[6] However, to date all of these approaches have seen limited success. Therefore, there remains a need for the development of better therapeutic approaches for immunotherapy.

Summary

[6.1] In one aspect, the present disclosure refers to a modified lymphocyte, wherein the modified lymphocyte: (a) does not express endogenous CD3, CD4, and/or CD8; and (b) expresses at least one endogenous gene encoding: (i) CD56 (NCAM), CD49, and/or CD45; (ii) NK cell receptor immunoglobulin gamma Fc region receptor III (FcγRIII, cluster of differentiation 16 (CD16)); (iii) natural killer group-2 member D (NKG2D); (iv) CD69; (v) a natural cytotoxicity receptor; or any combination of two or more thereof; wherein the modified lymphocyte comprises a loss of function of transforming growth factor beta receptor 2 (TGF□R2) and cytokine inducible SH2 containing protein (CISH), and optionally further: (1) comprises at least one exogenous nucleic acid expression construct comprising a nucleic acid sequence encoding: (i) a chimeric antigen receptor (CAR); (ii) a non-naturally occurring variant of FcγRIII (CD16); (iii) interleukin 15 (IL-15); (iv) IL-15 receptor (IL-15R), or a variant thereof; (v) interleukin 12 (IL-12); (vi) IL-12 receptor (IL-12R), or a variant thereof; (vii) human leukocyte antigen G (HLA-G); (viii) human leukocyte antigen E (HLA-E); (ix) leukocyte surface antigen cluster of differentiation CD47 (CD47); or any combination of two or more thereof; and/or (2) exhibits a loss of function of at least one of: ~~(i) transforming growth factor beta receptor 2 (TGFβR2);~~ (ii) adenosine A2a receptor (ADORA2A); (ii~~i~~) T cell immunoreceptor with Ig and ITIM domains (TIGIT); (iii~~v~~) β-2 microgobulin (B2M); (iv) programmed cell death protein 1 (PD-1); ~~(vi) cytokine inducible SH2 containing protein (CISH);~~ (v~~ii~~) class II, major histocompatibility complex, transactivator (CIITA); (vi~~ii~~) natural killer cell receptor NKG2A (natural killer group 2A); (~~ix~~vii) two or more HLA class II histocompatibility antigen alpha chain genes, and/or two or more HLA class II histocompatibility antigen beta chain genes; (~~x~~viii) cluster of differentiation 32B (CD32B, FCGR2B); (ix~~i~~) T cell receptor alpha constant (TRAC); or any combination of two or more thereof.

[6.2] In another aspect, the present disclosure refers to modified cell, wherein the modified cell comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further (1) comprises at least one exogenous nucleic acid expression construct comprising a nucleic acid sequence encoding: (i) a chimeric antigen receptor (CAR); (ii) a non-naturally occurring variant of FcγRIII (CD16); (iii) interleukin 15 (IL-15); (iv) IL-15 receptor (IL-15R), or a variant thereof; (v) interleukin 12 (IL-12); (vi) IL-12 receptor (IL-12R), or a variant thereof; (vii) human leukocyte antigen G (HLA-G); (viii) human leukocyte antigen E (HLA-E); (ix) leukocyte surface antigen cluster of differentiation CD47 (CD47); or any combination of two or more thereof; and/or (2) exhibits a loss of function of at least one of: ~~(i) transforming growth factor beta receptor 2 (TGFβR2);~~ (ii) adenosine A2a receptor (ADORA2A); (ii~~i~~) T cell immunoreceptor with Ig and ITIM domains (TIGIT); (iii~~v~~) β-2 microgobulin (B2M); (iv) programmed cell death protein 1 (PD-1); ~~(vi) cytokine inducible SH2 containing protein (CISH);~~ (v~~ii~~) class II, major histocompatibility complex, transactivator (CIITA); (vi~~ii~~) natural killer cell receptor NKG2A (natural killer group 2A); (~~ix~~vii) two or more HLA class II

histocompatibility antigen alpha chain genes, and/or two or more HLA class II histocompatibility antigen beta chain genes; (~~x~~viii) cluster of differentiation 32B (CD32B, FCGR2B); (ix~~xi~~) T cell receptor alpha constant (TRAC); or any combination of two or more thereof.

[6.3] In another aspect, the present disclosure refers to a population of cells comprising the modified lymphocyte as disclosed herein, or the modified cell disclosed herein.

[6.4] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the population of cells as disclosed herein.

[6.5] In another aspect, the present disclosure refers to an isolated *in vitro* population of lymphocytes, wherein the population comprises at least $1x10^3$, at least $1x10^4$, at least $1x10^5$, at least $2x10^5$, at least $3x10^5$, at least $4x10^5$, at least $5x10^5$,at least $1x10^6$, at least $2x10^6$, at least $3x10^6$, at least $4x10^6$, at least $5x10^6$,at least $1x10^7$, at least $1x10^7$, at least $2x10^7$, at least $3x10^7$, at least $4x10^7$, at least $5x10^7$,at least $1x10^8$, at least $2x10^8$, at least $3x10^8$, at least $4x10^8$, at least $5x10^8$,at least $1x10^9$, at least $1x10^9$, at least $2x10^9$, at least $3x10^9$, at least $4x10^9$, at least $5x10^9$,at least $1x10^{10}$, at least $2x10^{10}$, at least $3x10^{10}$, at least $4x10^{10}$, at least $5x10^{10}$, at least $1x10^{11}$, or at least $1x10^{12}$ cells, and wherein at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, at least 99.9%, at least 99.99%, at least 99.999%, or ~~virtually~~ 100% of the lymphocytes in the population: (a) comprise a rearranged T-cell receptor (TCR) locus; (b) do not express endogenous CD3; (c) express endogenous CD56 (NCAM), CD49, and/or CD45; and (d) expresses at least one endogenous gene encoding: (i) FcγRIII (CD16); (ii) natural killer group-2 member D (NKG2D); (iii) CD69; (iv) a natural cytotoxicity receptor; or any combination of two or more thereof; and wherein the modified lymphocyte comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further: (1) comprises at least one exogenous nucleic acid expression construct comprising a nucleic acid sequence encoding: (i) chimeric antigen receptor (CAR); (ii) non-naturally occurring variant of immunoglobulin gamma Fc region receptor III (FcγRIII, CD16); (iii) interleukin 15 (IL-15); (iv) IL-15 receptor (IL-15R), or a variant thereof; (v) interleukin 12 (IL-12); (vi) IL-12 receptor (IL-12R), or a variant thereof; (vii) human leukocyte antigen G (HLA-G); (viii) human leukocyte antigen E (HLA-E); (ix) leukocyte surface antigen cluster of differentiation CD47 (CD47); or any combination of two or more thereof; and/or (2) exhibits a loss of function of at least one of: ~~(i) transforming growth factor beta receptor 2 (TGFβR2);~~ (i~~i~~) adenosine A2a receptor (ADORA2A); (ii~~i~~) T cell immunoreceptor with Ig and ITIM domains (TIGIT); (iii~~v~~) β-2 microgobulin (B2M); (iv) programmed cell death protein 1 (PD-1); ~~(vi) cytokine inducible SH2 containing protein (CISH);~~ (v~~i~~i) class II, major histocompatibility complex, transactivator (CIITA); (vi~~i~~i) natural killer cell receptor NKG2A (natural killer group 2A); (vii~~x~~) two or more HLA class II histocompatibility antigen alpha chain genes, and/or two or more HLA class II histocompatibility antigen beta chain genes; (viii~~x~~) cluster of differentiation 32B (CD32B, FCGR2B); (ix~~xi~~) T cell receptor alpha constant (TRAC); or any combination of two or more thereof.

[6.6] In another aspect, the present disclosure refers to the use of the lymphocyte as disclosed herein, the modified cell as disclosed herein, the population of cells as disclosed herein, the pharmaceutical composition as disclosed herein, or the isolated *in vitro* population of lymphocytes as disclosed herein, in the manufacture of a medicament for treating a proliferative disease.

[6.7] In another aspect, the present disclosure refers to a method of generating the lymphocyte as disclosed herein, the modified cell as disclosed herein, the population of cells as disclosed herein, or the isolated *in vitro* population of lymphocytes as disclosed herein, the method comprising: (a) obtaining an induced pluripotent stem cell (iPSC); (b) modifying the iPSC, or an undifferentiated or differentiated daughter cell thereof, to comprise express at least one exogenous nucleic acid expression construct of (1) and/or to comprise a loss of function in at least one gene of (2); (c) directing differentiation of the iPSC to hematopoietic lineage cells, wherein the hematopoietic lineage cells retain the edited genetic loci comprised in the iPSCs.

[6.8] In another aspect, the present disclosure refers to a method, the method comprising: differentiating a genetically modified pluripotent stem cell into a lymphocyte, wherein the genetically modified pluripotent stem cell comprises: a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further comprises (1) an exogenous nucleic acid expression construct comprising: (i) a nucleic acid sequence encoding a chimeric antigen receptor (CAR); (ii) a nucleic acid sequence encoding a non-naturally occurring variant of FcγRIII (CD16); (iii) a nucleic acid sequence encoding interleukin 15 (IL-15); (iv) a nucleic acid sequence encoding interleukin 15 receptor (IL-15R) or a variant thereof; (v) a nucleic acid sequence encoding interleukin 12 (IL12); (vi) a nucleic acid sequence encoding interleukin-12 receptor (IL-12R) or a variant thereof; (vii) a nucleic acid sequence encoding human leukocyte antigen G (HLA-G); (viii) a nucleic acid sequence encoding human leukocyte antigen E (HLA-E); (ix) a nucleic acid sequence encoding leukocyte surface antigen cluster of differentiation CD47 (CD47); or any combination of two or more thereof; and (2) an indel, or an insertion of an exogenous nucleic acid in one or more of the following genetic loci: ~~(i) transforming growth factor beta receptor 2 (TGFβR2);~~ (i~~i~~) adenosine A2a receptor (ADORA2A); (ii~~i~~) T cell immunoreceptor with Ig and ITIM domains (TIGIT); (i~~v~~iii) β-2 microgobulin (B2M); (iv) programmed cell death protein 1 (PD-1, CD279); ~~(vi) cytokine inducible SH2 containing protein (CISH);~~ (v~~ii~~) class II, major histocompatibility complex, transactivator (CIITA); (vi~~ii~~) natural killer cell receptor NKG2A (natural killer group 2A); (i~~x~~vii) two or more HLA class II histocompatibility antigen alpha chain genes, and/or two or more HLA class II histocompatibility antigen beta chain genes; (~~x~~viii) cluster of differentiation 32B (CD32B, FCGR2B); (~~xi~~ix) T cell receptor alpha constant (TRAC); or any combination of two or more thereof, wherein the indel or insertion results in a loss-of-function of a gene product encoded by the respective genetic locus or loci.

[6.9] In another aspect, the present disclosure refers to a method, the method comprising: reprogramming a donor cell to a pluripotent state; editing a target locus in the donor cell genome; and differentiating the reprogrammed donor cell into a lymphocyte.

[6.10] In another aspect, the present disclosure refers to a modified lymphocyte as disclosed herein, the modified cell as disclosed herein, or the population of cells as disclosed herein for use in therapy.

[6.11] In yet another aspect, the present disclosure refers to the use of the modified lymphocyte as disclosed herein, the modified cell as disclosed herein, or the population of cells as disclosed herein in the manufacture of a medicament for treating a proliferative disease.

[6.12] In another aspect, the present disclosure refers to a modified lymphocyte, wherein the modified lymphocyte: (a) does not express endogenous CD3, CD4, and/or CD8; and (b) expresses at least one endogenous gene encoding: (i) CD56 (NCAM), CD49, and/or CD45; (ii) NK cell receptor (cluster of differentiation 16 (CD16)); (iii) natural killer group-2 member D (NKG2D); (iv) CD69; (v) a natural cytotoxicity receptor; or any combination of two or more thereof; wherein the modified lymphocyte comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further: (1) comprises at least one exogenous nucleic acid construct encoding: (i) a chimeric antigen receptor (CAR); (ii) a non-naturally occurring variant of immunoglobulin gamma Fc region receptor III (FcγRIII, CD16); (iii) interleukin 15 (IL-15); (iv) IL-15 receptor (IL-15R), or a variant thereof; (v) interleukin 12 (IL-12); (vi) human leukocyte antigen G (HLA-G); (vii) human leukocyte antigen E (HLA-E); or any combination of two or more thereof; and/or (2) exhibits a loss of function of at least one of: (i) adenosine A2a receptor (ADORA2A); (ii) T cell immunoreceptor with Ig and ITIM domains (TIGIT); (iii) β-2 microgobulin (B2M); (iv) programmed cell death protein 1 (PD-1); (v) class II, major histocompatibility complex, transactivator (CIITA); or any combination of two or more thereof.

[6.13] In another aspect, the present disclosure refers to a modified cell, wherein the modified cell comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further (1) comprises at least one exogenous nucleic acid construct encoding: (i) a chimeric antigen receptor (CAR); (ii) a non-naturally occurring variant of immunoglobulin gamma Fc region receptor III (FcγRIII, CD16); (iii) interleukin 15 (IL-15); (iv) IL-15 receptor (IL-15R), or a variant thereof; (v) interleukin 12 (IL-12); (vi) human leukocyte antigen G (HLA-G); (vii) human leukocyte antigen E (HLA-E); or any combination of two or more thereof; and/or (2) exhibits a loss of function of at least one of: (i) adenosine A2a receptor (ADORA2A); (ii) T cell immunoreceptor with Ig and ITIM domains (TIGIT); (iii) β-2 microgobulin (B2M); (iv) programmed cell death protein 1 (PD-1); (v) class II, major histocompatibility complex, transactivator (CIITA); or any combination of two or more thereof.

[6.14] In another aspect, the present disclosure refers to an isolated population of lymphocytes, wherein the population comprises at least $1x10^3$, at least $1x10^4$, at least $1x10^5$, at least $2x10^5$, at least $3x10^5$, at least $4x10^5$, at least $5x10^5$,at least $1x10^6$, at least $2x10^6$, at least $3x10^6$, at least $4x10^6$, at least $5x10^6$,at least $1x10^7$, at least $1x10^7$, at least $2x10^7$, at least $3x10^7$, at least $4x10^7$, at least $5x10^7$,at least $1x10^8$, at least $2x10^8$, at least $3x10^8$, at least $4x10^8$, at least $5x10^8$,at least $1x10^9$, at least $1x10^9$, at least $2x10^9$, at least $3x10^9$, at least $4x10^9$, at least $5x10^9$,at least $1x10^{10}$, at least $2x10^{10}$, at least $3x10^{10}$, at least $4x10^{10}$, at least $5x10^{10}$, at least $1x10^{11}$, or at least $1x10^{12}$ cells, and wherein at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, at least 99.9%, at least 99.99%, at least 99.999%, or virtually 100% of the lymphocytes in the population: (a) comprise a rearranged T-cell receptor (TCR) locus; (b) do not express endogenous CD3; (c) express endogenous CD56 (NCAM), CD49, and/or CD45; and (d) expresses at least endogenous gene encoding: (i) NK cell receptor (cluster of differentiation 16 (CD16)); (ii) natural killer group-2 member D (NKG2D); (iii) CD69; (iv) a natural cytotoxicity receptor; or any combination of two or more thereof; and wherein the modified lymphocyte comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further: (1) comprises at least one exogenous nucleic acid construct encoding: (i) chimeric antigen receptor (CAR); (ii) non-naturally occurring variant of immunoglobulin gamma Fc region receptor III (FcγRIII, CD16); (iii) interleukin 15 (IL-15); (iv) IL-15 receptor (IL-15R), or a variant thereof; (v) interleukin 12 (IL-12); (vi) human leukocyte antigen G (HLA-G); (vii) human leukocyte antigen E (HLA-E); or any combination of two or more thereof; and/or (2) exhibits a loss of function of at least one of: (i) adenosine A2a receptor (ADORA2A); (ii) T cell immunoreceptor with Ig and ITIM domains (TIGIT); (iii) β-2 microgobulin (B2M); (iv) programmed cell death protein 1 (PD-1); (v) class II, major histocompatibility complex, transactivator (CIITA); or any combination of two or more thereof.

[6.15] In another aspect, the present disclosure refers to a method, the method comprising: differentiating a genetically modified pluripotent stem cell into a lymphocyte, wherein the genetically modified pluripotent stem cell comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further comprises: (1) an exogenous nucleic acid comprising: (i) a nucleic acid encoding a chimeric antigen receptor (CAR); (ii) a nucleic acid encoding a non-naturally occurring variant of immunoglobulin gamma Fc region receptor III (FcγRIII, CD16); (iii) a nucleic acid encoding interleukin 15 (IL-15) and/or interleukin 12 (IL12); (iv) a nucleic acid encoding human leukocyte antigen G (HLA-G); (v) a nucleic acid encoding human leukocyte antigen E (HLA-E); or any combination of two or more thereof; and (2) an indel, or an insertion of an exogenous nucleic acid in one or more of the following genetic loci: (i) adenosine A2a receptor (ADORA2A); (ii) T cell immunoreceptor with Ig and ITIM domains (TIGIT); (iii) β-2 microgobulin (B2M); (iv) programmed cell death protein 1 (PD-1, CD279); (v) class II, major histocompatibility complex, transactivator (CIITA); or any combination of two or more thereof, wherein the indel or insertion results in a loss-of-function of a gene product encoded by the respective genetic locus or loci.

[7] Some examples of the present disclosure provide compositions, cells, cell populations, methods, strategies, and treatment modalities that are useful in the context of immunotherapeutic approaches, *e.g.*, immunooncology therapeutic approaches. In some examples, the present disclosure provides modified NK cells (or other lymphocytes) that are useful in NK cell therapy, *e.g.*, in the context of immunotherapeutic approaches. In some examples, the cells and cell populations provided herein are characterized by one or more modifications that enhance their efficacy in immunotherapeutic approaches. For example, in some examples, NK cells are provided that comprise one or more modifications that effect a loss-of-function in a gene or protein associated with inhibition of NK cell function in a therapeutic context, and/or one or more modifications that effect an expression of an exogenous nucleic acid or protein associated with an enhanced NK cell function in a therapeutic context. In some examples, the present disclosure provides modified NK cells that are derived from an induced pluripotent cell (iPSC). IPSC-derived NK cells are also referred to herein as iNK cells. In some examples, modified iNK cells are provided that are derived from a somatic cell, for example, and without limitation, from a fibroblast, a peripheral blood cell, or a developmentally mature T cell (T cell that have undergone thymic selection). In some examples, the NK or iNK cells provided herein comprise one or more genomic edits, *e.g.*, indels or insertions of exogenous nucleic acid constructs resulting from cutting a genomic locus with an RNA-guided nuclease. The use of RNA-guided nuclease technology in the context of the generation of modified NK and iNK cells allows for the engineering of complex alterations with enhanced characteristics relevant for clinical applications.

[8] Some examples of the present disclosure provide complex editing strategies, and resulting NK cells having complex genomic alterations, that allow for the generation of advanced NK cell products for clinical applications, *e.g.*, for immunooncology therapeutic approaches. In some examples, the modified NK cells provided herein can serve as an off-the-shelf clinical solution for patients having, or having been diagnosed with, a hyperproliferative disease, such as, for example, a cancer. In some examples, the modified NK cells exhibit an enhanced survival, proliferation, NK cell response level, NK cell response duration, resistance against NK cell exhaustion, and/or target recognition as compared to non-modified NK cells. For example, the modified NK cells provided herein may comprise genomic edits that result in: expression of a chimeric antigen receptor (CAR) of interest, *e.g.*, a CAR targeting mesothelin, EGFR, HER2 and/or MICA/B; expression of a CD16 variant, *e.g.*, a non-naturally occurring CD16 variant such as, for example, hnCD16 (see, e.g., Zhu et al., Blood 2017,

CLAIMS

1. A modified lymphocyte, wherein the modified lymphocyte:

(a) does not express endogenous CD3, CD4, and/or CD8; and

(b) expresses at least one endogenous gene encoding:

(i) CD56 (NCAM), CD49, and/or CD45;

(ii) NK cell receptor immunoglobulin gamma Fc region receptor III (FcγRIII, cluster of differentiation 16 (CD16));

(iii) natural killer group-2 member D (NKG2D);

(iv) CD69;

(v) a natural cytotoxicity receptor;

or any combination of two or more thereof;

wherein the modified lymphocyte comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further:

(1) comprises at least one exogenous nucleic acid expression construct comprising a nucleic acid sequence encoding:

(i) a chimeric antigen receptor (CAR);

(ii) a non-naturally occurring variant of FcγRIII (CD16);

(iii) interleukin 15 (IL-15);

(iv) IL-15 receptor (IL-15R), or a variant thereof;

(v) interleukin 12 (IL-12);

(vi) IL-12 receptor (IL-12R), or a variant thereof;

(vii) human leukocyte antigen G (HLA-G);

(viii) human leukocyte antigen E (HLA-E);

(ix) leukocyte surface antigen cluster of differentiation CD47 (CD47);

or any combination of two or more thereof;

and/or

(2) exhibits a loss of function of at least one of:

~~(i) transforming growth factor beta receptor 2 (TGFβR2);~~

(i~~i~~) adenosine A2a receptor (ADORA2A);

(ii~~i~~) T cell immunoreceptor with Ig and ITIM domains (TIGIT);

(~~iv~~iii) β-2 microgobulin (B2M);

(iv) programmed cell death protein 1 (PD-1);

~~(vi) cytokine inducible SH2 containing protein (CISH);~~

(v~~ii~~) class II, major histocompatibility complex, transactivator (CIITA);

(vi~~ii~~) natural killer cell receptor NKG2A (natural killer group 2A);

(viii~~ix~~) two or more HLA class II histocompatibility antigen alpha chain genes, and/or two or more HLA class II histocompatibility antigen beta chain genes;

(viii~~ix~~) cluster of differentiation 32B (CD32B, FCGR2B);

(ix~~xi~~) T cell receptor alpha constant (TRAC);

or any combination of two or more thereof.

2. The modified lymphocyte of claim 1, wherein the lymphocyte exhibits a loss of function of :

(i) ~~TGFβR2, CISH,~~ TIGIT, ADORA2A, or NKG2A;

(ii) ~~TGFβR2 and CISH,~~ TGFβR2 and TIGIT, TGFβR2 and ADORA2A, TGFβR2 and NKG2A, CISH and TIGIT, CISH and ADORA2A, CISH and NKG2A, TIGIT and ADORA2A, TIGIT and NKG2A, or ADORA2A and NKG2A; or

(iii) TGFβR2, CISH and TIGIT; TGFβR2, CISH and ADORA2A; TGFβR2, CISH and NKG2A; TGFβR2, TIGIT and ADORA2A; TGFβR2, TIGIT and NKG2A; TGFβR2, ADORA2A and NKG2A; CISH, TIGIT and ADORA2A; CISH, TIGIT and NKG2A; CISH, ADORA2A and NKG2A; or TIGIT, ADORA2A and NKG2A.

3. The modified lymphocyte of claim 1 or 2, wherein the lymphocyte comprises a rearranged endogenous T-cell receptor (TCR) locus.

4. The modified lymphocyte of claim 3, wherein the rearranged TCR comprises TCRα VJ and/or TCRβ V(D)J section rearrangements and complete V-domain exons.

5. The modified lymphocyte of claim 1, 2, 3 or 4 wherein the natural cytotoxicity receptor is NKp30, NKp44, NKp46, and/or CD158b.

6. The modified lymphocyte of any of claims 1-5, wherein the IL-15R variant is a constitutively active IL-15R variant and/or wherein the IL12-R variant is a constitutively active IL12-R variant.

7. The modified lymphocyte of claim 6, wherein the constitutively active IL-15R variant is a fusion between IL-15R and an IL-15R agonist (IL-15RA), and/or wherein the constitutively active IL-12R variant is a fusion between IL-12R and an IL-12R agonist (IL-12RA).

8. The modified lymphocyte of claim 7, wherein the IL-15R agonist is IL-15, or an IL-15R-binding variant thereof; and/or wherein the IL-12R agonist is IL-12, or an IL-12R-binding variant thereof.

9. The modified lymphocyte of any one of claims 1-8, wherein the loss of TGFβR2 is associated with exogenous expression of a dominant-negative variant of TGFβ receptor II (DN-TGFβR2).

10. The modified lymphocyte of claim 1, wherein the CAR is capable of binding mesothelin, EGFR, HER2, MICA/B, BCMA, CD19, CD22, CD20, CD33, CD123, androgen receptor, PSMA, PSCA, Muc1, HPV viral peptides (ie. E7), EBV viral peptides, CD70, WT1, CEA, EGFRvIII, IL13Rα2, ~~and~~ GD2, CA125, CD7, EpCAM, Muc16, or CD30,

11. The modified lymphocyte of any one of claims 1-10, wherein the lymphocyte is derived from a pluripotent or multipotent stem cell.

12. The modified lymphocyte of claim 11, wherein the multipotent stem cell is a hematopoietic stem cell (HSC).

13. The modified lymphocyte of claim 11, wherein the pluripotent stem cell is an induced pluripotent stem cell (iPSC).

14. The modified lymphocyte of claim 11, wherein the pluripotent stem cell is an embryonic stem cell (ESC).

15. The modified lymphocyte of any one of claims 1-11, wherein the lymphocyte is derived from a pluripotent or multipotent stem cell that comprises at least one or more exogenous nucleic acid constructs encoding any of (1)(i)-(1)(ix~~xi~~), or any combination thereof; and/or at least one genomic alteration that effects the loss-of-function of any of (2)(i)-(2)(ix~~xi~~), or any combination thereof, in the lymphocyte.

16. The modified lymphocyte of claim 15, wherein the lymphocyte is derived from a pluripotent or multipotent stem cell that comprises at least one genomic alteration that effects the loss-of-function of any of (2)(i)-(2)(ix~~xi~~), or any combination thereof, in the lymphocyte.

17. The modified lymphocyte of claim 15 or claim 16, wherein the at least one genomic alteration that effects the loss-of-function of one or more (2)(i)-(2)(ix~~xi~~) in the lymphocyte comprises an insertion of an exogenous nucleic acid construct.

18. The modified lymphocyte of claim 17, wherein the exogenous nucleic acid construct encodes any of (1)(i)-(1)(ix), or any combination thereof.

19. The modified lymphocyte of any one of claims 1-18, wherein the lymphocyte exhibits a loss-of-function in two or more of the genes/proteins listed under (2).

20. The modified lymphocyte of any one of claims 1-19, wherein the lymphocyte comprises an indel or an insertion of an exogenous nucleotide construct into a genomic locus harboring a gene or encoding a protein under (2).

21. The modified lymphocyte of any one of claims 1-20, wherein the lymphocyte comprises an indel or an insertion of an exogenous nucleotide construct into two or more genomic loci harboring a gene or encoding a protein under (2).

22. The modified lymphocyte of any one of claims 1-21, wherein the lymphocyte is obtained by editing a genomic locus with an RNA-guided nuclease.

23. The modified lymphocyte of claim 22, wherein the RNA-guided nuclease is a CRISPR/Cas nuclease.

24. The modified lymphocyte of claim 22, wherein the RNA-guided nuclease is selected from the group consisting of SpCas9, SaCas9, (KKH) SaCas9, AsCpf1 (AsCas12a), LbCpf1, (LbCas12a), CasX, CasY, Cas12h1, Cas12i1, Cas12c1, Cas12c2, eSpCas9, Cas9-HF1, HypaCas9, dCas9-Fokl, Sniper-Cas9, xCas9, AaCas12b, evoCas9, SpCas9-NG, VRQR, VRER, NmeCas9, CjCas9, BhCas12b, and BhCas12b V4.

25. The modified lymphocyte of any one of claims 1-24, wherein the lymphocyte is obtained by editing two or more genomic loci harboring genes encoding any of the proteins under (2).

26. The modified lymphocyte of claim 25, wherein at least two of the two or more genomic loci harboring genes encoding any of the proteins under (2) have been edited by a different RNA-guided nuclease.

27. The modified lymphocyte of claim 25, wherein at least one of the two or more genomic loci harboring genes encoding any of the proteins under (2) has been edited by Cas9, and wherein at least one of the loci has been edited by Cpf1.

28. The modified lymphocyte of any one of claims 1-27, wherein the modified lymphocyte expresses endogenous CD56, CD49, and CD45.

29. The modified lymphocyte of any one of claims 1-28, wherein the lymphocyte is a natural killer (NK) cell.

30. A modified cell, wherein the modified cell comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further

(1) comprises at least one exogenous nucleic acid expression construct comprising a nucleic acid sequence encoding:

(i) a chimeric antigen receptor (CAR);

(ii) a non-naturally occurring variant of FcγRIII (CD16);

(iii) interleukin 15 (IL-15);

(iv) IL-15 receptor (IL-15R), or a variant thereof;

(v) interleukin 12 (IL-12);

(vi) IL-12 receptor (IL-12R), or a variant thereof;

(vii) human leukocyte antigen G (HLA-G);

(viii)human leukocyte antigen E (HLA-E);

(ix) leukocyte surface antigen cluster of differentiation CD47 (CD47);

or any combination of two or more thereof;

and/or

(2) exhibits a loss of function of at least one of:

~~(i) transforming growth factor beta receptor 2 (TGFβR2);~~

(i~~i~~) adenosine A2a receptor (ADORA2A);

(ii~~i~~) T cell immunoreceptor with Ig and ITIM domains (TIGIT);

(iii~~iv~~) β-2 microgobulin (B2M);

(iv) programmed cell death protein 1 (PD-1);

~~(vi) cytokine inducible SH2 containing protein (CISH);~~

(v~~ii~~) class II, major histocompatibility complex, transactivator (CIITA);

(vi~~ii~~) natural killer cell receptor NKG2A (natural killer group 2A);

(~~ix~~vii) two or more HLA class II histocompatibility antigen alpha chain genes, and/or two or more HLA class II histocompatibility antigen beta chain genes;

(~~x~~viii) cluster of differentiation 32B (CD32B, FCGR2B);

(ix~~xi~~) T cell receptor alpha constant (TRAC);

or any combination of two or more thereof.

31. The modified cell of claim 30, wherein the modified cell exhibits a loss of function of:

(i) ~~TGFβR2, CISH,~~ TIGIT, ADORA2A, or NKG2A;

(ii) ~~TGFβR2 and CISH,~~ TGFβR2 and TIGIT, TGFβR2 and ADORA2A, TGFβR2 and NKG2A, CISH and TIGIT, CISH and ADORA2A, CISH and NKG2A, TIGIT and ADORA2A, TIGIT and NKG2A, or ADORA2A and NKG2A; or

(iii) TGFβR2, CISH and TIGIT; TGFβR2, CISH and ADORA2A; TGFβR2, CISH and NKG2A; TGFβR2, TIGIT and ADORA2A; TGFβR2, TIGIT and NKG2A; TGFβR2, ADORA2A and NKG2A; CISH, TIGIT and ADORA2A; CISH, TIGIT and NKG2A; CISH, ADORA2A and NKG2A; or TIGIT, ADORA2A and NKG2A.

32. The modified cell of claim 30 or 31, wherein the modified cell is an immune cell.

33. The modified cell of claim 32, wherein the immune cell is a lymphocyte.

34. The modified cell of claim 33, wherein the lymphocyte is an NK cell.

35. The modified cell of claim 30, wherein the cell is a pluripotent stem cell, or a differentiated daughter cell derived therefrom.

36. The modified cell of claim 34 or claim 35, wherein the modified cell does not express an endogenous T-cell co-receptor.

37. The modified cell of claim 33, wherein the lymphocyte is a T cell.

38. The modified cell of claim 30, wherein the cell comprises a rearranged endogenous TCR locus, wherein the rearranged TCR comprises TCRα VJ and/or TCRβ V(D)J section rearrangements and complete V-domain exons.

39. The modified cell of any one of claims 30-38, wherein the modified cell expresses at least one endogenous gene encoding:

(i) CD56 (NCAM), CD49, and/or CD45;

(ii) FcγRIII (CD16);

(iii) natural killer group-2 member D (NKG2D);

(iv) CD69;

(v) a natural cytotoxicity receptor;

or any combination of two or more thereof.

40. The modified cell of claim 39, wherein the natural cytotoxicity receptor is NKp30, NKp44, NKp46, and/or CD158b.

41. The modified cell of any one of claims 30-40, wherein the cell expresses at least one NK cell biomarker.

42. The modified cell of claim 41, wherein the NK cell biomarker is CD56, CD49, and/or CD45.

43. A population of cells comprising the modified lymphocyte of any one of claims 1-~~28~~29, or the modified cell of any one of claims 30-42.

44. A pharmaceutical composition comprising the population of cells of claim 43.

45. An isolated *in vitro* population of lymphocytes, wherein the population comprises at least $1x10^3$, at least $1x10^4$, at least $1x10^5$, at least $2x10^5$, at least $3x10^5$, at least $4x10^5$, at least $5x10^5$,at least $1x10^6$, at least $2x10^6$, at least $3x10^6$, at least $4x10^6$, at least $5x10^6$,at least $1x10^7$, at least $1x10^7$, at least $2x10^7$, at least $3x10^7$, at least $4x10^7$, at least $5x10^7$,at least $1x10^8$, at least $2x10^8$, at least $3x10^8$, at least $4x10^8$, at least $5x10^8$,at least $1x10^9$, at least $1x10^9$, at least $2x10^9$, at least $3x10^9$, at least $4x10^9$, at least $5x10^9$,at least $1x10^{10}$, at least $2x10^{10}$, at least $3x10^{10}$, at least $4x10^{10}$, at least $5x10^{10}$, at least $1x10^{11}$, or at least $1x10^{12}$ cells, and wherein at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, at least 99.9%, at least 99.99%, at least 99.999%, or ~~virtually~~ 100% of the lymphocytes in the population:

(a) comprise a rearranged T-cell receptor (TCR) locus;

(b) do not express endogenous CD3;

(c) express endogenous CD56 (NCAM), CD49, and/or CD45; and

(d) expresses at least one endogenous gene encoding:

(i) FcγRIII (CD16);

(ii) natural killer group-2 member D (NKG2D);

(iii) CD69;

(iv) a natural cytotoxicity receptor;

or any combination of two or more thereof; and

wherein the modified lymphocyte comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further:

(1) comprises at least one exogenous nucleic acid expression construct comprising a nucleic acid sequence encoding:

(i) chimeric antigen receptor (CAR);

(ii) non-naturally occurring variant of immunoglobulin gamma Fc region receptor III (FcγRIII, CD16);

(iii) interleukin 15 (IL-15);

(iv) IL-15 receptor (IL-15R), or a variant thereof;

(v) interleukin 12 (IL-12);

(vi) IL-12 receptor (IL-12R), or a variant thereof;

(vii) human leukocyte antigen G (HLA-G);

(viii) human leukocyte antigen E (HLA-E);

(ix) leukocyte surface antigen cluster of differentiation CD47 (CD47);

or any combination of two or more thereof;

and/or

(2) exhibits a loss of function of at least one of:

~~(i) transforming growth factor beta receptor 2 (TGFβR2);~~

(i~~i~~) adenosine A2a receptor (ADORA2A);

(ii~~i~~) T cell immunoreceptor with Ig and ITIM domains (TIGIT);

(iii~~v~~) β-2 microgobulin (B2M);

(iv) programmed cell death protein 1 (PD-1);

~~(vi) cytokine inducible SH2 containing protein (CISH);~~

(v~~ii~~) class II, major histocompatibility complex, transactivator (CIITA);

(vi~~ii~~) natural killer cell receptor NKG2A (natural killer group 2A);

(viii~~ix~~) two or more HLA class II histocompatibility antigen alpha chain genes, and/or two or more HLA class II histocompatibility antigen beta chain genes;

(viii~~x~~) cluster of differentiation 32B (CD32B, FCGR2B);

(ix~~xi~~) T cell receptor alpha constant (TRAC);

or any combination of two or more thereof.

46. The isolated *in vitro* population of lymphocytes of claim 45, wherein the modified lymphocyte exhibits a loss of function of :

(i) ~~TGFβR2, CISH,~~ TIGIT, ADORA2A, or NKG2A;

(ii) ~~TGFβR2 and CISH,~~ TGFβR2 and TIGIT, TGFβR2 and ADORA2A, TGFβR2 and NKG2A, CISH and TIGIT, CISH and ADORA2A, CISH and NKG2A, TIGIT and ADORA2A, TIGIT and NKG2A, or ADORA2A and NKG2A; or

(iii) TGFβR2, CISH and TIGIT; TGFβR2, CISH and ADORA2A; TGFβR2, CISH and NKG2A; TGFβR2, TIGIT and ADORA2A; TGFβR2, TIGIT and NKG2A; TGFβR2, ADORA2A and NKG2A; CISH, TIGIT and ADORA2A; CISH, TIGIT and NKG2A; CISH, ADORA2A and NKG2A; or TIGIT, ADORA2A and NKG2A.

47. The isolated *in vitro* population of lymphocytes of claim 45 or 46, wherein the rearranged TCR locus comprises of TCRα VJ and/or TCRβ V(D)J section rearrangements and complete V-domain exons.

48. The isolated *in vitro* population of lymphocytes of claim 47, wherein the rearranged endogenous TCR locus consists of no more than two rearranged alleles.

49. The isolated *in vitro* population of lymphocytes of claim 45, wherein the natural cytotoxicity receptor is NKp30, NKp44, NKp46, and/or CD158b.

50. The isolated *in vitro* population of lymphocytes of any one of claims 45-49, wherein the population does not comprise more than 1%, more than 0.1%, more than 0.001%, more than 0.0001%, more than 0.00001%, more than 0.000001%, more than 0.0000001%, more than 0.00000001%, more than 0.000000001%, more than 0.0000000001%, or more than more than 0.00000000001% of cells expressing a reprogramming factor from an exogenous nucleic acid construct.

51. The isolated *in vitro* population of lymphocytes of claim 50, wherein the population does not comprise a cell expressing a reprogramming factor from an exogenous nucleic acid construct.

52. The isolated *in vitro* population of lymphocytes of claim 50 or claim 51, wherein the reprogramming factor is Oct-4 and/or Sox-2.

53. The isolated *in vitro* population of lymphocytes of claim 45, wherein the population does not comprise cells harboring episomal expression constructs encoding a reprogramming factor.

54. The isolated *in vitro* population of lymphocytes of any one of claims 45-53, wherein each cell in the population of cells comprises the same combination of (1) and (2).

55. The isolated *in vitro* population of lymphocytes of any one of claims 45-54, wherein the cell population comprises less than 0.001%, less than 0.002%, less than 0.003%, less than 0.004%, less than 0.005%, less than 0.006%, less than 0.007%, less than 0.008%, less than 0.009%, less than 0.01%, less than 0.02%, less than 0.03%, less than 0.04%, less than 0.05%, less than 0.06%, less than 0.07%, less than 0.08%, less than 0.09%, less than 0.1%, less than 0.2%, less than 0.3%, less than 0.4%, less than 0.5%, less than 0.6%, less than 0.7%, less than 0.8%, less than 0.9%, less than 1%, less than 2%, less than 3%, less than 4%, less than 5%, less than 6%, less than 7%, less than 8%, less than 9%, or less than 10% cell that harbor a chromosomal translocation.

56. The lymphocyte of any one of claims 1-29, the modified cell of any one of claims 30-42, the population of cells of claim ~~41~~43, the pharmaceutical composition of claim 44, or the isolated *in vitro* population of lymphocytes of any one of claims 45-55, for use in therapy.

57. Use of the lymphocyte of any one of claims 1-29, the modified cell of any one of claims 30-42, the population of cells of claim ~~41~~43, the pharmaceutical composition of claim 44, or the isolated *in vitro* population of lymphocytes of any one of claims 45-55, in the manufacture of a medicament for treating a proliferative disease.

58. The use of claim 57, wherein the proliferative disease is cancer.

59. The use of claim 58, wherein the cancer is selected from the group consisting of breast cancer, colorectal cancer, gastric cancer, renal cell carcinoma (RCC), or non-small cell lung cancer (NSCLC), solid tumors, bladder cancer, hepatocellular carcinoma, prostate cancer, ovarian/uterine cancer, pancreatic cancer, mesothelioma, melanoma, glioblastoma, HPV-associated and/or HPV-positive cancers such as cervical and HPV+ head and neck cancer, oral cavity cancer, cancer of the pharynx, thyroid cancer, gallbladder cancer, soft

tissue sarcomas, and hematological cancers like ALL, CLL, NHL, DLBCL, AML, CML, multiple myeloma (MM).

60. A method of generating the lymphocyte of any one of claims 1-29, the modified cell of any one of claims 30-42, the population of cells of claim 43, or the isolated *in vitro* population of lymphocytes of any one of claims ~~44-54~~45-55, the method comprising:

(a) obtaining an induced pluripotent stem cell (iPSC);

(b) modifying the iPSC, or an undifferentiated or differentiated daughter cell thereof, to comprise express at least one exogenous nucleic acid expression construct of (1) and/or to comprise a loss of function in at least one gene of (2);

(c) directing differentiation of the iPSC to hematopoietic lineage cells,

wherein the hematopoietic lineage cells retain the edited genetic loci comprised in the iPSCs.

61. The method of claim 60, wherein directing differentiation comprises:

(i) contacting iPSCs with a composition comprising a BMP pathway activator, and optionally bFGF, to obtain mesodermal cells; and

(ii) contacting the mesodermal cells with a composition comprising a BMP pathway activator, bFGF, and a WNT pathway activator, to obtain mesodermal cells having definitive hemogenic endothelium (HE) potential, wherein the mesodermal cells having definitive hemogenic endothelium (HE) potential are capable of providing hematopoietic lineage cells;

wherein mesodermal cells and mesodermal cells having definitive HE potential are obtained in steps (i) and (ii) without the step of forming embryoid bodies;

wherein the hematopoietic lineage cells comprise definitive hemogenic endothelium cells, hematopoietic stem and progenitor cells (HSC), hematopoietic multipotent progenitor cell (MPP), pre-T cell progenitor cells, pre-NK cell progenitor cells, T cell progenitor cells, NK cell progenitor cells, T cells, NK cells, NKT cells, or B cells.

62. The method of claim 61, wherein directing differentiation of iPSCs to hematopoietic lineage cells further comprises: contacting the mesodermal cells having definitive HE potential with a composition comprising bFGF and a ROCK inhibitor to obtain definitive HE cells.

63. The method of claim 60, claim 61, or claim 62, further comprising: contacting the definitive HE cells with a composition comprising a BMP activator, and optionally a ROCK inhibitor, and one or more growth factors and cytokines selected from the group consisting of TPO, IL3, GMCSF, EPO, bFGF, VEGF, SCF, IL6, Flt3L and IL11 to obtain hematopoietic multipotent progenitor cells (MPP).

64. The method of any one of claims 60-63, further comprising: contacting the definitive HE cells with a composition comprising one or more growth factors and cytokines selected from the group consisting of SCF, Flt3L, and IL7; and optionally one or more of a BMP activator, a ROCK inhibitor, TPO, VEGF and bFGF to obtain pre-T cell progenitors, T cell progenitors, and/or T cells.

65. The method of any one of claims 60-63, further comprising: contacting the definitive HE cells with a composition comprising one or more growth factors and cytokines selected from the group consisting of SCF, Flt3L, TPO, IL7 and IL15, and optionally one or more of a BMP activator, a ROCK inhibitor, VEGF and bFGF to obtain pre-NK cell progenitors, NK cell progenitors, and/or NK cells.

66. The method of any one of claims 60-65, further comprising: prior to step c), contacting the pluripotent stem cells with a composition comprising a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor, to seed and expand the cells.

67. The method of any one of claims 60-65, further comprising detecting a rearranged T-cell receptor (TCR) locus in the hematopoietic lineage cells.

68. The method of claim 67, further comprising selecting the hematopoietic lineage cells comprising the rearranged TCR locus based on the TCR encoded by the rearranged TCR locus binding an antigen of interest.

69. The method of claim 68, wherein the antigen of interest is a tumor antigen.

70. A method, the method comprising:
reprogramming a donor cell to a pluripotent state;
editing a target locus in the donor cell genome; and

differentiating the reprogrammed donor cell into a lymphocyte.

71. The method of claim 70, wherein the editing is performed before or during the step of reprogramming of the donor cell to a pluripotent state.

72. The method of claim 70 or 71, wherein the donor cell is a fibroblast, a peripheral blood cell, a lymphocyte, or a T cell.

73. A method, the method comprising:

differentiating a genetically modified pluripotent stem cell into a lymphocyte, wherein the genetically modified pluripotent stem cell comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further comprises:

(1) an exogenous nucleic acid expression construct comprising:

(i) a nucleic acid sequence encoding a chimeric antigen receptor (CAR);

(ii) a nucleic acid sequence encoding a non-naturally occurring variant of FcγRIII (CD16);

(iii) a nucleic acid sequence encoding interleukin 15 (IL-15);

(iv) a nucleic acid sequence encoding interleukin 15 receptor (IL-15R) or a variant thereof;

(v) a nucleic acid sequence encoding interleukin 12 (IL12);

(vi) a nucleic acid sequence encoding interleukin-12 receptor (IL-12R) or a variant thereof;

(vii) a nucleic acid sequence encoding human leukocyte antigen G (HLA-G);

(viii) a nucleic acid sequence encoding human leukocyte antigen E (HLA-E);

(ix) a nucleic acid sequence encoding leukocyte surface antigen cluster of differentiation CD47 (CD47);

or any combination of two or more thereof; and

(2) an indel, or an insertion of an exogenous nucleic acid in one or more of the following genetic loci:

~~(i) transforming growth factor beta receptor 2 (TGFβR2);~~

(i~~i~~) adenosine A2a receptor (ADORA2A);

(ii~~i~~) T cell immunoreceptor with Ig and ITIM domains (TIGIT);

(~~iv~~iii) β-2 microgobulin (B2M);

(iv) programmed cell death protein 1 (PD-1, CD279);

~~(vi) cytokine inducible SH2 containing protein (CISH);~~

(v~~ii~~) class II, major histocompatibility complex, transactivator (CIITA);

(vi~~ii~~) natural killer cell receptor NKG2A (natural killer group 2A);

(~~ix~~vii) two or more HLA class II histocompatibility antigen alpha chain genes, and/or two or more HLA class II histocompatibility antigen beta chain genes;

(~~x~~viii) cluster of differentiation 32B (CD32B, FCGR2B);

(~~xi~~ix) T cell receptor alpha constant (TRAC);

or any combination of two or more thereof,

wherein the indel or insertion results in a loss-of-function of a gene product encoded by the respective genetic locus or loci.

74. The method of claim 73, wherein the indel, or the insertion of an exogenous nucleic acid is in the following genetic loci :

(i) ~~TGFβR2, CISH,~~ TIGIT, ADORA2A, or NKG2A;

(ii) ~~TGFβR2 and CISH,~~ TGFβR2 and TIGIT, TGFβR2 and ADORA2A, TGFβR2 and NKG2A, CISH and TIGIT, CISH and ADORA2A, CISH and NKG2A, TIGIT and ADORA2A, TIGIT and NKG2A, or ADORA2A and NKG2A; or

(iii) TGFβR2, CISH and TIGIT; TGFβR2, CISH and ADORA2A; TGFβR2, CISH and NKG2A; TGFβR2, TIGIT and ADORA2A; TGFβR2, TIGIT and NKG2A; TGFβR2, ADORA2A and NKG2A; CISH, TIGIT and ADORA2A; CISH, TIGIT and NKG2A; CISH, ADORA2A and NKG2A; or TIGIT, ADORA2A and NKG2A,

wherein the indel or insertion results in a loss-of-function of a gene product encoded by the respective genetic locus or loci.

75. The method of claim 73 or claim 74, wherein the exogenous nucleic acid of (2) is the exogenous nucleic acid of (1).

76. The method of claim 73 or claim 75, wherein the pluripotent stem cell is an iPS cell.

77. The method of claim 73 or claim 75, wherein the differentiating comprises contacting the pluripotent stem cell with a differentiation medium or a sequence of differentiation media.

78. The modified lymphocyte of any ~~preceding claim~~one of claims 1-29, wherein the two or more HLA class II histocompatibility antigen alpha chain genes are selected from HLA-DQA1, HLA-DRA, HLA-DPA1, HLA-DMA, HLA-DQA2, and HLA-DOA.

79. The modified lymphocyte of any ~~preceding claim~~one of claims 1-29, wherein the two or more HLA class II histocompatibility antigen beta chain genes are selected from HLA-DMB, HLA-DOB, HLA-DPB1, HLA-DQB1, HLA-DQB3, HLA-DQB2, HLA-DRB1, HLA-DRB3, HLA-DRB4, and HLA-DRB5.

80. The modified lymphocyte of any one of claims 1-29 and 78-79, the modified cell of any one of claims 30-42, the population of cells of claim 43, the pharmaceutical composition of claim 44, or the isolated *in vitro* population of lymphocytes of any one of claims 45-55~~, or the method of any one of claims 56-77~~, wherein the exogenous nucleic acid expression construct comprises the encoding nucleic acid sequence listed under (1) under the control of a heterologous promoter.

81. The modified lymphocyte, modified cell, population of cells, pharmaceutical composition, or isolated *in vitro* population of lymphocytes~~, or method~~ of claim 80, wherein the heterologous promoter is an NK-cell specific promoter.

82. The modified lymphocyte, modified cell, population of cells, pharmaceutical composition, or isolated *in vitro* population of lymphocytes~~, or method~~ of claim 80, wherein the NK-cell specific promoter is a promoter of a gene known to be expressed specifically in NK cells, or a variant thereof.

83. The modified lymphocyte, modified cell, population of cells, pharmaceutical composition, or isolated *in vitro* population of lymphocytes, ~~or method~~ of claim 80, wherein the NK-cell specific promoter is a CD56 (NCAM), CD49, or CD45 promoter, or a variant thereof.

84. The modified lymphocyte, modified cell, population of cells, pharmaceutical composition, or isolated in vitro population of lymphocytes, ~~or method~~ of claim 80, wherein the NK-cell specific promoter is an FcγRIII promoter, an NKG2D promoter, a CD69 promoter, or a natural cytotoxicity receptor promoter, or a variant thereof.

85. The modified lymphocyte of any one of the claims 78-80, the modified cell of any one of the claims 80-84, or the population of cells of any one of the claims 80-84 for use in therapy.

86. Use of the modified lymphocyte of any one of the claims 78-80, the modified cell of any one of the claims 80-84, or the population of cells of any one of the claims 80-84 in the manufacture of a medicament for treating a proliferative disease.

87. The use of claim 86, wherein the proliferative disease is cancer.

88. The use of claim 87, wherein the cancer is selected from the group consisting of breast cancer, colorectal cancer, gastric cancer, renal cell carcinoma (RCC), or non-small cell lung cancer (NSCLC), solid tumors, bladder cancer, hepatocellular carcinoma, prostate cancer, ovarian/uterine cancer, pancreatic cancer, mesothelioma, melanoma, glioblastoma, HPV-associated and/or HPV-positive cancers such as cervical and HPV+ head and neck cancer, oral cavity cancer, cancer of the pharynx, thyroid cancer, gallbladder cancer, soft tissue sarcomas, and hematological cancers like ALL, CLL, NHL, DLBCL, AML, CML, multiple myeloma (MM).

89. A modified lymphocyte, wherein the modified lymphocyte:

(a) does not express endogenous CD3, CD4, and/or CD8; and

(b) expresses at least one endogenous gene encoding:

(i) CD56 (NCAM), CD49, and/or CD45;

(ii) NK cell receptor (cluster of differentiation 16 (CD16));

(iii) natural killer group-2 member D (NKG2D);

(iv) CD69;

(v) a natural cytotoxicity receptor;

or any combination of two or more thereof;

wherein the modified lymphocyte comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further:

(1) comprises at least one exogenous nucleic acid construct encoding:

(i) a chimeric antigen receptor (CAR);

(ii) a non-naturally occurring variant of immunoglobulin gamma Fc region receptor III (FcγRIII, CD16);

(iii) interleukin 15 (IL-15);

(iv) IL-15 receptor (IL-15R), or a variant thereof;

(v) interleukin 12 (IL-12);

(vi) human leukocyte antigen G (HLA-G);

(vii) human leukocyte antigen E (HLA-E);

or any combination of two or more thereof;

and/or

(2) exhibits a loss of function of at least one of:

(i) adenosine A2a receptor (ADORA2A);

(ii) T cell immunoreceptor with Ig and ITIM domains (TIGIT);

(iii) β-2 microgobulin (B2M);

(iv) programmed cell death protein 1 (PD-1);

(v) class II, major histocompatibility complex, transactivator (CIITA);

or any combination of two or more thereof.

90. A modified cell, wherein the modified cell comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further

(1) comprises at least one exogenous nucleic acid construct encoding:

(i) a chimeric antigen receptor (CAR);

(ii) a non-naturally occurring variant of immunoglobulin gamma Fc region receptor III (FcγRIII, CD16);

(iii) interleukin 15 (IL-15);

(iv) IL-15 receptor (IL-15R), or a variant thereof;

(v) interleukin 12 (IL-12);

(vi) human leukocyte antigen G (HLA-G);

(vii) human leukocyte antigen E (HLA-E);

or any combination of two or more thereof;

and/or

(2) exhibits a loss of function of at least one of:

(i) adenosine A2a receptor (ADORA2A);

(ii) T cell immunoreceptor with Ig and ITIM domains (TIGIT);

(iii) β-2 microgobulin (B2M);

(iv) programmed cell death protein 1 (PD-1);

(v) class II, major histocompatibility complex, transactivator (CIITA);

or any combination of two or more thereof.

91. An isolated population of lymphocytes, wherein the population comprises at least $1x10^3$, at least $1x10^4$, at least $1x10^5$, at least $2x10^5$, at least $3x10^5$, at least $4x10^5$, at least $5x10^5$,at least $1x10^6$, at least $2x10^6$, at least $3x10^6$, at least $4x10^6$, at least $5x10^6$,at least $1x10^7$, at least $1x10^7$, at least $2x10^7$, at least $3x10^7$, at least $4x10^7$, at least $5x10^7$,at least $1x10^8$, at least $2x10^8$, at least $3x10^8$, at least $4x10^8$, at least $5x10^8$,at least $1x10^9$, at least $1x10^9$, at least $2x10^9$, at least $3x10^9$, at least $4x10^9$, at least $5x10^9$,at least $1x10^{10}$, at least $2x10^{10}$, at least $3x10^{10}$, at least $4x10^{10}$, at least $5x10^{10}$, at least $1x10^{11}$, or at least $1x10^{12}$ cells, and wherein at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, at least 99.9%, at least 99.99%, at least 99.999%, or virtually 100% of the lymphocytes in the population:

(a) comprise a rearranged T-cell receptor (TCR) locus;

(b) do not express endogenous CD3;

(c) express endogenous CD56 (NCAM), CD49, and/or CD45; and

(d) expresses at least endogenous gene encoding:

(i) NK cell receptor (cluster of differentiation 16 (CD16));

(ii) natural killer group-2 member D (NKG2D);

(iii) CD69;

(iv) a natural cytotoxicity receptor;

or any combination of two or more thereof; and

wherein the modified lymphocyte comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further:

(1) comprises at least one exogenous nucleic acid construct encoding:

(i) chimeric antigen receptor (CAR);

(ii) non-naturally occurring variant of immunoglobulin gamma Fc region receptor III (FcγRIII, CD16);

(iii) interleukin 15 (IL-15);

(iv) IL-15 receptor (IL-15R), or a variant thereof;

(v) interleukin 12 (IL-12);

(vi) human leukocyte antigen G (HLA-G);

(vii) human leukocyte antigen E (HLA-E);

or any combination of two or more thereof;

and/or

(2) exhibits a loss of function of at least one of:

(i) adenosine A2a receptor (ADORA2A);

(ii) T cell immunoreceptor with Ig and ITIM domains (TIGIT);

(iii) β-2 microgobulin (B2M);

(iv) programmed cell death protein 1 (PD-1);

(v) class II, major histocompatibility complex, transactivator (CIITA);

or any combination of two or more thereof.

92. A method, the method comprising:

differentiating a genetically modified pluripotent stem cell into a lymphocyte, wherein the genetically modified pluripotent stem cell comprises a loss of function of transforming growth factor beta receptor 2 (TGFβR2) and cytokine inducible SH2 containing protein (CISH), and optionally further comprises:

(1) an exogenous nucleic acid comprising:

(i) a nucleic acid encoding a chimeric antigen receptor (CAR);

(ii) a nucleic acid encoding a non-naturally occurring variant of immunoglobulin gamma Fc region receptor III (FcγRIII, CD16);

(iii) a nucleic acid encoding interleukin 15 (IL-15) and/or interleukin 12 (IL12);

(iv) a nucleic acid encoding human leukocyte antigen G (HLA-G);

(v) a nucleic acid encoding human leukocyte antigen E (HLA-E);

or any combination of two or more thereof; and

(2) an indel, or an insertion of an exogenous nucleic acid in one or more of the following genetic loci:

(i) adenosine A2a receptor (ADORA2A);

(ii) T cell immunoreceptor with Ig and ITIM domains (TIGIT);

(iii) β-2 microgobulin (B2M);

(iv) programmed cell death protein 1 (PD-1, CD279);

(v) class II, major histocompatibility complex, transactivator (CIITA);

or any combination of two or more thereof,

wherein the indel or insertion results in a loss-of-function of a gene product encoded by the respective genetic locus or loci.