

Claims

1. A method of making an engineered human cell, which has reduced or eliminated surface expression of HLA-A protein relative to an unmodified cell, wherein the cell is homozygous for HLA-B and homozygous for HLA-C, comprising contacting a cell with composition comprising:
 - a. an HLA-A guide RNA comprising
 - i. a guide sequence selected from SEQ ID NOs: 1-211; or
 - ii. at least 17, 18, 19, or 20 contiguous nucleotides of a sequence selected from SEQ ID NOs: 1-211; or
 - iii. a guide sequence at least 95%, 90%, or 85% identical to a sequence selected from SEQ ID NOs: 1-211; or
 - iv. a guide sequence that binds a target site comprising a genomic region listed in Tables 2-5; or
 - v. a guide sequence that is complementary to at least 17, 18, 19, or 20 contiguous nucleotides of a genomic region listed in Tables 1-2 and 5, or a guide sequence that is complementary to at least 17, 18, 19, 20, 21, 22, 23, or 24 contiguous nucleotides of a genomic region listed in Table 4; or
 - vi. a guide sequence that is at least 95%, 90%, or 85% identical to a sequence selected from (v); and optionally
 - b. an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent.
2. A method of reducing surface expression of HLA-A protein in a human cell relative to an unmodified cell, comprising contacting a cell with composition comprising:
 - a. an HLA-A guide RNA comprising
 - i. a guide sequence selected from SEQ ID NOs: 1-211; or
 - ii. at least 17, 18, 19, or 20 contiguous nucleotides of a sequence selected from SEQ ID NOs: 1-211; or
 - iii. a guide sequence at least 95%, 90%, or 85% identical to a sequence selected from SEQ ID NOs: 1-211; or
 - iv. a guide sequence that binds a target site comprising a genomic region listed in Tables 2-5; or

- v. a guide sequence that is complementary to at least 17, 18, 19, or 20 contiguous nucleotides of a genomic region listed in Tables 1-2 and 5, or a guide sequence that is complementary to at least 17, 18, 19, 20, 21, 22, 23, or 24 contiguous nucleotides of a genomic region listed in Table 4; or
 - vi. a guide sequence that is at least 95%, 90%, or 85% identical to a sequence selected from (v); and optionally
 - b. an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent.
- 3. The method of claim 1 or 2, wherein the RNA-guided DNA binding agent comprises a Cas9 protein; or wherein the RNA-guided DNA-binding agent is *S. pyogenes* Cas9, *N. meningitidis* Cas9, *S. thermophilus* Cas9, *S. aureus* Cas9, Cpf1 from *F. novicida*, Cpf1 from *Acidaminococcus sp.*, or Cpf1 from *Lachnospiraceae bacterium ND2006*; or wherein the RNA-guided DNA-binding agent is a C to T base editor, an A to G base editor, or a APOBEC3A deaminase (A3A) and an RNA-guided nickase.
- 4. The method of any one of claims 1-3, further comprising reducing or eliminating the surface expression of MHC class II protein in the cell relative to an unmodified cell, by contacting the cell with a gene editing system targeting a gene selected from CIITA, HLA-DR, HLA-DQ, HLA-DP, RFX5, RFXB/ANK, RFXAP, CREB, NF-YA, NF-YB, and NF-YC; and/or further comprising contacting the cell with a CIITA guide RNA; and/or further comprising reducing or eliminating the surface expression of a TCR protein in the cell relative to an unmodified cell.
- 5. The method of any one of claims 1-4, further comprising contacting the cell with an exogenous nucleic acid, and optionally wherein the exogenous nucleic acid encodes a targeting receptor or a polypeptide that is secreted by the cell.
- 6. The method of claim 5, further comprising contacting the cell with a DNA-dependent protein kinase inhibitor (DNAPKi), optionally wherein the DNAPKi is Compound 1.
- 7. An engineered human cell, which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell, comprising a genetic modification in the HLA-A gene, wherein:
 - (i) the cell is homozygous for HLA-B and homozygous for HLA-C; or

(ii) the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from:

- a. chr6:29942854-chr6:29942913 and
- b. chr6:29943518-chr6:29943619;

wherein the cell is homozygous for HLA-B and homozygous for HLA-C.

8. The engineered cell of claim 7, wherein the cell has reduced or eliminated expression of at least one HLA-A allele selected from: HLA-A1, HLA-A2, HLA-A3, HLA-A11, and HLA-A24.

9. The engineered cell of claim 7 or 8, wherein:

(i) the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942864-chr6:29942903;

(ii) the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-chr6:29943609;

(iii) the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from: chr6:29942864-29942884; chr6:29942868-29942888; chr6:29942876-29942896; chr6:29942877-29942897; and chr6:29942883-29942903;

(iv) the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from: chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557; chr6:29943549-29943569; and chr6:29943589-29943609;

(v) the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942876-29942897;

(vi) the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-29943550;

(vii) the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from: chr6:29942864-29942884, chr6:29942868-29942888, chr6:29942876-29942896, and chr6:29942877-29942897; and/or

(viii) the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from: chr6:29943528-29943548, chr6:29943529-29943549, and chr6:29943530-29943550.

10. An engineered human cell, which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell, comprising a genetic modification in the HLA-A gene,

(i) wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from: chr6:29942864-29942884; chr6:29942868-29942888; chr6:29942876-29942896; chr6:29942877-29942897; chr6:29942883-29942903; chr6:29943126-29943146; chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557; chr6:29943549-29943569; chr6:29943589-29943609; and chr6:29944026-29944046; or

(ii) wherein the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates chosen from: chr6:29942864-29942884; chr6:29942868-29942888; chr6:29942876-29942896; chr6:29942877-29942897; chr6:29942883-29942903; chr6:29943126-29943146; chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557; chr6:29943549-29943569; chr6:29943589-29943609; and chr6:29944026-29944046.

11. The engineered cell of claim 10, wherein:

(i) the cell is homozygous for HLA-B and homozygous for HLA-C;

(ii) the genetic modification comprises at least 5, 6, 7, 8, 9, or 10 contiguous nucleotides within the genomic coordinates; and/or

(iii) the genetic modification comprises at least one C to T substitution or at least one A to G substitution within the genomic coordinates.

12. The engineered cell of any one of claims 7-11, wherein the HLA-A expression is reduced or eliminated by a gene editing system that binds to an HLA-A genomic target sequence comprising at least 5 contiguous nucleotides within the genomic coordinates chosen from:

- a. chr6:29942864-29942884; chr6:29942868-29942888; chr6:29942876-29942896; chr6:29942877-29942897; chr6:29942883-29942903; chr6:29943126-29943146; chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557; chr6:29943549-29943569; chr6:29943589-29943609; and chr6:29944026-29944046, chr6:29934330-29934350, chr6:29943115-29943135, chr6:29943135-29943155, chr6:29943140-29943160, chr6:29943590-29943610, chr6:29943824-29943844, chr6:29943858-29943878, chr6:29944478-29944498, and chr6:29944850-29944870;
- b. chr6:29942864-29942884; chr6:29942868-29942888; chr6:29942876-29942896; chr6:29942877-29942897; chr6:29942883-29942903; chr6:29943126-29943146;

- chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550;
chr6:29943537-29943557; chr6:29943549-29943569; chr6:29943589-29943609; and
chr6:29944026-29944046;
- c. chr6:29942864-29942884; chr6:29942868-29942888; chr6:29942876-29942896;
chr6:29942877-29942897; chr6:29942883-29942903; chr6:29943528-29943548;
chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557;
chr6:29943549-29943569; and chr6:29943589-29943609;
- d. chr6:29942864-29942884; chr6:29942868-29942888; chr6:29942876-29942896;
chr6:29942877-29942897; and chr6:29942883-29942903;
- e. chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550;
chr6:29943537-29943557; chr6:29943549-29943569; and chr6:29943589-29943609;
- f. chr6:29942864-29942884, chr6:29942868-29942888, chr6:29942876-29942896, and
chr6:29942877-29942897;
- g. chr6:29943528-29943548, chr6:29943529-29943549, and chr6:29943530-29943550;
- h. chr6:29945290-29945310, chr6:29945296-29945316, and chr6:29945297-29945317,
chr6:29945300-29945320;
- i. chr6:29890117-29890137, chr6:29927058-29927078, chr6:29934330-29934350,
chr6:29942541-29942561, chr6:29942542-29942562, chr6:29942543-29942563,
chr6:29942543-29942563, chr6:29942550-29942570, chr6:29942864-29942884,
chr6:29942868-29942888, chr6:29942876-29942896, chr6:29942876-29942896,
chr6:29942877-29942897, chr6:29942883-29942903, chr6:29943062-29943082,
chr6:29943063-29943083, chr6:29943092-29943112, chr6:29943115-29943135,
chr6:29943118-29943138, chr6:29943119-29943139, chr6:29943120-29943140,
chr6:29943126-29943146, chr6:29943128-29943148, chr6:29943129-29943149,
chr6:29943134-29943154, chr6:29943134-29943154, chr6:29943135-29943155,
chr6:29943136-29943156, chr6:29943140-29943160, chr6:29943142-29943162,
chr6:29943143-29943163, chr6:29943188-29943208, chr6:29943528-29943548,
chr6:29943529-29943549, chr6:29943530-29943550, chr6:29943536-29943556,
chr6:29943537-29943557, chr6:29943538-29943558, chr6:29943549-29943569,
chr6:29943556-29943576, chr6:29943589-29943609, chr6:29943590-29943610,
chr6:29943590-29943610, chr6:29943599-29943619, chr6:29943600-29943620,

- chr6:29943601-29943621, chr6:29943602-29943622, chr6:29943603-29943623,
chr6:29943774-29943794, chr6:29943779-29943799, chr6:29943780-29943800,
chr6:29943822-29943842, chr6:29943824-29943844, chr6:29943857-29943877,
chr6:29943858-29943878, chr6:29943859-29943879, chr6:29943860-29943880,
chr6:29944026-29944046, chr6:29944077-29944097, chr6:29944078-29944098,
chr6:29944458-29944478, chr6:29944478-29944498, chr6:29944597-29944617,
chr6:29944642-29944662, chr6:29944643-29944663, chr6:29944772-29944792,
chr6:29944782-29944802, chr6:29944850-29944870, chr6:29944907-29944927,
chr6:29945024-29945044, chr6:29945097-29945117, chr6:29945104-29945124,
chr6:29945105-29945125, chr6:29945116-29945136, chr6:29945118-29945138,
chr6:29945119-29945139, chr6:29945124-29945144, chr6:29945176-29945196,
chr6:29945177-29945197, chr6:29945177-29945197, chr6:29945180-29945200,
chr6:29945187-29945207, chr6:29945188-29945208, chr6:29945228-29945248,
chr6:29945230-29945250, chr6:29945231-29945251, chr6:29945232-29945252,
chr6:29945308-29945328, chr6:29945361-29945381, chr6:29945362-29945382, and
chr6:31382543-31382563;
- j. chr6:29942815-29942835, chr6:29942816-29942836, chr6:29942817-29942837,
chr6:29942817-29942837, chr6:29942828-29942848, chr6:29942837-29942857,
chr6:29942885-29942905, chr6:29942895-29942915, chr6:29942896-29942916,
chr6:29942898-29942918, chr6:29942899-29942919, chr6:29942900-29942920,
chr6:29942904-29942924, chr6:29942905-29942925, chr6:29942912-29942932,
chr6:29942913-29942933, chr6:29943490-29943510, chr6:29943497-29943517,
chr6:29943498-29943518, chr6:29943502-29943522, chr6:29943502-29943522,
chr6:29943511-29943531, chr6:29943520-29943540, chr6:29943521-29943541,
chr6:29943566-29943586, chr6:29943569-29943589, chr6:29943569-29943589,
chr6:29943570-29943590, chr6:29943573-29943593, chr6:29943578-29943598,
chr6:29943585-29943605, chr6:29943589-29943609, chr6:29943568-29943588, and
chr6:29942815-29942835;
- k. chr6:29942884-29942904, chr6:29943519-29943539, chr6:29942863-29942883;
- l. chr6:29943517-29943537, and chr6:29943523-29943543;

- m. chr6:29942845-29942869, chr6:29942852-29942876, chr6:29942865-29942889,
chr6:29942891-29942915, chr6:29942895-29942919, chr6:29942903-29942927,
chr6:29942904-29942928, chr6:29943518-29943542, chr6:29943525-29943549,
chr6:29943535-29943559, chr6:29943538-29943562, chr6:29943539-29943563,
chr6:29943547-29943571, chr6:29943547-29943571, chr6:29943548-29943572,
chr6:29943555-29943579, chr6:29943556-29943580, chr6:29943557-29943581,
chr6:29943558-29943582, chr6:29943559-29943583, chr6:29943563-29943587,
chr6:29943564-29943588, chr6:29943565-29943589, chr6:29943568-29943592,
chr6:29943571-29943595, chr6:29943572-29943596, chr6:29943595-29943619,
chr6:29943596-29943620, and chr6:29943600-29943624;
- n. chr6:29942885-29942905, chr6:29942895-29942915, chr6:29942896-29942916,
chr6:29942898-29942918, chr6:29942899-29942919, chr6:29942900-29942920,
chr6:29942904-29942924, chr6:29943511-29943531, chr6:29943520-29943540,
chr6:29943521-29943541, chr6:29943529-29943549, chr6:29943566-29943586,
chr6:29943568-29943588, chr6:29943569-29943589, chr6:29943569-29943589,
chr6:29943570-29943590, chr6:29943573-29943593, chr6:29943578-29943598,
chr6:29943585-29943605, and chr6:29943589-29943609; and
- o. chr6:29942469-29942489, chr6:29943058-29943078, chr6:29943063-29943083,
chr6:29943080-29943100, chr6:29943187-29943207, chr6:29943192-29943212,
chr6:29943197-29943217, chr6:29943812-29943832, chr6:29944349-29944369,
chr6:29944996-29945016, chr6:29945018-29945038, and chr6:29945341-29945361,
chr6:29945526-29945546.

13. The engineered cell of any one of claims 7-12,

- (i) wherein the HLA-A expression is reduced or eliminated by a gene editing system that binds to an HLA-A genomic target sequence comprising at least 5 contiguous nucleotides within the genomic coordinates chosen from chr6:29942854-chr6:29942913 and chr6:29943518-chr6:29943619;
- (ii) wherein the HLA-A expression is reduced or eliminated by a gene editing system that binds to an HLA-A genomic target sequence comprising at least 5 contiguous nucleotides within the genomic coordinates chr6:29942876-29942897;

(iii) wherein the HLA-A expression is reduced or eliminated by a gene editing system that binds to an HLA-A genomic target sequence comprising at least 5 contiguous nucleotides within the genomic coordinates chr6:29943528-29943550; and/or

(iv) wherein the HLA-A expression is reduced or eliminated by a gene editing system that binds to an HLA-A genomic target sequence comprising at least 5 contiguous nucleotides within the genomic coordinates chosen from: chr6:29942864-29942884; chr6:29942868-29942888; chr6:29942876-29942896; chr6:29942877-29942897; chr6:29942883-29942903; chr6:29943126-29943146; chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557; chr6:29943549-29943569; chr6:29943589-29943609; and chr6:29944026-29944046.

14. The engineered cell of claim 12 or 13, wherein the HLA-A genomic target sequence comprises at least 10, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleotides within the genomic coordinates.

15. The engineered cell of any one of claims 10-14, wherein the cell is homozygous for HLA-B and homozygous for HLA-C.

16. The engineered cell of any one of claims 7-15,

(i) wherein the HLA-B allele is selected from any one of the following HLA-B alleles: HLA-B*07:02; HLA-B*08:01; HLA-B*44:02; HLA-B*35:01; HLA-B*40:01; HLA-B*57:01; HLA-B*14:02; HLA-B*15:01; HLA-B*13:02; HLA-B*44:03; HLA-B*38:01; HLA-B*18:01; HLA-B*44:03; HLA-B*51:01; HLA-B*49:01; HLA-B*15:01; HLA-B*18:01; HLA-B*27:05; HLA-B*35:03; HLA-B*18:01; HLA-B*52:01; HLA-B*51:01; HLA-B*37:01; HLA-B*53:01; HLA-B*55:01; HLA-B*44:02; HLA-B*44:03; HLA-B*35:02; HLA-B*15:01; and HLA-B*40:02;

(ii) wherein the HLA-C allele is selected from any one of the following HLA-C alleles: HLA-C*07:02; HLA-C*07:01; HLA-C*05:01; HLA-C*04:01; HLA-C*03:04; HLA-C*06:02; HLA-C*08:02; HLA-C*03:03; HLA-C*06:02; HLA-C*16:01; HLA-C*12:03; HLA-C*07:01; HLA-C*04:01; HLA-C*15:02; HLA-C*07:01; HLA-C*03:04; HLA-C*12:03; HLA-C*02:02; HLA-C*04:01; HLA-C*05:01; HLA-C*12:02; HLA-C*14:02; HLA-C*06:02; HLA-C*04:01; HLA-C*03:03; HLA-C*07:04; HLA-C*07:01; HLA-C*04:01; HLA-C*04:01; and HLA-C*02:02;

(iii) wherein the HLA-B allele is selected from any one of the following HLA-B alleles: HLA-B*07:02; HLA-B*08:01; HLA-B*44:02; HLA-B*35:01; HLA-B*40:01; HLA-B*57:01; HLA-B*14:02; HLA-B*15:01; HLA-B*13:02; HLA-B*44:03; HLA-B*38:01; HLA-B*18:01; HLA-B*44:03; HLA-B*51:01; HLA-B*49:01; HLA-B*15:01; HLA-B*18:01; HLA-B*27:05; HLA-B*35:03; HLA-B*18:01; HLA-B*52:01; HLA-B*51:01; HLA-B*37:01; HLA-B*53:01; HLA-B*55:01; HLA-B*44:02; HLA-B*44:03; HLA-B*35:02; HLA-B*15:01; and HLA-B*40:02; and the HLA-C allele is selected from any one of the following HLA-C alleles: HLA-C*07:02; HLA-C*07:01; HLA-C*05:01; HLA-C*04:01; HLA-C*03:04; HLA-C*06:02; HLA-C*08:02; HLA-C*03:03; HLA-C*06:02; HLA-C*16:01; HLA-C*12:03; HLA-C*07:01; HLA-C*04:01; HLA-C*15:02; HLA-C*07:01; HLA-C*03:04; HLA-C*12:03; HLA-C*02:02; HLA-C*04:01; HLA-C*05:01; HLA-C*12:02; HLA-C*14:02; HLA-C*06:02; HLA-C*04:01; HLA-C*03:03; HLA-C*07:04; HLA-C*07:01; HLA-C*04:01; HLA-C*04:01; and HLA-C*02:02;

(iv) wherein the HLA-B and HLA-C alleles are selected from any one of the following HLA-B and HLA-C alleles: HLA-B*07:02 and HLA-C*07:02; HLA-B*08:01 and HLA-C*07:01; HLA-B*44:02 and HLA-C*05:01; HLA-B*35:01 and HLA-C*04:01; HLA-B*40:01 and HLA-C*03:04; HLA-B*57:01 and HLA-C*06:02; HLA-B*14:02 and HLA-C*08:02; HLA-B*15:01 and HLA-C*03:03; HLA-B*13:02 and HLA-C*06:02; HLA-B*44:03 and HLA-C*16:01; HLA-B*38:01 and HLA-C*12:03; HLA-B*18:01 and HLA-C*07:01; HLA-B*44:03 and HLA-C*04:01; HLA-B*51:01 and HLA-C*15:02; HLA-B*49:01 and HLA-C*07:01; HLA-B*15:01 and HLA-C*03:04; HLA-B*18:01 and HLA-C*12:03; HLA-B*27:05 and HLA-C*02:02; HLA-B*35:03 and HLA-C*04:01; HLA-B*18:01 and HLA-C*05:01; HLA-B*52:01 and HLA-C*12:02; HLA-B*51:01 and HLA-C*14:02; HLA-B*37:01 and HLA-C*06:02; HLA-B*53:01 and HLA-C*04:01; HLA-B*55:01 and HLA-C*03:03; HLA-B*44:02 and HLA-C*07:04; HLA-B*44:03 and HLA-C*07:01; HLA-B*35:02 and HLA-C*04:01; HLA-B*15:01 and HLA-C*04:01; and HLA-B*40:02 and HLA-C*02:02;

(v) wherein the HLA-B and HLA-C alleles are HLA-B*07:02 and HLA-C*07:02;

(vi) wherein the HLA-B and HLA-C alleles are HLA-B*08:01 and HLA-C*07:01;

(vii) wherein the HLA-B and HLA-C alleles are HLA-B*44:02 and HLA-C*05:01; and/or

(viii) wherein the HLA-B and HLA-C alleles are HLA-B*35:01 and HLA-C*04:01.

17. The engineered cell of any one of claims 7-16, wherein the cell has reduced expression of MHC class II protein on the surface of the cell; and/or wherein the cell has a genetic modification of a gene selected from CIITA, HLA-DR, HLA-DQ, HLA-DP, RFX5, RFXB/ANK, RFXAP, CREB, NF-YA, NF-YB, and NF-YC; and/or wherein the cell has a genetic modification in the CIITA gene; and/or wherein the cell has reduced expression of TRAC protein or TRBC protein on the surface of the cell.
18. The engineered cell of any one of claims 7-17, wherein the engineered cell comprises an exogenous nucleic acid encoding a targeting receptor that is expressed on the surface of the engineered cell or a ligand for the receptor, and optionally wherein the targeting receptor is a CAR or a TCR; and/or wherein the engineered cell further comprises an exogenous nucleic acid encoding a polypeptide that is secreted by the engineered cell.
19. The engineered cell of any one of claims 7-18, wherein
- (i) the engineered cell is an immune cell;
 - (ii) the engineered cell is a primary cell;
 - (iii) the engineered cell is a monocyte, macrophage, mast cell, dendritic cell, or granulocyte;
 - (iv) the engineered cell is a lymphocyte; and/or
 - (v) the engineered cell is a T cell.
20. The engineered cell of any one of claims 7-19, wherein the genetic modification comprises at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 contiguous nucleotides within the genomic coordinates; and/or wherein the genetic modification comprises an indel; and/or wherein the genetic modification comprises at least one C to T substitution or at least one A to G substitution within the genomic coordinates.
21. A pharmaceutical composition comprising the engineered cell of any one of claims 7-20.
22. A population of cells comprising the engineered cell of any one of claims 7-20.
23. A pharmaceutical composition comprising the population of cells of claim 22.
24. The population of cells of claim 22 or pharmaceutical composition of claim 21 or 23, wherein the population of cells is at least 65%, at least 70%, at least 80%, at least 90%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% HLA-A negative as measured by flow cytometry; and/or

wherein the population of cells is at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% CIITA negative as measured by flow cytometry; and/or

wherein the population of cells is at least 95%, at least 97%, at least 98%, at least 99%, or at least 99.5% endogenous TCR protein negative as measured by flow cytometry.

25. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-24, wherein the engineered cell is an allogeneic cell and/or a primary cell; and/or wherein the engineered cell is a T cell, and optionally wherein the T cell is a CD4⁺ T cell, a CD8⁺ T cell, or a memory T cell; or

wherein the engineered cell is a B cell, and optionally wherein the B cell is a plasma B cell or a memory B cell; or

wherein the engineered cell is a stem cell, and optionally wherein the stem cell is a pluripotent stem cell (PSC), a hematopoietic stem cell (HSC), an induced pluripotent stem cell (iPSC), a mesenchymal stem cell (MSC), a neural stem cell (NSC), or a limbal stem cell (LSC).

26. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-25, comprising an exogenous nucleic acid encoding a polypeptide that is secreted by the cell or contacting the cell with said exogenous nucleic acid, wherein the secreted polypeptide is an antibody or antibody fragment, or wherein the secreted polypeptide is a full-length IgG antibody, a single chain antibody, or a neutralizing antibody, or wherein the secreted polypeptide is a cytokine; or

comprising an exogenous nucleic acid encoding a targeting receptor or contacting the cell with an exogenous nucleic acid encoding a targeting receptor, wherein the targeting receptor is a T cell receptor (TCR), a CAR, or a proliferation-inducing ligand (APRIL).

27. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-26, wherein the cell is engineered with a gene editing system, and optionally wherein the gene editing system comprises a transcription activator-like effector nuclease (TALEN) or a zinc finger nuclease, or optionally

wherein the gene editing system comprises an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent, optionally wherein the RNA-guided DNA binding agent is Cas9.

28. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-6 and 25-27, wherein the HLA-A guide RNA, the RNA-guided DNA binding

agent, and/or the exogenous nucleic acid is provided to the cell in a vector, optionally wherein the HLA-A guide RNA and the RNA-guided DNA binding agent are provided in the same vector.

29. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-6 and 25-28, wherein a lipid nucleic acid assembly composition comprising the HLA-A guide RNA and/or the exogenous nucleic acid, and optionally the RNA-guided DNA binding agent, is provided to the cell, optionally wherein the lipid nucleic acid assembly composition is a lipid nanoparticle (LNP).

30. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-6 and 25-29, wherein

(i) the HLA-A guide RNA comprises a single guide RNA comprising any one of the sequences of SEQ ID NOs: 344-438, 472-504, 533-560, and 1016 or a sequence that is at least 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, or 90% identical to any one of the sequences of SEQ ID NOs: 344-438, 472-504, and 533-560, and 1016;

(ii) the HLA-A guide RNA comprises a guide sequence comprising any one of SEQ ID NOs: 13-18, 26, 37-39, 41, 43, 45, and 62; or wherein the HLA-A guide RNA comprises a single guide RNA comprising any one of the sequences of SEQ ID NOs: 356-361, 369, 380-382, 384, 386, 388, and 405, or a sequence that is at least 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, or 90% identical to any one of the sequences of SEQ ID NOs: 356-361, 369, 380-382, 384, 386, 388, and 405; and/or

(iii) the HLA-A guide RNA comprises at least one modification, and optionally wherein the at least one modification includes (i) a 2'-O-methyl (2'-O-Me) modified nucleotide, (ii) a phosphorothioate (PS) bond between nucleotides, (iii) a 2'-fluoro (2'-F) modified nucleotide, (iv) a modification at one or more of the first five nucleotides at the 5' end of the guide RNA, (v) a modification at one or more of the last five nucleotides at the 3' end of the guide RNA, (vi) a PS bond between the first four nucleotides of the guide RNA, (vii) a PS bond between the last four nucleotides of the guide RNA, (viii) a 2'-O-Me modified nucleotide at the first three nucleotides at the 5' end of the guide RNA, (ix) a 2'-O-Me modified nucleotide at the last three nucleotides at the 3' end of the guide RNA, or combinations of one or more of (i)-(ix).

31. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-30, for use in expressing a TCR with specificity for a polypeptide expressed by cancer cells.

32. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-30, for use as an adoptive cell transfer (ACT) therapy to be administered to a subject.

33. Use of the engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-30, in the manufacture of a medicament for treating a cancer, an infectious disease, or an autoimmune disease in a subject.

34. A cell bank comprising:

- a. the engineered cell of any one of claims 7-20 and 25-33, or the engineered cell produced by the method of any one of claims 1-6 and 25-30; and
- b. a catalogue comprising information documenting the HLA-B and HLA-C alleles of the donor cells in the cell bank, and optionally

wherein the cell bank comprises at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40 donor cells that have a unique combination of HLA-B and HLA-C alleles as compared to other donor cells in the cell bank.

35. Use of an engineered cell in the manufacture of a medicament for treating a cancer, an infectious disease, or an autoimmune disease, wherein the medicament is to be administered to a recipient subject in need thereof according to a method, the method comprising:

- a. determining the HLA-B and HLA-C alleles of the recipient subject;
- b. selecting the medicament comprising the engineered cell or population of cells of any one of claims 7-20, 22, and 24-32, or the engineered cell produced by the method of any one of claims 1-6 and 25-30, wherein the engineered cell comprises at least one of the same HLA-B or HLA-C alleles as the recipient subject optionally

wherein the subject has the HLA-B and HLA-C alleles of the engineered cell.

36. Use of the engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-30, in the manufacture of a medicament for treating a cancer, an infectious disease, or an autoimmune disease as an adoptive cell transfer (ACT) therapy, to be administered to a partially matched subject, wherein the partially matched subject has the HLA-B and HLA-C alleles of the engineered cell or population of cells.

37. The engineered cell, population of cells, pharmaceutical composition, or use of any one of claims 32, 33, 35, or 36, wherein the engineered cell or population of cells comprises HLA-B and HLA-C alleles shared with the subject; or
wherein the HLA-B and HLA-C alleles of the engineered cell or population of cells comprise one or more HLA-B and HLA-C alleles of the subject; or
wherein the HLA-B and HLA-C alleles of the engineered cell or population of cells comprise one or both HLA-B alleles and/or one or both HLA-C alleles of the subject.