (iv) a CD28 transmembrane region; and (v) an intracellular region

comprising a CD28 co-stimulatory sequence and CD3zeta ITAM 1, 2 and 3 intracellular sequences; and wherein

- b) ~~the second polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 8, 9, 10, 13, 15, 17, 19, 21, 23, 25, 27 or 30; and (ii) an antibody light chain constant region, wherein the antibody heavy chain constant region and the antibody light chain constant region form a dimerization domain, and wherein the antibody heavy chain variable region and the antibody light chain variable region form an antigen binding domain that binds a BCMA protein, optionally wherein the dimeric antigen receptor (DAR) construct is a DAR V2b construct.~~

43. ~~The dimeric antigen receptor (DAR) construct of claim 27, wherein~~

- a) ~~the first polypeptide chain comprises a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6, 12, 14, 16, 18, 20, 22, 24, 26, or 28; (ii) an antibody heavy chain constant region; (iii) a hinge region comprising a CD28 hinge region; (iv) a CD28 transmembrane region; and (v) an intracellular region comprising a 4-1BB co-stimulatory sequence, a CD28 co-stimulatory sequence, and CD3zeta ITAM 1, 2 and 3 intracellular sequences; and wherein~~
- b) ~~the second polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 8, 9, 10, 13, 15, 17, 19, 21, 23, 25, 27 or 30; and (ii) an antibody light chain constant region, wherein the antibody heavy chain constant region and the antibody light chain constant region form a dimerization domain, and wherein the antibody heavy chain variable region and the antibody light chain variable region form an antigen binding domain that binds a BCMA protein,~~

optionally wherein the dimeric antigen receptor (DAR) construct is a DAR-V2c construct.

44. — The dimeric antigen receptor (DAR) construct of claim 27, wherein

- a) — the first polypeptide chain comprises a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody heavy chain variable region comprising the amino acid sequence selected from a group consisting of SEQ ID NO: 6, 12, 14, 16, 18, 20, 22, 24, 26, or 28; (ii) an antibody heavy chain constant region; (iii) a hinge region comprising a CD28 hinge region; (iv) a CD28 transmembrane region; and (v) an intracellular region comprising a 4-1BB co-stimulatory sequence and a CD3zeta-ITAM-3 intracellular sequence, wherein the intracellular region optionally includes an intracellular CD28 co-stimulatory sequence; and wherein
- b) — the second polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 8, 9, 10, 13, 15, 17, 19, 21, 23, 25, 27 or 30; and (ii) an antibody light chain constant region, wherein the antibody heavy chain constant region and the antibody light chain constant region form a dimerization domain, and wherein the antibody heavy chain variable region and the antibody light chain variable region form an antigen binding domain that binds a BCMA protein, optionally wherein the dimeric antigen receptor (DAR) construct is a DAR-V3 construct.

45. — The dimeric antigen receptor (DAR) construct of claim 27, wherein

- a) — the first polypeptide chain comprises a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6, 12, 14, 16, 18, 20, 22, 24, 26, or 28; (ii) an antibody heavy chain constant region; (iii) a CD28 transmembrane region; and (iv) an intracellular region comprising a 4-1BB

co-stimulatory sequence and a CD3zeta ITAM 3 intracellular sequence; and wherein

- b) ~~the second polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody light chain variable region comprising the amino acid sequence of SEQ ID NO:8, 9, 10, 13, 15, 17, 19, 21, 23, 25, 27 or 30; and (ii) an antibody light chain constant region, wherein the antibody heavy chain constant region and the antibody light chain constant region form a dimerization domain, and wherein the antibody heavy chain variable region and the antibody light chain variable region form an antigen binding domain that binds a BCMA protein, optionally wherein the dimeric antigen receptor (DAR) construct is a DAR V4 construct.~~

46. ~~The dimeric antigen receptor (DAR) construct of claim 27, wherein~~

- a) ~~the first polypeptide chain comprises a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody heavy chain variable region comprising the amino acid sequence selected from a group consisting of SEQ ID NO:6, 12, 14, 16, 18, 20, 22, 24, 26, or 28; (ii) an antibody heavy chain constant region; (iii) a hinge region comprising a CD28 hinge region; (iv) a CD28 transmembrane region; and (v) an intracellular region comprising a CD28 co-stimulatory sequence and a CD3zeta ITAM 3 intracellular sequence, wherein the intracellular region optionally includes an intracellular CD28 and 4-1BB co-stimulatory sequence; and wherein~~
- b) ~~the second polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody light chain variable region comprising the amino acid sequence of SEQ ID NO:8, 9, 10, 13, 15, 17, 19, 21, 23, 25, 27 or 30; and (ii) an antibody light chain constant region, wherein the antibody heavy chain constant region and the antibody light chain constant region form a dimerization domain, and wherein the antibody heavy chain variable region and the antibody light chain variable region form an antigen binding domain that binds a BCMA protein,~~

optionally wherein the dimeric antigen receptor (DAR) construct is a DAR-V3c construct.

~~47.—The dimeric antigen receptor (DAR) construct of claim 27, wherein~~

- ~~c)—the first polypeptide chain comprises a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO:6, 12, 14, 16, 18, 20, 22, 24, 26, or 28; (ii) an antibody heavy chain constant region; (iii) a CD28 transmembrane region; and (iv) an intracellular region comprising a 4-1BB co-stimulatory sequence and a CD3zeta ITAM 3 intracellular sequence; and wherein~~
- ~~d)—the second polypeptide chain comprising a plurality of regions ordered from the amino terminus to the carboxyl terminus: (i) a BCMA antibody light chain variable region comprising the amino acid sequence of SEQ ID NO:8, 9, 10, 13, 15, 17, 19, 21, 23, 25, 27 or 30; and (ii) an antibody light chain constant region; wherein the antibody heavy chain constant region and the antibody light chain constant region form a dimerization domain, and wherein the antibody heavy chain variable region and the antibody light chain variable region form an antigen binding domain that binds a BCMA protein; optionally wherein the dimeric antigen receptor (DAR) construct is a DAR-V4 construct.~~

~~48.—The DAR construct of claim 41, wherein the intracellular region comprising the 4-1BB co-stimulatory sequence and CD3zeta ITAM 1, 2 and 3 intracellular sequences comprises the amino acid sequence of SEQ ID NO:49.~~

~~49.—The DAR construct of claim 42, wherein the intracellular region comprising the CD28 co-stimulatory sequence and CD3zeta ITAM 1, 2 and 3 intracellular sequences comprises the amino acid sequence of SEQ ID NO:50.~~

- ~~50. The DAR construct of claim 43, wherein the intracellular region comprising the 4-1BB co-stimulatory sequence, a CD28 co-stimulatory sequence, and CD3zeta ITAM 1, 2 and 3 intracellular sequences comprises the amino acid sequence of SEQ ID NO:51 or 88.~~
- ~~51. The DAR construct of claim 44, wherein the intracellular region comprising the 4-1BB co-stimulatory sequence and a CD3zeta ITAM 3 intracellular sequence comprises the amino acid sequence of SEQ ID NO:52, or the intracellular region comprising a 4-1BB co-stimulatory sequence, a CD28 co-stimulatory sequence and a CD3zeta ITAM 3 intracellular sequence comprises the amino acid sequence of SEQ ID NO:53 or 89.~~
- ~~52. The DAR construct of claim 45, wherein the intracellular region comprising the 4-1BB co-stimulatory sequence and a CD3zeta ITAM 3 intracellular sequence comprises the amino acid sequence of SEQ ID NO:52.~~
- ~~53. The DAR construct of claim 46, wherein the intracellular region comprising the CD28 co-stimulatory sequence and a CD3zeta ITAM 3 intracellular sequence comprises the amino acid sequence of SEQ ID NO:87.~~
- ~~54. The DAR construct of claim 47, wherein the intracellular region comprising the 4-1BB co-stimulatory sequence and a CD3zeta ITAM 3 intracellular sequence comprises the amino acid sequence of SEQ ID NO:52.~~
- ~~55. The DAR construct of claim 40 or 51, wherein the CD8 and CD28 hinge region comprises the amino acid sequence of SEQ ID NO:36.~~
- ~~56. The DAR construct of any one of claims 41-44, 46-49, or 54, wherein the hinge region comprises a CD28 hinge any one of claims region comprising the amino acid sequence of SEQ ID NO:35.~~
- ~~57. The DAR construct of any one of claims 40, 45, or 50, wherein the CD28 transmembrane region comprises the amino acid sequence of SEQ ID NO:37.~~

~~58.— The DAR construct of any one of claims 40-55, wherein the heavy chain constant region comprises:~~

- ~~a) a human IgG, IgA, IgD, IgE, or IgM CH1 domain;~~
- ~~b) a human IgG1, IgG2, IgG3, or IgG4 CH1 domain;~~
- ~~c) a human IgG1 domain;~~
- ~~d) an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:7 or 29; or~~
- ~~e) the amino acid sequence of SEQ ID NO:7 or 29.~~

~~59.— The DAR construct of any one of claims 40-56, wherein the light chain constant region comprises:~~

- ~~a) a human Ig kappa constant domain;~~
- ~~b) a human Ig lambda constant domain;~~
- ~~c) an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:11 or 31; or~~
- ~~d) the amino acid sequence of SEQ ID NO:11 or 31.~~

~~60.— A nucleic acid encoding the precursor polypeptide of any one of claims 1-18.~~

~~61.~~18. An expression vector comprising the nucleic acid of any one of claims 60-17 operably linked to a promoter.

~~62.~~19. A host cell, or a population of host cells, harboring the nucleic acid of any one of claims 60-17 operably linked to a promoter, optionally wherein the nucleic acid is present in an expression vector.

~~63.~~20. The host cell or the population of host cells of claim 6219, wherein the host cell is a T lymphocyte (e.g., regulatory T cell, gamma-delta T cell or cytotoxic T cell), a NK (natural killer) cell, a macrophages, a dendritic cell, a mast cell, an eosinophil, a B lymphocyte, or a monocyte, or the population of host cells comprises T lymphocytes (e.g., regulatory T cells,

gamma-delta T cells or cytotoxic T cells), NK (natural killer) cells, macrophages, dendritic cells, mast cells, eosinophils, B lymphocytes or monocytes.

~~64. The host cell or the population of host cells of claim 62, wherein the host cell is an autologous host cell or the population comprises autologous host cells.~~

~~65. The host cell or the population of host cells of claim 62, wherein the host cell is an allogeneic host cell or the population comprises allogeneic host cells.~~

~~66. A method for preparing a population of host cells expressing a plurality of a dimeric antigen receptor (DAR), comprising: culturing the population of host cells of any one of claims 62-65 under conditions suitable for expressing a plurality of the precursor polypeptide by the population of host cells, and suitable for processing the plurality of precursor polypeptides into a plurality of dimeric antigen receptors (DARs) by the population of host cells, wherein the processing by the population of host cells comprises cleaving the plurality of precursor polypeptide into a plurality of first and second polypeptide chains, assembling the plurality of first and second polypeptide chains with each other to form a plurality of dimeric antigen receptors (DARs), and anchoring the plurality of dimeric antigen receptors (DARs) in the cellular membrane of the population of host cells.~~

~~67. The method of claim 66, wherein the expression vector directs transient introduction of the nucleic acid encoding the precursor polypeptide into the host cell or the population of host cells.~~

~~68. The method of claim 66, wherein the expression vector directs stable insertion of the nucleic acid encoding the precursor polypeptide into the host cells' genome.~~

~~69. The method of claim 66, wherein the expression vector directs transcription and/or translation of the nucleic acid encoding the precursor polypeptide in the host cell or the population of host cells.~~

~~70.—The method of claim 66, wherein the expression vector directs expression of the nucleic acid encoding the precursor polypeptide in the host cell or the population of host cells, wherein expression includes transcription and/or translation of the nucleic acid encoding the precursor polypeptide.~~

~~71.—A population of host cells comprising a plurality of dimeric antigen receptors (DARs) anchored in the cellular membrane of the population of host cells prepared by the method of any one of claims 66-70.~~

~~72.—A population of host cells expressing a plurality of a dimeric antigen receptor (DAR) construct according to any one of claims 19-59, wherein the DAR construct is anchored in the cellular membrane of the population of the host cells.~~

~~73.21.~~ A pharmaceutical composition comprising the population of host cells of claim ~~74-19~~ or ~~72-20~~ and a pharmaceutically-acceptable excipient.

~~74.22.~~ Use of ~~A method for treating a subject having a disease, disorder or condition associated with detrimental expression of a tumor antigen in the subject, comprising: administering to the subject~~ the population of host cells of claim ~~74-19~~ or ~~72-20~~ or the pharmaceutical composition of claim ~~73-21~~ in the manufacture of a medicament for treating a subject having a disease, disorder or condition associated with detrimental expression of a tumor antigen in the subject.

~~75.23.~~ The ~~method-use~~ of claim ~~74-22~~, wherein the disease is a hematologic cancer selected from the group consisting of non-Hodgkin's lymphoma (NHL), Burkitt's lymphoma (BL), B chronic lymphocytic leukemia (B-CLL), B and T acute lymphocytic leukemia (ALL), T cell lymphoma (TCL), acute myeloid leukemia (AML), hairy cell leukemia (HCL), Hodgkin's Lymphoma (HL), chronic myeloid leukemia (CML) and multiple myeloma (MM).

~~76.—A first nucleic acid encoding the first polypeptide of any one of claims 19-59.~~

~~77.—A second nucleic acid encoding the second polypeptide of any one of claims 19-59.~~

~~78.—A first nucleic acid encoding the first polypeptide and a second nucleic acid encoding the second polypeptide of any one of claims 19-59.~~

~~79.—A first expression vector comprising the first nucleic acid of claim 78 operably linked to a promoter and a second expression vector comprising the second nucleic acid of claim 78 operably linked to a promoter.~~

~~80.—An expression vector comprising the first and second nucleic acid of claim 78 operably linked to a promoter.~~

~~81.—A first host cell, or a first population of host cells, harboring the first expression vector of claim 79.~~

~~82.—A second host cell, or a second population of host cells, harboring the second expression vector of claim 79.~~

~~83.—A first host cell, or a first population of host cells, harboring the first expression vector of claim 79, and a second host cell, or a second population of host cells, harboring the second expression vector of claim 79.~~

~~84.—A host cell, or a population of host cells, harboring the first and second expression vectors of claim 79.~~

~~85.—A host cell, or a population of host cells, harboring the expression vector of claim 80.~~

~~86.—The host cell or the population of host cells of any one of claims 81-84, wherein the host cell is a T lymphocyte (e.g., regulatory T cell, gamma-delta T cell or cytotoxic T cell), a NK (natural killer) cell, a macrophages, a dendritic cell, a mast cell, an eosinophil, a B lymphocyte, or a monocyte or the population comprises T lymphocytes (e.g., regulatory T~~

cells, gamma-delta T cells or cytotoxic T cells), NK (natural killer) cells, macrophages, dendritic cells, mast cells, eosinophils, B lymphocytes or monocytes.

87. — ~~The host cell or the population of host cells of any one of claims 81-84, wherein the host cell is an autologous host cell or the population comprises autologous host cells.~~

88. — ~~The host cell or the population of host cells of any one of claims 81-84, wherein the host cell is an allogeneic host cell or the population comprises allogeneic host cells.~~

89. — ~~A method for preparing a plurality of a dimeric antigen receptor (DAR), comprising: culturing the first and second population of host cells of claim 83 under conditions suitable for expressing a plurality of the first and second polypeptide chains.~~

90. — ~~A method for preparing a plurality of a dimeric antigen receptor (DAR), comprising: culturing the population of host cells of claim 84 under conditions suitable for expressing a plurality of the first and second polypeptide chains by the population of host cells, and suitable for processing the plurality of first and second polypeptides into a plurality of dimeric antigen receptors (DARs) by the population of host cells, wherein the processing by the population of host cells comprises assembling the plurality of first and second polypeptide chains with each other to form a plurality of dimeric antigen receptors (DARs), and anchoring the plurality of dimeric antigen receptors (DARs) in the cellular membrane of the population of host cells.~~

91. — ~~A method for preparing a plurality of a dimeric antigen receptor (DAR), comprising: culturing the population of host cells of claim 85 under conditions suitable for expressing a plurality of the first and second polypeptide chains by the population of host cells, and suitable for processing the plurality of first and second polypeptides into a plurality of dimeric antigen receptors (DARs) by the population of host cells, wherein the processing by the population of host cells comprises assembling the plurality of first and second polypeptide chains with each other to form a plurality of dimeric antigen receptors (DARs), and anchoring the plurality of dimeric antigen receptors (DARs) in the cellular membrane of the population of host cells.~~

92.—~~The method of claim 89, wherein the first expression vector directs transient introduction of the nucleic acid encoding the first polypeptide chain into the first host cell or the first population of host cells, and wherein the second expression vector directs transient introduction of the nucleic acid encoding the second polypeptide chain into the second host cell or the second population of host cells.~~

93.—~~The method of claim 89, wherein the first expression vector directs stable insertion of the nucleic acid encoding the first polypeptide chain into the first host cells' genome, and wherein the second expression vector directs stable insertion of the nucleic acid encoding the second polypeptide chain into the second host cells' genome.~~

94.—~~The method of claim 89, wherein the first expression vector directs transcription and/or translation of the nucleic acid encoding the first polypeptide chain in the first host cell or the first population of host cells, and wherein the second expression vector directs transcription and/or translation of the nucleic acid encoding the second polypeptide chain in the second host cell or the second population of host cells.~~

95.—~~The method of claim 90, wherein the first expression vector directs transient introduction of the nucleic acid encoding the first polypeptide chain into the host cell or the population of host cells, and wherein the second expression vector directs transient introduction of the nucleic acid encoding the second polypeptide chain into the host cell or the population of host cells.~~

96.—~~The method of claim 90, wherein the first expression vector directs stable insertion of the nucleic acid encoding the first polypeptide chain into the host cells' genome, and wherein the second expression vector directs stable insertion of the nucleic acid encoding the second polypeptide chain into the host cells' genome.~~

97.—~~The method of claim 90, wherein the first expression vector directs transcription and/or translation of the nucleic acid encoding the first polypeptide chain in the host cell or the population of host cells, and wherein the second expression vector directs transcription~~

and/or translation of the nucleic acid encoding the second polypeptide chain in the host cell or the population of host cells.

98. ~~The method of claim 91, wherein the expression vector directs transient introduction of the nucleic acid encoding the first and second polypeptide chains into the host cell or the population of host cells.~~

99. ~~The method of claim 91, wherein the expression vector directs stable insertion of the nucleic acid encoding the first and second polypeptide chains into the host cells' genome.~~

100. ~~The method of claim 91, wherein the expression vector directs transcription and/or translation of the nucleic acid encoding the first and second polypeptide chains in the host cell or the population of host cells.~~

101. ~~A population of host cells comprising a plurality of dimeric antigen receptors (DARs) anchored in the cellular membrane of the population of host cells prepared by the method of any one of claims 90-100.~~

102. ~~A population of host cells expressing a plurality of a dimeric antigen receptor (DAR) construct according to any one of claims 19-59 anchored in the cellular membrane of the population of the host cells.~~

103. ~~A pharmaceutical composition comprising the population of host cells of claim 101 or 102 and a pharmaceutically acceptable excipient.~~

104. ~~A method for treating a subject having a disease, disorder or condition associated with detrimental expression or over-expression of a tumor antigen in the subject, comprising: administering to the subject the population of host cells of claim 101 or 102 or the pharmaceutical composition of claim 103.~~

105. ~~The method of claim 104, wherein the disease is a hematologic cancer selected from the group consisting of non-Hodgkin's lymphoma (NHL), Burkitt's lymphoma (BL), B chronic lymphocytic leukemia (B-CLL), B and T acute lymphocytic leukemia (ALL), T cell~~

~~lymphoma (TCL), acute myeloid leukemia (AML), hairy cell leukemia (HCL), Hodgkin's Lymphoma (HL), chronic myeloid leukemia (CML) and multiple myeloma (MM).~~

24. A polypeptide encoded by the nucleic acid of any one of claims 1-17.

25. The population of host cells of claim 19 or 20 or the pharmaceutical composition of claim 21 for use in therapy.