therapies that can be delivered immediately upon need (*see, e.g.*, Graham *et al.*, Cells 2018, 7, 155; doi:10.3390/cells7100155). Additionally, allogeneic therapies enable selection on desirable product characteristics (e.g. gene editing efficiency, site of integration, lack of deleterious off-target gene edits, haplotype, etc.), and facilitate more sophisticated cell engineering (e.g. multiple gene edits improving potency, persistence, homing, etc.). A major hurdle to implementing allogeneic CAR-modified cell therapies is the potential for rejection of the product (donor) by the immune system of the patient (host).

[0006] While allogeneic cell therapies present a number of advantages over autologous cell therapies, allogeneic cells also face rejection by host or recipient immune system cells reactive with T and NK epitope determinants on the surface of the allogeneic cell product that are distinct from host. The present disclosure provides the advantages of improved allogeneic therapies that provide increased persistence of the administered cells despite the recipients' natural defenses.

SUMMARY

[0007] Described herein are immune cells that have been engineered e.g. genetically engineered to improve their persistence in a host or recipient into which or whom the cells have been introduced, compositions and populations comprising the engineered cells and methods of treating a condition e.g. a cancer in a patient using the same. The immune cells of the instant disclosure are engineered to functionally express a first antigen binding protein and a second, different antigen binding protein, e.g. a first CAR and a second CAR. The first antigen binding protein e.g. CAR is selected for its suitability for therapeutic treatment of a condition e.g. a cancer in a patient. For example, the first antigen binding protein may be a CAR that recognizes an antigen that is expressed by e.g. that is characteristic of cells that cause the condition, e.g. cancer cells and/or tumor cells. The second antigen binding protein e.g. a CD70-binding protein such as a CAR has binding specificity for CD70, which is expressed on recipient immune cells in response to, for example, allogeneic CAR T cells. The engineered cell thus can defend itself against the recipient's immune response, thereby prolonging the survival of the allogeneic cells after administration. Alternatively, one antigen binding protein e.g. one CAR may comprise both the "therapeutic" binding activity and the CD70 binding activity. The present disclosure thus describes a method of increasing persistence of e.g. allogeneic CAR T cells or any other allogeneic CAR immune cell (e.g. CAR NK cell), the method comprising engineering the CAR cell e.g. CAR T cell, CAR NK cell, CAR monocyte or CAR macrophages

to functionally express an anti-CD70 antigen binding protein e.g. a CD70-binding protein such as an anti-CD70 CAR in addition to the first antigen binding protein e.g. CAR that the cell functionally expresses.

[0008] This approach potentially provides a safer alternative to deep lymphodepletion regimens since CD70-negative immune cells are not expected to be targeted by the CD70 CAR, thus avoiding long-term immunosuppression. Additionally, CD70 is also expressed by malignant cells in a variety of tumors, including renal cell carcinoma, lymphoma and acute myeloid leukemia. Engineering T cells to express CARs against CD70 and a second tumor-specific target, such as CD19 or CD20, either as separate CARs or as a single CAR with dual specificity, may therefore enhance the antitumor efficacy and persistence of CAR T cells and delay rejection by the host immune system. In one aspect, the present disclosure refers to the use of engineered T cells in the manufacture of a medicament for lymphodepletion in a patient in need thereof, wherein the engineered T cells comprise or functionally express a CD70 binding protein that comprises a CD70 binding domain comprising a CD70 antibody or fragment thereof, a transmembrane domain, a CD3ζ signaling domain and does not comprise a costimulatory domain, wherein the engineered T cells further comprise or functionally express an additional antigen binding protein specific for a target of interest, wherein the additional antigen binding protein is expressed as a separate protein from the CD70 binding protein, and wherein the engineered T cells inhibit proliferation and/or activity of CD70 positive cells in the patient.

[0009] In one example, the present disclosure refers to a method of inhibiting proliferation and/or activity of CD70 positive cells in vitro or in a patient, comprising the step of contacting the CD70 positive cells with engineered immune cells that comprise or functionally express a CD70-binding protein comprising an extracellular ligand-binding domain that binds to CD70 (or a CD70 binding domain) and a transmembrane domain. In a related example, the present disclosure describes a method of lymphodepletion in a patient in need thereof, comprising the step of administering engineered immune cells to the patient, wherein the engineered immune cells comprise or functionally express a CD70-binding protein comprising an extracellular ligand-binding domain that binds to CD70 (or a CD70 binding domain) and a transmembrane domain, and wherein the engineered immune cells inhibit proliferation and/or activity of CD70 positive cells in the patient. In one

aspect, the present disclosure refers to the use of engineered T cells and optionally a separate therapeutic agent in the manufacture of a medicament for treating a disease condition in a patient in need thereof, wherein the engineered T cells comprise or functionally express a CD70 binding protein that comprises a CD70 binding domain comprising an anti-CD70 scFv, a transmembrane domain, and a CD3ζ signaling domain and does not comprise a costimulatory domain, wherein the engineered T cells further comprise or functionally express an additional antigen binding domain specific for a target of interest, wherein the additional antigen binding domain is expressed as a separate protein from the CD70 binding protein, wherein the disease condition is a cancer or an autoimmune disorder, and wherein the engineered T cells inhibit proliferation and/or activity of CD70 positive cells in the patient. In some examples, the CD70 positive cells are T cells, B cells or NK cells. In some examples, the CD70 positive cells are normal or non-cancerous lymphocytes. In some examples, the CD70 positive cells are activated lymphocytes. In some examples, the CD70 positive cells are activated T cells.

[0010] In another example, the present disclosure refers to an engineered T cell that functionally expresses a protein comprising a first antigen binding domain and a protein comprising a second antigen binding domain, wherein the first antigen binding domain specifically binds a target of interest and the second antigen binding domain specifically binds CD70 (e.g., a CD70-binding protein). In one aspect, the present disclosure refers to an engineered T cell that functionally expresses a protein comprising a first antigen binding domain and a protein comprising a second antigen binding domain, wherein the first antigen binding domain specifically binds a target of interest and the second antigen binding domain specifically binds CD70, wherein optionally the second antigen binding domain comprises an anti-CD70 scFv, an anti-CD70 VHH, an anti-CD70 VH or a receptor for CD70, wherein optionally the receptor for CD70 is CD27 or a CD70-binding fragment thereof, wherein the protein comprising the first antigen binding domain is a first CAR and the protein comprising the second antigen binding domain is a second CAR, wherein the first antigen binding domain is expressed as a separate protein from the second antigen binding domain, and wherein the second antigen binding domain comprises a CD3ζ signaling domain and does not comprise a costimulatory domain. In various examples, the protein comprising the first antigen binding domain is a first protein and the protein comprising the second antigen binding domain is a second protein separate and distinct from the first protein. In various examples, the protein comprising the first antigen binding domain is a first CAR and the protein

Ther.-Nucleic Acids 4:e252 (2015), doi:10.1038/mtna.2015.23; Sridharan and Gogtay, Brit. J. Clin. Pharmacol. 82: 659-72 (2016)). In some examples, the engineered immune cell disclosed herein exhibits a reduced level of expression of an MHC class I protein or complex at the cell surface relative to a suitable control. In various examples, the cell is a T cell e.g. a human T cell. In some examples, the cell comprises a mutation in one or more of the CD70, CD52 and TRAC locus or gene and/or a disruption in one or more of the CD70, CD52 and TRAC locus or gene that causes a reduction in functional expression of the disrupted locus or gene. In an example, the mutation or disruption is introduced into one or more of the CD70, CD52 and TRAC genes or loci by any gene mutation or gene editing technique, including but not limited to known homologous recombination techniques and techniques that employ any one or more of meganucleases, TALEN, zinc fingers, shRNA, Cas-CLOVER, and a CRISPR/Cas system. In some examples, the cell is a non-human cell, e.g. a primate cell or a non-primate mammalian cell. In some examples, the cell is a human cell. In some examples, the mutation or disruption is produced by knocking in a nucleic acid e.g. a nucleic acid that encodes one or more proteins or gene products to be expressed in the cell. In some examples, the nucleic acid encodes either or both of the first CAR and the second CAR.

[0014] Described herein is an engineered immune cell that functionally expresses a protein comprising a first antigen binding domain and a protein comprising a second antigen binding domain, wherein the first antigen binding domain specifically binds a target of interest and the second antigen binding domain specifically binds CD70 (or a CD70-binding protein), and the uses thereof.

[0015] In various examples, the protein comprising the first antigen binding domain is a first CAR and the protein comprising the second antigen binding domain is a second CAR. In some examples, the second antigen binding domain is a CAR e.g. second CAR that comprises one or more than one costimulatory domains. In some examples, the second antigen binding domain is a CAR e.g. second CAR that does not comprise a costimulatory domain. In some examples, the second antigen binding domain is a CAR e.g. second CAR that optionally comprises one or more than one costimulatory domains.

[0016] In various examples, one protein comprises both the first antigen binding domain and the second antigen binding domain. In certain examples, the one protein is a bispecific CAR.

examples, one or both vectors are adeno-associated virus (AAV) vectors. In certain examples, the first nucleic acid and/or the second nucleic acid is located within a disrupted TRAC, CD52 or CD70 locus. In certain examples, one vector comprises both the first nucleic acid and the second nucleic acid. In some examples, the vector is a lentiviral vector or an AAV vector.

[0021] In certain examples, the engineered immune cell comprises one nucleic acid that encodes both the protein comprising a first antigen binding domain and the protein comprising a second antigen binding domain. In some examples, a vector comprises the one nucleic acid. In some examples, the vector is a lentiviral vector or an AAV vector. In certain examples, the one nucleic acid is located within a disrupted TRAC, CD52 or CD70 locus.

[0022] In various examples, the engineered immune cell comprises or further comprises one or more genomic modifications, e.g. a modification of an endogenous genetic locus, for example, of one or both alleles of one or more of the following: an endogenous CD70 gene, an endogenous TCRa gene and an endogenous CD52 gene. In various examples, the one or more genomic modifications cause a reduction or absence of functional expression of the gene that contains the modification. In various examples, the modification comprises a disruption of the locus, e.g. a knockout, knockdown or knock-in. In various examples, the disruption comprises the insertion of a first nucleic acid encoding the protein comprising a first antigen binding domain and/or a second nucleic acid encoding the protein comprising a second antigen binding domain. In various examples, the modification causes a reduction or absence of functional expression of the gene by knockdown, e.g., antisense RNA, siRNA, miRNA, shRNA-mediated knockdown.

[0023] The engineered immune cell described herein can be derived from or prepared from cells from any of various sources. The engineered immune cell can be prepared or derived from one or more cells e.g. stem cells or immune cells from a person other than the person to whom the engineered immune cells will be administered, e.g. a donor (e.g. a healthy volunteer) other than the recipient, or can be prepared or derived from cells e.g. stem cells or immune cells from the person to whom the engineered immune cells will be administered (the recipient), or can be derived from one or more induced pluripotent stem cells (iPSCs). In various examples, the engineered immune cell disclosed herein is or is derived from an immune cell obtained from a healthy volunteer, is obtained from a patient, or is derived from an iPSC.

[0024] Also described herein is a population of engineered immune cells as disclosed herein. In various examples, the population comprises between 10^3 and 10^{10} engineered immune cells described herein, e.g. 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, or 10^{10} engineered immune cells, or any range between any two of those values. In one aspect, the present disclosure refers to a population of cells comprising between 10^3 and 10^{10} T immune cells. In certain examples, no more than 75%, no more than 50%, or no more than 25% of the engineered immune cells of the population functionally express any one of TRAC, CD52 and CD70 or any two or more of TRAC, CD52 and CD70. In another aspect, the present disclosure refers to a population of engineered T cells as described herein wherein no more than 75% of the engineered T cells functionally express one or more of TRAC, CD52 and CD70. In certain examples, no more than 75%, no more than 50%, or no more than 25% of the engineered immune cells of the population functionally express TRAC. In certain examples, no more than 75%, no more than 50%, or no more than 25% of the engineered immune cells of the population functionally express CD52. In certain examples, no more than 75%, no more than 50%, or no more than 25% of the engineered immune cells of the population functionally express TRAC, and no more than 75%, no more than 50%, or no more than 25% of the engineered immune cells of the population functionally express CD52.

[0025] Also described herein is a population of cells, wherein the population of cells comprises at least 10% engineered immune cells disclosed herein, at least 20% engineered immune cells disclosed herein, at least 30% engineered immune cells disclosed herein, at least 40% engineered immune cells disclosed herein, at least 50% engineered immune cells disclosed herein, at least 75% engineered immune cells disclosed herein, or at least 90% engineered immune cells disclosed herein. In certain examples, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 75%, or at least 90% of the engineered cells comprise one or more genomic modifications of one or more of an endogenous TCRa (or TRAC) gene, an endogenous CD52 gene and an endogenous CD70 gene. In various examples, the population of cells comprises between 10^3 and 10^{10} cells.

[0026] In various examples, the populations of cells and of engineered immune cells disclosed herein are derived from one or more immune cells obtained from a healthy volunteer, from one or more immune cells obtained from a patient, or from one or more induced pluripotent stem cells (iPSCs).

[0027] Also described herein is a pharmaceutical composition comprising one or more of the engineered immune cells disclosed herein or comprising a population of cells or of

engineered immune cells disclosed herein, and further comprising at least one pharmaceutically acceptable carrier or excipient. In one aspect, the present disclosure refers to a pharmaceutical composition comprising one or more of the engineered T cells as described herein or the population of T immune cells as described herein, and further comprising at least one pharmaceutically acceptable carrier or excipient.

[0028] Further described herein is a method of making the engineered immune cell disclosed herein that comprises one or more genomic modifications of one or more of an endogenous TCRa gene, an endogenous CD52 gene and an endogenous CD70 gene, the method comprising the use of one or more gene editing technologies selected from the group consisting of TALENs, zinc fingers, Cas-CLOVER, and a CRISPR/Cas system and/or the use of any known gene knockdown methods e.g. those that employ any of various RNA-based techniques (e.g. shRNA, antisense RNA, miRNA, siRNA; *see, e.g.*, Lam *et al.*, Mol. Ther.-Nucleic Acids 4:e252 (2015), doi:10.1038/mtna.2015.23; Sridharan and Gogtay, Brit. J. Clin. Pharmacol. 82: 659-72 (2016)) to reduce functional expression of one or more than one of TRAC, CD52 and CD70 in an engineered immune cell disclosed herein, and/or functional expression from any other locus. In yet another aspect, the present disclosure refers to a method of making the engineered T cell as described herein comprising the use of one or more gene editing technologies selected from the group consisting of TALENs, zinc fingers, Cas-CLOVER, and a CRISPR/Cas system to reduce functional expression of one or more of TRAC, CD52 and CD70 in an immune cell.

[0029] In another aspect, the present disclosure refers to a method of making the engineered T cell as described herein comprising introducing into a T cell a first nucleic acid encoding the protein comprising a first antigen binding domain and a second nucleic acid encoding the protein comprising a second antigen binding domain. In certain examples, one vector comprises both the first nucleic acid and the second nucleic acid. In various examples, the vector is a lentiviral vector. In various examples, a first vector comprises the first nucleic acid and a second vector comprises the second nucleic acid. In certain examples, either or both of the first vector and the second vector are lentiviral vectors. In various examples, the protein comprising a first antigen binding domain is a CAR and/or the protein comprising a second antigen binding domain is a CD70 CAR. In various examples, the protein comprising a first antigen binding domain and the protein comprising a second antigen binding domain (i.e. CD70 binding domain) are physically separate and distinct proteins. In certain examples, the separate and distinct proteins are expressed from a bicistronic expression cassette, separated by, for example, a P2A or T2A peptide. In some examples, the protein comprising the first antigen binding domain is N-terminal to the protein comprising the CD70 binding domain. In some examples, the protein comprising the CD70 binding domain is N-terminal to the protein comprising the first antigen binding domain. In various examples, the protein comprising a first

antigen binding domain and the protein comprising a second antigen binding domain (i.e. CD70 binding domain) are the same protein, e.g. a bispecific CAR.

[0030] Also described herein is a method of treating a condition or disease in a patient comprising administering to the patient one or more of any one or more of the engineered immune cells disclosed herein, or a population of cells or of engineered immune cells as

disclosed herein, or a composition as disclosed herein. In another aspect, the present disclosure refers to the use of one or more of the engineered T cells as described herein, the population of engineered T cells as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a condition or disease in a patient, wherein the condition or disease is a cancer or an autoimmune disease. In various examples, the condition or disease is a solid tumor or a hematological tumor. In various examples, the condition or disease is a viral disease, a bacterial disease, a cancer, an inflammatory disease, an immune disease, or an aging-associated disease. In various examples, the condition or disease is selected from the group consisting of gastric cancer, sarcoma, lymphoma (including Non-Hodgkin's lymphoma), leukemia, head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma, leukemia, multiple myeloma, renal cell carcinoma, bladder cancer, cervical cancer, choriocarcinoma, colon cancer, oral cancer, skin cancer, and melanoma. In various examples, the patient is a previously treated adult subject with locally advanced or metastatic melanoma, squamous cell head and neck cancer (SCHNC), ovarian carcinoma, sarcoma, or relapsed or refractory classic Hodgkin's Lymphoma (cHL).

[0031] In various examples, the method comprises administering about 10^3 or 10^4 to about 10^9 engineered immune cells disclosed herein per kg body weight, or about 10^5 to about 10^6 cells of engineered immune cells disclosed herein per kg body weight, or between $0.1x10^6$ and $5x10^6$ engineered immune cells disclosed herein per kg body weight.

[0032] In various examples, the cells are administered as a single dose. In various examples, the cells are administered as more than one dose over a period of time.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] FIG. 1 illustrates the functions of an allogeneic CAR T cell that comprises both a first CAR that can recognize and bind to a tumor antigen and a second CAR, termed "CD70 Dagger" in the drawing, that can recognize and bind to CD70. The first, anti-tumor antigen CAR, causes the recognized tumor cell to lyse. The second, anti-CD70 CAR, a.k.a. CD70 Dagger, causes the lysis of immune cells (e.g. NK and/or T cells) of the patient (recipient of the allogeneic CAR T cell) that respond to and/or attack the allogeneic CAR T cell. The allogeneic CAR T cell thereby persists longer by preventing or limiting the attack by the patient's immune cells.

[0034] **FIGs. 2A-2D.** Graft donor CD70 CAR T cells are protected from killing by recipient alloreactive T cells. PBMCs from eight recipient donors were co-cultured with irradiated graft donor T cells for 7 days to allow for priming and expansion of alloreactive recipient T cells (RTCs). **FIG. 2A.** Primed alloreactive RTCs were then isolated and co-cultured either with

WHAT IS CLAIMED IS

1. Use of engineered T cells in the manufacture of a medicament for lymphodepletion in a patient in need thereof, wherein the engineered T cells comprise or functionally express a CD70 binding protein that comprises a CD70 binding domain comprising a CD70 antibody or fragment thereof, a transmembrane domain, and a CD3ζ signaling domain and does not comprise a costimulatory domain, wherein the engineered T cells further comprise or functionally express an additional antigen binding protein specific for a target of interest, wherein the additional antigen binding protein is expressed as a separate protein from the CD70 binding protein, and wherein the engineered T cells inhibit proliferation and/or activity of CD70 positive cells in the patient.

2. The use of claim 1, wherein the CD70 binding protein further comprises a hinge domain, optionally the hinge domain comprises a CD8 hinge.

3. The use of claim 1 or 2, wherein the CD3ζ signaling domain comprises the amino acid sequence of one or more of SEQ ID NOs:272, 283-285, 289-295, 311-319, 323-327, 329-331, and 335.

4. The use of any one of the preceding claims, wherein the CD70 positive cells are normal or non-cancerous or alloreactive lymphocytes in the patient.

5. The use of claim 4, wherein the CD70 positive cells are T cells, B cells, or NK cells, optionally wherein the CD70 positive cells are activated T cells.

6. The use of any one of the preceding claims, wherein the engineered T cells are autologous or allogeneic to the patient.

7. The use of any one of the preceding claims, wherein the engineered T cells further comprise one or more genomic modifications of one or more of an endogenous TCRa gene, an endogenous CD52 gene, and an endogenous CD70 gene, wherein the engineered T cells exhibit reduced level of TCRa, CD52 and/or CD70 protein expression and/or activity as compared to a control T cell without the one or more genomic modifications.

8. The use of any one of the preceding claims, wherein the patient has or is expected to have a host v. graft rejection.

9. The use of any one of the preceding claims, wherein the patient is in need for a transplant, optionally wherein the transplant is a bone marrow transplant, stem cell transplant, or tissue transplant.

10. The use of claim 1, wherein the separate protein further comprises a transmembrane domain, and an intracellular signaling domain.

11. The use of claim 10, wherein the separate protein comprises an intracellular signaling domain selected from the group consisting of a CD3ζ signaling domain, a CD28 signaling domain and a 4-1BB signaling domain.

12. The use of claim 10 or 11, wherein the separate protein is a CAR specific for the target of interest, and wherein the engineered T cells are CAR T cells.

13. The use of claim 12, wherein the patient is to be further administered a chemotherapy agent before, simultaneously, or following administration of the CAR T cells, and optionally the chemotherapy agent is cyclophosphamide.

14. The use of claim 12 or 13, wherein the patient is not to be administered fludarabine before, simultaneously, or following administration of the CAR T cells.

15. The use of any one of claims 1-14, wherein the target of interest is a target associated with a disease condition.

16. The use of claim 15, wherein the disease condition is cancer or an autoimmune disorder.

17. The use of claim 15 or 16, wherein the target of interest is BCMA, EGFRvIII, Flt-3, CD20, CD22, CD23, CD30, CD38, CD33, CD133, WT1, TSPAN10, MHC-PRAME, HER2, MSLN, PSMA, PSCA, GPC3, Liv1, ADAM10, CHRNA2, LeY, NKG2D, CS1, CD44v6, ROR1 , CD19, Claudin-18.2 (Claudin-18A2, or Claudin18 isoform 2), DLL3 (Delta-like protein 3, Drosophila Delta homolog 3, Delta3), Muc17, Muc3, Muc16, FAP alpha (Fibroblast Activation Protein alpha), Ly6G6D (Lymphocyte antigen 6 complex locus protein G6d, c6orf23, G6D, MEGT1, NG25), or RNF43 (E3 ubiquitin-protein ligase RNF43, RING finger protein 43).

18. The use of any one of the preceding claims, wherein the engineered T cells are genetically modified at the CD70 locus to reduce the level of CD70 expression.

19. Use of engineered T cells that comprise or functionally express a CD70 binding protein that comprises a CD70 binding domain comprising an anti-CD70 scFv, a transmembrane domain, and a CD3ζ signaling domain and does not comprise a costimulatory domain, wherein the engineered T cells further comprise or functionally express an additional antigen binding domain specific for a target of interest, wherein the additional antigen binding domain is expressed as a separate protein from the CD70 binding protein, and optionally a separate therapeutic agent in the manufacture of a medicament for treating a disease condition in a patient in need thereof, wherein the disease condition is a cancer or an

autoimmune disorder, wherein the engineered T cells inhibit proliferation and/or activity of CD70 positive cells in the patient.

20. The use of claim 19, wherein the CD70 positive cells are normal or non-cancerous or alloreactive lymphocytes.

21. The use of claim 19 or 20, wherein the additional antigen binding domain comprises an antibody that binds to the target of interest, and optionally the antibody that binds to the target of interest is a scFv.

22. The use of any one of claims 19 to 21, wherein the separate protein is a CAR specific for the target of interest, and the engineered T cells are CAR T cells.

23. The use of claim 22, wherein the patient is to be administered a chemotherapy agent before, simultaneously, or following administration of the CAR T cells, and optionally the chemotherapy agent is cyclophosphamide.

24. The use of claim 22 or 23, wherein the patient is not to be administered fludarabine before, simultaneously, or following administration of the CAR T cells.

25. The use of claim 22, wherein the CAR specific for the target of interest further comprises a transmembrane domain, and an intracellular signaling domain.

26. The use of claim 25, wherein the intracellular signaling domain comprises a CD3z signaling domain, a CD28 signaling domain or a 4-1BB signaling domain.

27. The use of any one of claims 19-26, wherein the target of interest is a target associated with the disease condition.

28. The use of any one of claims 19-27, wherein the target of interest is BCMA, EGFRvIII, Flt-3, CD20, CD22, CD23, CD30, CD38, CD33, CD133, WT1, TSPAN10, MHC-PRAME, HER2, MSLN, PSMA, PSCA, GPC3, Liv1, ADAM10, CHRNA2, LeY, NKG2D, CS1, CD44v6, ROR1 , CD19, Claudin-18.2 (Claudin-18A2, or Claudin18 isoform 2), DLL3 (Delta-like protein 3, Drosophila Delta homolog 3, Delta3), Muc17, Muc3, Muc16, FAP alpha (Fibroblast Activation Protein alpha), Ly6G6D (Lymphocyte antigen 6 complex locus protein G6d, c6orf23, G6D, MEGT1, NG25), or RNF43 (E3 ubiquitin-protein ligase RNF43, RING finger protein 43).

29. The use of any one of claims 19 to 28, wherein the disease condition is cancer and the cancer is selected from the group consisting of gastric cancer, sarcoma, lymphoma (including Non-Hodgkin's lymphoma), leukemia, head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma,

leukemia, multiple myeloma, renal cell carcinoma, bladder cancer, cervical cancer, choriocarcinoma, colon cancer, oral cancer, skin cancer, and melanoma.

30. An engineered T cell that functionally expresses a protein comprising a first antigen binding domain and a protein comprising a second antigen binding domain, wherein the first antigen binding domain specifically binds a target of interest and the second antigen binding domain specifically binds CD70, wherein optionally the second antigen binding domain comprises an anti-CD70 scFv, an anti-CD70 VHH, an anti-CD70 VH or a receptor for CD70, wherein optionally the receptor for CD70 is CD27 or a CD70-binding fragment thereof, wherein the protein comprising the first antigen binding domain is a first CAR and the protein comprising the second antigen binding domain is a second CAR, wherein the first antigen binding domain is expressed as a separate protein from the second antigen binding domain, and wherein the second antigen binding domain comprises a CD3ζ signaling domain and does not comprise a costimulatory domain.

31. The engineered T cell of claim 30, wherein the target of interest is a protein selected from the group consisting of BCMA, EGFRvIII, Flt-3, CD20, CD22, CD23, CD30, CD38, CD33, CD133, WT1, TSPAN10, MHC-PRAME, HER2, MSLN, PSMA, PSCA, GPC3, Liv1, ADAM10, CHRNA2, LeY, NKG2D, CS1, CD44v6, ROR1, CD19, Claudin-18.2 (Claudin-18A2, or Claudin18 isoform 2), DLL3 (Delta-like protein 3, Drosophila Delta homolog 3, Delta3), Muc17, Muc3, Muc16, FAP alpha (Fibroblast Activation Protein alpha), Ly6G6D (Lymphocyte antigen 6 complex locus protein G6d, c6orf23, G6D, MEGT1, NG25), or RNF43 (E3 ubiquitin-protein ligase RNF43, RING finger protein 43).

32. The engineered T cell of claim 30 or 31, wherein the engineered T cell further comprises one or more genomic modifications of one or more of an endogenous TCRa gene, an endogenous CD52 gene, and an endogenous CD70 gene, optionally wherein the one or more genomic modifications comprise a knockout, wherein the engineered T cell exhibits a reduced level of TCRa, CD52 and/or CD70 protein expression and/or activity as compared to a control T cell without the one or more genomic modifications.

33. The engineered T cell of any one of claims 30-32, wherein the engineered T cell comprises a first nucleic acid encoding the protein comprising the first antigen binding domain and a second nucleic acid encoding the protein comprising the second antigen binding domain or wherein a single nucleic acid comprises both the first nucleic acid and the second nucleic acid.

34. The engineered T cell of claim 33, wherein a first vector comprises the first nucleic acid and a second vector comprises the second nucleic acid, and optionally wherein one or both vectors are lentiviral vectors or adeno-associated virus vectors, or wherein one vector comprises both the first nucleic acid and the second nucleic acid, and optionally wherein the vector is a lentiviral vector or an adeno-associated virus vector.

35. The engineered T cell of claim 33, wherein the first nucleic acid and/or the second nucleic acid is located within a disrupted TRAC locus, a disrupted CD52 locus or a disrupted CD70 locus or wherein the single nucleic acid is located within a disrupted TRAC locus, a disrupted CD52 locus or a disrupted CD70 locus.

36. The engineered T cell of any one of claims 30-35, wherein the T cell is or is derived from an T cell obtained from a healthy volunteer, is obtained from a patient, or is derived from an iPSC.

37. A population of engineered T cells of any one of claims 32-36, wherein no more than 75% of the engineered T cells functionally express one or more of TRAC, CD52 and CD70.

38. A population of cells comprising between 10^3 and 10^{10} engineered T cells of one or more of claims 30-36.

39. A pharmaceutical composition comprising one or more of the engineered T cells of any one of claims 30-36 or the population of engineered T cells of claim 37 or 38, and further comprising at least one pharmaceutically acceptable carrier or excipient.

40. A method of making the engineered T cell of any one of claims 32-36 comprising the use of one or more gene editing technologies selected from the group consisting of TALENs, zinc fingers, Cas-CLOVER, and a CRISPR/Cas system to reduce functional expression of one or more of TRAC, CD52 and CD70 in the T cell.

41. A method of making the engineered T cell of any one of claims 30-36 comprising introducing into an T cell a first nucleic acid encoding the protein comprising the first antigen binding domain and a second nucleic acid encoding the protein comprising the second antigen binding domain.

42. The method of claim 41, wherein one vector comprises both the first nucleic acid and the second nucleic acid, optionally wherein the vector is a lentiviral vector or adeno-associated viral vector.

43. The method of claim 41, wherein a first vector comprises the first nucleic acid and a second vector comprises the second nucleic acid, optionally wherein either or both of the first

vector and the second vector are lentiviral vectors or either or both of the first vector and the second vector are adeno-associated viral vectors.

44. The method of 43, wherein the first nucleic acid and the second nucleic acid are introduced into the engineered T cell by site-specific integration and optionally either or both of the first vector and the second vector are adeno-associated viral vectors.

45. Use of one or more of the engineered T cells of any one of claims 30-36, the population of engineered T cells of claim 37 or 38, or the pharmaceutical composition of claim 39 in the manufacture of a medicament for treating a condition or disease in a patient, wherein the condition or disease is a cancer or an autoimmune disease.

46. The use of claim 45, wherein the condition or disease is cancer and the cancer is selected from the group consisting of gastric cancer, sarcoma, lymphoma (including Non-Hodgkin's lymphoma), leukemia, head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma, leukemia, multiple myeloma, renal cell carcinoma, bladder cancer, cervical cancer, choriocarcinoma, colon cancer, oral cancer, skin cancer, and melanoma.

47. The use of claim 45, wherein the patient is a previously treated adult subject with locally advanced or metastatic melanoma, squamous cell head and neck cancer (SCHNC), ovarian carcinoma, sarcoma, or relapsed or refractory classic Hodgkin's Lymphoma (cHL).

48. The use of any one of claims 45-47, wherein the engineered T cells inhibit proliferation and/or activity of CD70 positive lymphocytes of the patient.

49. The use of claim 48, wherein the CD70 positive lymphocytes of the patient are normal or non-cancerous or alloreactive lymphocytes of the patient.