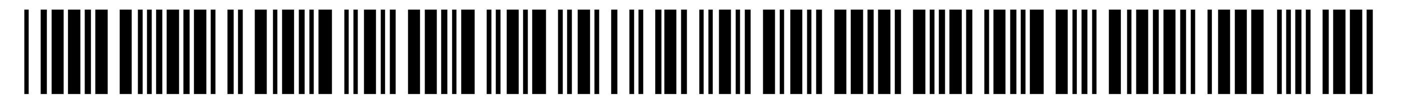
(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) **World Intellectual Property Organization**
International Bureau



(10) **International Publication Number**
WO 2022/140586 A3

(43) **International Publication Date**
30 June 2022 (30.06.2022)

(51) **International Patent Classification:**
C12N 5/0783 (2010.01)

(21) **International Application Number:** PCT/US2021/064930

(22) **International Filing Date:** 22 December 2021 (22.12.2021)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**

63/130,095	23 December 2020 (23.12.2020)	US
63/250,996	30 September 2021 (30.09.2021)	US
63/254,970	12 October 2021 (12.10.2021)	US
63/288,492	10 December 2021 (10.12.2021)	US

(71) **Applicant: INTELLIA THERAPEUTICS, INC.** [US/US]; 40 Erie Street, Cambridge, Massachusetts 02139 (US).

(72) **Inventors: GOEL, Surbhi**; 40 Erie Street, Cambridge, Massachusetts 02139 (US). **ZHANG, Yong**; 40 Erie Street, Cambridge, Massachusetts 02139 (US). **LESCARBEAU, Reynald Michael**; 40 Erie Street, Cambridge, Massachusetts 02139 (US). **MURRAY, Bradley Andrew**; 40 Erie Street, Cambridge, Massachusetts 02139 (US). **SRIDHAR, Srijani**; 40 Erie Street, Cambridge, Massachusetts 02139 (US).

(74) **Agent: BAUR, Amelia Feulner** et al.; MCNEILL BAUR PLLC, 125 Cambridge Park Drive, Suite 301, Cambridge, Massachusetts 02140 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) **Title:** COMPOSITIONS AND METHODS FOR REDUCING HLA-A IN A CELL

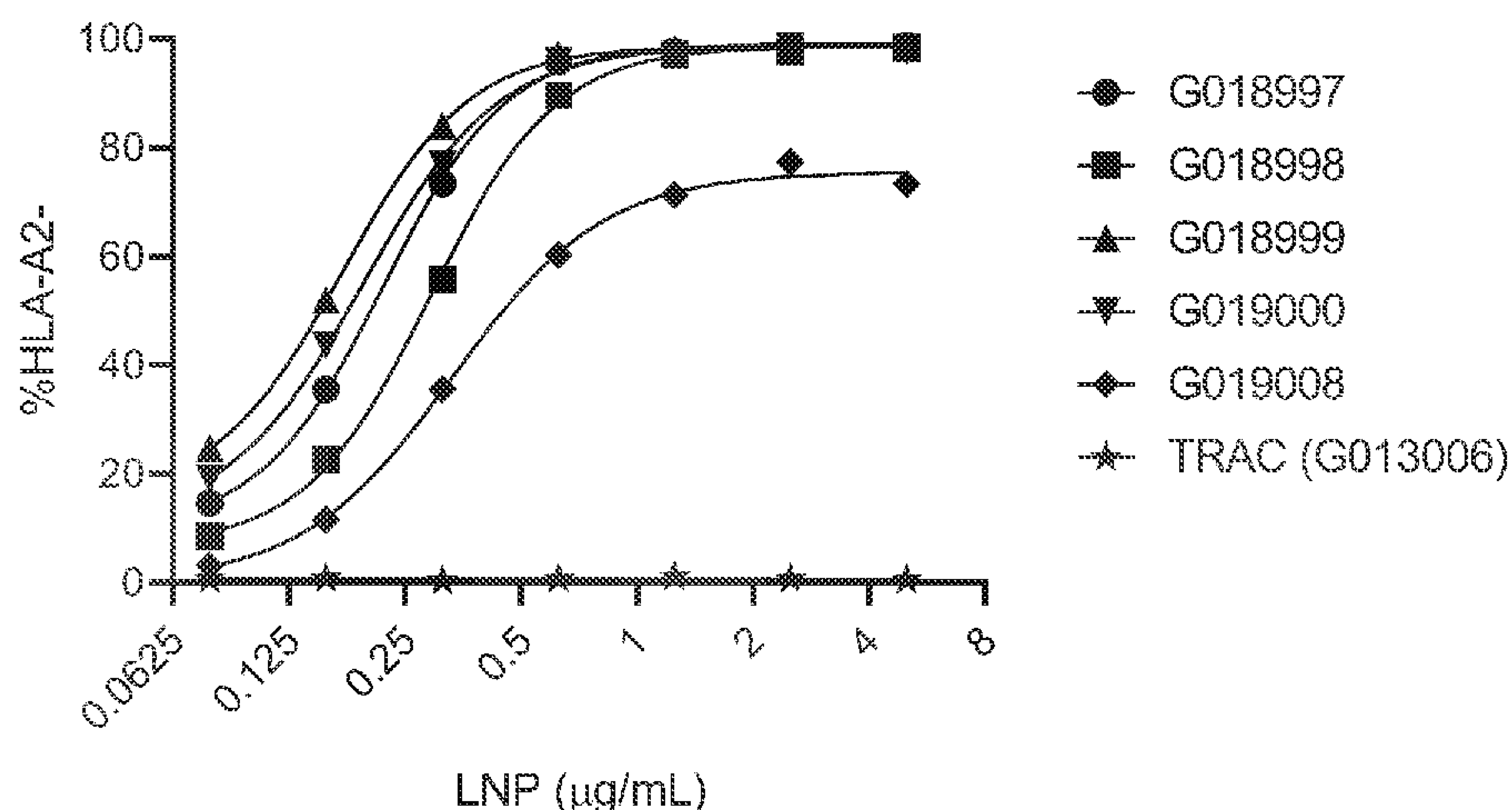


FIG. 1A

(57) **Abstract:** Compositions and methods for reducing HLA-A protein expression in a cell comprising genetically modifying HLA-A for use *e.g.*, in adoptive cell transfer therapies.

WO 2022/140586 A3

[Continued on next page]

WO 2022/140586 A3

Published:

— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
04 August 2022 (04.08.2022)

COMPOSITIONS AND METHODS FOR REDUCING HLA-A IN A CELL

[0001] This application claims the benefit under 35 U.S.C. 119(e) of US Provisional Application No. 63/130,095, filed December 23, 2020, US Provisional Application No. 63/250,996, filed September 30, 2021, US Provisional Application No. 63/254,970, filed October 12, 2021, and US Provisional Application No. 63/288,492, filed December 10, 2021; each of which disclosures is herein incorporated by reference in its entirety.

[0002] This application is filed with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled "2021-12-20_01155-0036-00PCT_Seq_List_ST25.txt" created on December 20, 2021, which is 320,511 bytes in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

I. INTRODUCTION AND SUMMARY

[0003] The ability to downregulate MHC class I is critical for many *in vivo* and *ex vivo* utilities, e.g., when using allogeneic cells (originating from a donor) for transplantation and/or e.g., for creating a cell population in vitro that does not activate T cells. In particular, the transfer of allogeneic cells into a subject is of great interest to the field of cell therapy. The use of allogeneic cells has been limited due to the problem of rejection by the recipient subject's immune cells, which recognize the transplanted cells as foreign and mount an attack. To avoid the problem of immune rejection, cell-based therapies have focused on autologous approaches that use a subject's own cells as the cell source for therapy, an approach that is time-consuming and costly.

[0004] Typically, immune rejection of allogeneic cells results from a mismatching of major histocompatibility complex (MHC) molecules between the donor and recipient. Within the human population, MHC molecules exist in various forms, including e.g., numerous genetic variants of any given MHC gene, i.e., alleles, encoding different forms of MHC protein. The primary classes of MHC molecules are referred to as MHC class I and MHC class II. MHC class I molecules (e.g., HLA-A, HLA-B, and HLA-C in humans) are expressed on all nucleated cells and present antigens to activate cytotoxic T cells (CD8+ T cells or CTLs). MHC class II molecules (e.g., HLA-DP, HLA-DQ, and HLA-DR in humans) are expressed on only certain cell types (e.g., B cells, dendritic cells, and macrophages) and present antigens to activate helper T cells (CD4+ T cells or Th cells), which in turn provide signals to B cells to produce antibodies.

[0005] Slight differences, *e.g.*, mismatches in MHC alleles between individuals can cause the T cells in a recipient to become activated. During T cell development, an individual's T cell repertoire is tolerized to one's own MHC molecules, but T cells that recognize another individual's MHC molecules may persist in circulation and are referred to as alloreactive T cells. Alloreactive T cells can become activated *e.g.*, by the presence of another individual's cells expressing MHC molecules in the body, causing *e.g.*, graft versus host disease and transplant rejection.

[0006] While fully matching HLA types between donor and recipient is theoretically possible as a means of reducing transplant rejection, such an approach is logistically and practically challenging given the diversity of HLA alleles across the population to fully match *e.g.*, 10 out 10 alleles (*i.e.*, 2 alleles for each of HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1).

[0007] Methods and compositions for reducing the susceptibility of an allogeneic cell to rejection are of interest, including *e.g.*, reducing the cell's expression of MHC protein to avoid recipient T cell responses. In practice, the ability to genetically modify an allogeneic cell for transplantation into a subject has been hampered by the requirement for multiple gene edits to reduce all MHC protein expression, while at the same time, avoiding other harmful recipient immune responses. For example, while strategies to deplete MHC class I protein may reduce activation of CTLs, cells that lack MHC class I on their surface are susceptible to lysis by natural killer (NK) cells of the immune system because NK cell activation is regulated by MHC class I-specific inhibitory receptors. Therefore, safely reducing or eliminating expression of MHC class I has proven challenging.

[0008] Gene editing strategies to deplete MHC class II molecules have also proven difficult particularly in certain cell types for reasons including low editing efficiencies and low cell survival rates, preventing practical application as a cell therapy.

[0009] Thus, there exists a need for improved methods and compositions for modifying allogeneic cells to overcome the problem of recipient immune rejection and the technical difficulties associated with the multiple genetic modifications required to produce a safer cell for transplant.

[0010] The present disclosure provides engineered human cells with reduced or eliminated surface expression of HLA-A relative to an unmodified cell, wherein the cell is homozygous for HLA-B and homozygous for HLA-C. The engineered human cells disclosed herein therefore provide a "partial matching" approach to the problem of allogeneic cell transfer and MHC class I compatibility. The use of cells that are homozygous for HLA-B and

HLA-C, in addition to reducing or eliminating expression of HLA-A in the cells, limits the number of donors that are necessary to provide a therapy that covers a majority of recipients in population because the disclosed partial matching approach requires only one matching HLA-B allele (as opposed to two) and only one HLA-C allele (as opposed to two). Surprisingly, the engineered human cells that have reduced or eliminated surface expression of HLA-A relative to an unmodified cell, disclosed herein, demonstrate persistence and are protective against NK-mediated rejection, especially as compared to engineered cells with reduced or eliminated B2M expression. The disclosure provides methods and compositions for generating such engineered human cells with reduced or eliminated surface expression of HLA-A relative to an unmodified cell, wherein the cell is homozygous for HLA-B and homozygous for HLA-C. In some embodiments, the disclosure provides engineered human cells, and methods and compositions for generating engineered human cells, wherein the cell further has reduced expression of MHC class II protein on the surface of the cell, e.g., wherein the cell has a genetic modification in the CIITA gene. In some embodiments, the disclosure provides for further engineering of the cell, including to reduce or eliminate the expression of endogenous T cell receptor proteins (*e.g.*, TRAC, TRBC), and to introduce an exogenous nucleic acid, e.g., encoding a polypeptide expressed on the cell surface or a polypeptide that is secreted by the cell. Thus, the disclosure thus provides a flexible platform for genetically engineering human cells for a variety of desired adoptive cell therapy purposes.

[0011] Provided herein is 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 the cell is homozygous for HLA-B and homozygous for HLA-C. Also provided is 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from: chr6:29942854-chr6:29942913 and chr6:29943518-chr6: 29943619, wherein the cell is homozygous for HLA-B and homozygous for HLA-C.

[0012] Provided herein is 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 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.

[0013] Provided herein is an engineered human cell, which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell, comprising a genetic modification in an HLA-A gene, 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.

[0014] Provided herein is 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.

[0015] Provided herein is 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.

[0016] Provided herein is a method of administering an engineered cell to a recipient subject in need thereof, the method comprising: (a) determining the HLA-B and HLA-C alleles of the recipient subject; (b) selecting an engineered cell or cell population of any one of the preceding embodiments, or engineered cell or cell population produced by the method of any one of the preceding embodiments, wherein the engineered cell comprises at least one of the same HLA-B or HLA-C alleles as the recipient subject; (c) administering the selected engineered cell to the recipient subject.

[0017] Further embodiments are provided throughout and described in the claims and Figures.

II. BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIGS. 1A and 1B show the percentage of activated T cells negative for HLA-A2 by flow cytometry. FIG. 1A shows data for guides (G018997, G018998, G018999, G019000, G019008, G013006). FIG. 1B shows data for guides (G018091, G018933, G018935, G018954, G018995, G018996).

[0019] FIG. 2 shows resistance to NK-cell mediated killing of HLA-A knockout (HLA-B/C match) T cells versus B2M knockout T cells, optionally including an exogenous HLA-E construct, as percent T cell lysis. HLA-A knockout, HLA-A, CIITA double knockout, B2M knockout, B2M + HLA-E, and wild type cells are compared.

[0020] FIGS. 3A-F show results for sequential editing in CD8+ T cells. FIG. 3A shows the percentage of HLA-A positive cells. FIG. 3B shows the percentage of MHC class II positive cells. FIG. 3C shows the percentage of WT1 TCR positive CD3+, Vb8+ cells. FIG. 3D shows the percentage cells displaying mis-paired TCRs. FIG. 3E shows the percentage of CD3+, vb8- cells displaying only endogenous TCRs. FIG. 3F shows the percentage of CD3+, Vb8+, positive for the WT1 TCR and negative for HLA-A and MHC class II.

[0021] FIGS. 4A-F show results for sequential editing in CD4+ T cells. FIG. 4A shows the percentage of HLA-A positive cells. FIG. 4B shows the percentage of MHC class II positive cells. FIG. 4C shows the percentage of WT1 TCR positive CD3+, Vb8+ cells. FIG. 4D shows the percentage of cells displaying mis-paired TCRs. FIG. 4E shows the percentage

of CD3+, vb8- cells displaying only endogenous TCRs. FIG. 4F shows the percentage of CD3+, Vb8+, positive for the WT1 TCR and negative for HLA-A and MHC class II.

[0022] FIGS. 5A-D show the percent indels following sequential editing of T cells for CIITA (FIG. 5A), HLA-A (FIG. 5B), TRBC1 (FIG. 5C), and TRBC2 (FIG. 5D) in T cells.

[0023] FIGS. 6A-B show luciferase expression from B2M, CIITA, HLA-A, or double (HLA-A, CIITA) knockout human T cells administered to mice inoculated with human natural killer cells. FIG. 6A shows radiance (photons/s/cm2/sr) from luciferase expressing T cells present at the various time points after injection. FIG. 6B shows radiance (photons/s/cm2/sr) from luciferase expressing T cells present in the various mice groups on Day 27.

[0024] FIGS. 7A-B show luciferase expression from B2M and AlloWT1 knockout human T cells administered to mice inoculated with human natural killer cells. FIG. 7A shows total flux (p/s) from luciferase expressing T cells present at the various time points after injection. FIG. 7B shows total flux (p/s)from luciferase expressing T cells present in the various mice groups after 31 days.

[0025] FIGS. 8A-B show the percent normalized proliferation of host CD4 (FIG. 8A) or host CD8 (FIG. 8B) T cells triggered by HLA class I + HLA class II double knockout or HLA-A and HLA class II double knockout engineered autologous or allogeneic T cells.

[0026] FIGS. 9A-F shows a panel of percent CD8+ (FIG. 9A), endogenous TCR+ (FIG. 9B), WT1 TCR+ (FIG. 9C), HLA-A2 knockout (FIG. 9D), HLA-DRDPDQ knockout (FIG. 9E), and % Allo WT1 (FIG. 9F).

[0027] FIG. 10 shows total flux (p/s) from luciferase expressing T cells present at the various time points after injection out to 18 days.

[0028] FIGS. 11A-11B respectively show release of IFN-γ and IL-2 in supernatants from a killing assay containing a co-culture of engineered T cells from the Allo-WT1, Auto-WT1, TCR KO, and Wildtype (WT) groups with target tumor cells.

[0029] FIGS. 12A-12B show CIITA, HLA-A, TRAC, and TRBC editing and WT1 TCR insertion rates in CD8+ T cells in three conditions. The percentage of cells expressing relevant cell surface proteins following sequential T cell engineering are shown in FIG. 12A for CD8+ T cells. The percent of T cells with all intended edits (insertion of the WT1-TCR, combined with knockout of HLA-A and CIITA) is shown in FIG 12B.

[0030] FIG. 13 shows the percent lysis of T cells targeted by NK cells at different effector:target (E:T) ratios treated with sgRNA and base editor and UGI mRNAs.

[0031] FIG. 14 shows the mean percentage of CD8+ T cells that are negative for HLA-A surface receptors following treatment with sgRNAs in the 100-mer or 91-mer formats targeting HLA-A.

[0032] FIGS. 15A-15C respectively show HLA-A gene editing correlation to protein knockout in Donors A-C.

III. DETAILED DESCRIPTION

[0033] The present disclosure provides engineered human cells, as well as methods and compositions for genetically modifying a human cell to make engineered human cells that are useful, for example, for adoptive cell transfer (ACT) therapies. The disclosure provides engineered human cells with reduced or eliminated surface expression of HLA-A relative to an unmodified cell, wherein the cell is homozygous for HLA-B and homozygous for HLA-C. Thus, the engineered human cells disclosed herein provide a "partial matching" solution to hurdles associated with allogeneic cell transfer.

[0034] In some embodiments, the disclosure provides engineered human cells with reduced or eliminated surface expression of HLA-A as a result of a genetic modification in the HLA-A gene, wherein the cell is homozygous for HLA-B and homozygous for HLA-C. In some embodiments, the disclosure provides compositions and methods for reducing or eliminating expression of HLA-A protein relative to an unmodified cell and compositions and methods to reduce the cell's susceptibility to immune rejection. In some embodiments, the engineered human cells with reduced or eliminated surface expression of HLA-A relative to an unmodified cell are not susceptible to lysis by NK cells, a problem observed with other approaches that reduce or eliminate MHC class I protein expression. In some embodiments, the methods and compositions comprise reducing or eliminating surface expression of HLA-A protein by genetically modifying HLA-A with a gene editing system, and inserting an exogenous nucleic acid encoding a targeting receptor, or other polypeptide (expressed on the cell surface or secreted) into the cell by genetic modification. The engineered cell compositions produced by the methods disclosed herein have desirable properties, including *e.g.*, reduced expression of HLA-A, reduced immunogenicity *in vitro* and *in vivo*, increased survival, and increased genetic compatibility with greater subjects for transplant.

[0035] The term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined, or a degree of variation that does not substantially affect the properties of the described subject matter, or within the tolerances accepted in the art, *e.g.*,

within 10%, 5%, 2%, or 1%. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

A. Definitions

[0036] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

[0037] The term “or combinations thereof” as used herein refers to all permutations and combinations of the listed terms preceding the term. For example, “A, B, C, or combinations thereof” is intended to include at least one of: A, B, C, AB, AC, BC, or ABC, and if order is important in a particular context, also BA, CA, CB, ACB, CBA, BCA, BAC, or CAB. Continuing with this example, expressly included are combinations that contain repeats of one or more item or term, such as BB, AAA, AAB, BBC, CBBA, CABA, and so forth. The skilled artisan will understand that typically there is no limit on the number of items or terms in any combination, unless otherwise apparent from the context.

[0038] As used herein, the term “kit” refers to a packaged set of related components, such as one or more polynucleotides or compositions and one or more related materials such as delivery devices (e.g., syringes), solvents, solutions, buffers, instructions, or desiccants.

[0039] An “allogeneic” cell, as used herein, refers to a cell originating from a donor subject of the same species as a recipient subject, wherein the donor subject and recipient subject have genetic dissimilarity, *e.g.*, genes at one or more loci that are not identical. Thus, *e.g.*, a cell is allogeneic with respect to the subject to be administered the cell. As used herein, a cell that is removed or isolated from a donor, that will not be re-introduced into the original donor, is considered an allogeneic cell.

[0040] An “autologous” cell, as used herein, refers to a cell derived from the same subject to whom the material will later be re-introduced. Thus, *e.g.*, a cell is considered autologous if it is removed from a subject and it will then be re-introduced into the same subject.

[0041] “β2M” or “B2M,” as used herein, refers to nucleic acid sequence or protein sequence of “β-2 microglobulin”; the human gene has accession number NC_000015 (range 44711492..44718877), reference GRCh38.p13. The B2M protein is associated with MHC

class I molecules as a heterodimer on the surface of nucleated cells and is required for MHC class I protein expression.

[0042] "*CIITA*" or "CIITA" or "C2TA," as used herein, refers to the nucleic acid sequence or protein sequence of "class II major histocompatibility complex transactivator;" the human gene has accession number NC_000016.10 (range 10866208..10941562), reference GRCh38.p13. The CIITA protein in the nucleus acts as a positive regulator of MHC class II gene transcription and is required for MHC class II protein expression.

[0043] As used herein, "MHC" or "MHC molecule(s)" or "MHC protein" or "MHC complex(es)," refers to a major histocompatibility complex molecule (or plural), and includes *e.g.*, MHC class I and MHC class II molecules. In humans, MHC molecules are referred to as "human leukocyte antigen" complexes or "HLA molecules" or "HLA protein." The use of terms "MHC" and "HLA" are not meant to be limiting; as used herein, the term "MHC" may be used to refer to human MHC molecules, *i.e.*, HLA molecules. Therefore, the terms "MHC" and "HLA" are used interchangeably herein.

[0044] The term "HLA-A," as used herein in the context of HLA-A protein, refers to the MHC class I protein molecule, which is a heterodimer consisting of a heavy chain (encoded by the HLA-A gene) and a light chain (*i.e.*, beta-2 microglobulin). The term "HLA-A" or "HLA-A gene," as used herein in the context of nucleic acids refers to the gene encoding the heavy chain of the HLA-A protein molecule. The HLA-A gene is also referred to as "HLA class I histocompatibility, A alpha chain;" the human gene has accession number NC_000006.12 (29942532..29945870). The HLA-A gene is known to have thousands of different genotypic versions of the HLA-A gene across the population (and an individual may receive two different alleles of the HLA-A gene). A public database for HLA-A alleles, including sequence information, may be accessed at IPD-IMGT/HLA: www.ebi.ac.uk/ipd/imgt/hla/. All alleles of HLA-A are encompassed by the terms "HLA-A" and "HLA-A gene."

[0045] "HLA-B" as used herein in the context of nucleic acids refers to the gene encoding the heavy chain of the HLA-B protein molecule. The HLA-B is also referred to as "HLA class I histocompatibility, B alpha chain;" the human gene has accession number NC_000006.12 (31353875..31357179).

[0046] "HLA-C" as used herein in the context of nucleic acids refers to the gene encoding the heavy chain of the HLA-C protein molecule. The HLA-C is also referred to as "HLA class I histocompatibility, C alpha chain;" the human gene has accession number NC_000006.12 (31268749..31272092).

[0047] As used herein, the term "within the genomic coordinates" includes the boundaries of the genomic coordinate range given. For example, if chr6:29942854-chr6:29942913 is given, the coordinates chr6:29942854- chr6:29942913 are encompassed. Throughout this application, the referenced genomic coordinates are based on genomic annotations in the GRCh38 (also referred to as hg38) assembly of the human genome from the Genome Reference Consortium, available at the National Center for Biotechnology Information website. Tools and methods for converting genomic coordinates between one assembly and another are known in the art and can be used to convert the genomic coordinates provided herein to the corresponding coordinates in another assembly of the human genome, including conversion to an earlier assembly generated by the same institution or using the same algorithm (e.g., from GRCh38 to GRCh37), and conversion of an assembly generated by a different institution or algorithm (e.g., from GRCh38 to NCBI33, generated by the International Human Genome Sequencing Consortium). Available methods and tools known in the art include, but are not limited to, NCBI Genome Remapping Service, available at the National Center for Biotechnology Information website, UCSC LiftOver, available at the UCSC Genome Brower website, and Assembly Converter, available at the Ensembl.org website.

[0048] As used herein, the term "homozygous" refers to having two identical alleles of a particular gene.

[0049] As used herein, an HLA "allele" can refer to a named HLA-A, HLA-B, or HLA-C gene wherein the first four digits (or the first two sets of digits separated by a colon, e.g., HLA-A****02:101***:01:02N where the first two sets of digits are bolded and in italics) of the name following "HLA-A", HLA-B", or "HLA-C" are specified. As known in the art, the first four digits (or first two sets of digits separated by a colon) specify the protein of the allele. For example, HLA-A*02:01 and HLA-A*01:02 are distinct HLA-A alleles. Further genotypes of each allele exist, such as, e.g., HLA-A*02:01:02:01. Further genotypes of a given allele are considered to be identical alleles, e.g., HLA-A*02:01:02:01 and HLA-A*02:01 are identical alleles. Thus, HLA alleles are homozygous when the alleles are identical (i.e., when the alleles have the same first four digits or same first two sets of digits separated by a colon).

[0050] "Matching" or "matched" refers to shared alleles between the donor and the recipient, e.g., identical alleles.

[0051] "Polynucleotide" and "nucleic acid" are used herein to refer to a multimeric compound comprising nucleosides or nucleoside analogs which have nitrogenous

heterocyclic bases or base analogs linked together along a backbone, including conventional RNA, DNA, mixed RNA-DNA, and polymers that are analogs thereof. A nucleic acid "backbone" can be made up of a variety of linkages, including one or more of sugar-phosphodiester linkages, peptide-nucleic acid bonds ("peptide nucleic acids" or PNA; PCT No. WO 95/32305), phosphorothioate linkages, methylphosphonate linkages, or combinations thereof. Sugar moieties of a nucleic acid can be ribose, deoxyribose, or similar compounds with substitutions, e.g., 2' methoxy or 2' halide substitutions. Nitrogenous bases can be conventional bases (A, G, C, T, U), analogs thereof (e.g., modified uridines such as 5-methoxyuridine, pseudouridine, or N1-methylpseudouridine, or others); inosine; derivatives of purines or pyrimidines (e.g., N^4-methyl deoxyguanosine, deaza- or aza-purines, deaza- or aza-pyrimidines, pyrimidine bases with substituent groups at the 5 or 6 position (e.g., 5-methylcytosine), purine bases with a substituent at the 2, 6, or 8 positions, 2-amino-6-methylaminopurine, O^6-methylguanine, 4-thio-pyrimidines, 4-amino-pyrimidines, 4-dimethylhydrazine-pyrimidines, and O^4-alkyl-pyrimidines; US Pat. No. 5,378,825 and PCT No. WO 93/13121). For general discussion see *The Biochemistry of the Nucleic Acids* 5-36, Adams et al., ed., 11th ed., 1992). Nucleic acids can include one or more "abasic" residues where the backbone includes no nitrogenous base for position(s) of the polymer (US Pat. No. 5,585,481). A nucleic acid can comprise only conventional RNA or DNA sugars, bases and linkages, or can include both conventional components and substitutions (e.g., conventional bases with 2' methoxy linkages, or polymers containing both conventional bases and one or more base analogs). Nucleic acid includes "locked nucleic acid" (LNA), an analogue containing one or more LNA nucleotide monomers with a bicyclic furanose unit locked in an RNA mimicking sugar conformation, which enhance hybridization affinity toward complementary RNA and DNA sequences (Vester and Wengel, 2004, *Biochemistry* 43(42):13233-41). RNA and DNA have different sugar moieties and can differ by the presence of uracil or analogs thereof in RNA and thymine or analogs thereof in DNA.

[0052] "Guide RNA", "gRNA", and simply "guide" are used herein interchangeably to refer to, for example, the guide that directs an RNA-guided DNA binding agent to a target DNA and can be a single guide RNA, or the combination of a crRNA and a trRNA (also known as tracrRNA). Exemplary gRNAs include Class II Cas nuclease guide RNAs, in modified or unmodified forms. The crRNA and trRNA may be associated as a single RNA molecule (single guide RNA, sgRNA) or in two separate RNA strands (dual guide RNA, dgRNA). "Guide RNA" or "gRNA" refers to each type. The trRNA may be a naturally

occurring sequence, or a trRNA sequence with modifications or variations compared to naturally-occurring sequences.

[0053] As used herein, a "guide sequence" refers to a sequence within a guide RNA that is complementary to a target sequence and functions to direct a guide RNA to a target sequence for binding or modification (e.g., cleavage) by an RNA-guided DNA binding agent. A "guide sequence" may also be referred to as a "targeting sequence," or a "spacer sequence." A guide sequence can be 20 base pairs in length, e.g., in the case of Streptococcus pyogenes (*i.e.*, Spy Cas9 (SpCas9)) and related Cas9 homologs/orthologs. Shorter or longer sequences can also be used as guides, e.g., 15-, 16-, 17-, 18-, 19-, 21-, 22-, 23-, 24-, or 25-nucleotides in length. In some embodiments, the target sequence is in a gene or on a chromosome, for example, and is complementary to the guide sequence. In some embodiments, the degree of complementarity or identity between a guide sequence and its corresponding target sequence may be about 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, the guide sequence and the target region may be 100% complementary or identical. In other embodiments, the guide sequence and the target region may contain at least one mismatch. For example, the guide sequence and the target sequence may contain 1, 2, 3, or 4 mismatches, where the total length of the target sequence is at least 17, 18, 19, 20 or more base pairs. In some embodiments, the guide sequence and the target region may contain 1-4 mismatches where the guide sequence comprises at least 17, 18, 19, 20 or more nucleotides. In some embodiments, the guide sequence and the target region may contain 1, 2, 3, or 4 mismatches where the guide sequence comprises 20 nucleotides.

[0054] Target sequences for RNA-guided DNA binding agents include both the positive and negative strands of genomic DNA (*i.e.*, the sequence given and the sequence's reverse compliment), as a nucleic acid substrate for an RNA-guided DNA binding agent is a double stranded nucleic acid. Accordingly, where a guide sequence is said to be "complementary to a target sequence", it is to be understood that the guide sequence may direct a guide RNA to bind to the reverse complement of a target sequence. Thus, in some embodiments, where the guide sequence binds the reverse complement of a target sequence, the guide sequence is identical to certain nucleotides of the target sequence (e.g., the target sequence not including the PAM) except for the substitution of U for T in the guide sequence.

[0055] As used herein, an "RNA-guided DNA binding agent" means a polypeptide or complex of polypeptides having RNA and DNA binding activity, or a DNA-binding subunit of such a complex, wherein the DNA binding activity is sequence-specific and depends on the sequence of the RNA. Exemplary RNA-guided DNA binding agents include Cas

cleavases/nickases and inactivated forms thereof ("dCas DNA binding agents"). "Cas nuclease", also called "Cas protein" as used herein, encompasses Cas cleavases, Cas nickases, and dCas DNA binding agents. Cas cleavases/nickases and dCas DNA binding agents include a Csm or Cmr complex of a type III CRISPR system, the Cas10, Csm1, or Cmr2 subunit thereof, a Cascade complex of a type I CRISPR system, the Cas3 subunit thereof, and Class 2 Cas nucleases. As used herein, a "Class 2 Cas nuclease" is a single-chain polypeptide with RNA-guided DNA binding activity. Class 2 Cas nucleases include Class 2 Cas cleavases/nickases (e.g., H840A, D10A, or N863A variants), which further have RNA-guided DNA cleavases or nickase activity, and Class 2 dCas DNA binding agents, in which cleavase/nickase activity is inactivated. Class 2 Cas nucleases include, for example, Cas9, Cpf1, C2c1, C2c2, C2c3, HF Cas9 (e.g., N497A, R661A, Q695A, Q926A variants), HypaCas9 (e.g., N692A, M694A, Q695A, H698A variants), eSPCas9(1.0) (*e.g.*, K810A, K1003A, R1060A variants), and eSPCas9(1.1) (*e.g.*, K848A, K1003A, R1060A variants) proteins and modifications thereof. Cpf1 protein, Zetsche et al., *Cell*, 163: 1-13 (2015), is homologous to Cas9, and contains a RuvC-like nuclease domain. Cpf1 sequences of Zetsche are incorporated by reference in their entirety. *See*, *e.g.*, Zetsche, Tables S1 and S3. See, *e.g.*, Makarova et al., *Nat Rev Microbiol*, 13(11): 722-36 (2015); Shmakov et al., *Molecular Cell,* 60:385-397 (2015).

[0056] As used herein, the term "editor" refers to an agent comprising a polypeptide that is capable of making a modification within a DNA sequence. In some embodiments, the editor is a cleavase, such as a Cas9 cleavase. In some embodiments, the editor is capable of deaminating a base within a DNA molecule. In some embodiments, the editor is capable of deaminating a cytosine (C) in DNA. In some embodiments, the editor is a fusion protein comprising an RNA-guided nickase fused to a cytidine deaminase. In some embodiments, the editor is a fusion protein comprising an RNA-guided nickase fused to an APOBEC3A deaminase (A3A). In some embodiments, the editor comprises a Cas9 nickase fused to an APOBEC3A deaminase (A3A). In some embodiments, the editor is a fusion protein comprising an RNA-guided nickase fused to a cytidine deaminase and a UGI. In some embodiments, the editor lacks a UGI.

[0057] As used herein, a "cytidine deaminase" means a polypeptide or complex of polypeptides that is capable of cytidine deaminase activity, that is catalyzing the hydrolytic deamination of cytidine or deoxycytidine, typically resulting in uridine or deoxyuridine. Cytidine deaminases encompass enzymes in the cytidine deaminase superfamily, and in particular, enzymes of the APOBEC family (APOBEC1, APOBEC2, APOBEC4, and

APOBEC3 subgroups of enzymes), activation-induced cytidine deaminase (AID or AICDA) and CMP deaminases (see, e.g., Conticello et al., Mol. Biol. Evol. 22:367-77, 2005; Conticello, Genome Biol. 9:229, 2008; Muramatsu et al., J. Biol. Chem. 274: 18470-6, 1999); Carrington et al., Cells 9:1690 (2020)).

[0058] As used herein, the term "APOBEC3" refers to a APOBEC3 protein, such as an APOBEC3 protein expressed by any of the seven genes (A3A-A3H) of the human APOBEC3 locus. The APOBEC3 may have catalytic DNA or RNA editing activity. An amino acid sequence of APOBEC3A has been described (UniPROT accession ID: p31941) and is included herein as SEQ ID NO: 40. In some embodiments, the APOBEC3 protein is a human APOBEC3 protein and/or a wild-type protein. Variants include proteins having a sequence that differs from wild-type APOBEC3 protein by one or several mutations (i.e. substitutions, deletions, insertions), such as one or several single point substitutions. For instance, a shortened APOBEC3 sequence could be used, e.g. by deleting several N-term or C-term amino acids, preferably one to four amino acids at the C-terminus of the sequence. As used herein, the term "variant" refers to allelic variants, splicing variants, and natural or artificial mutants, which are homologous to a APOBEC3 reference sequence. The variant is "functional" in that it shows a catalytic activity of DNA or RNA editing. In some embodiments, an APOBEC3 (such as a human APOBEC3A) has a wild-type amino acid position 57 (as numbered in the wild-type sequence). In some embodiments, an APOBEC3 (such as a human APOBEC3A) has an asparagine at amino acid position 57 (as numbered in the wild-type sequence).

[0059] As used herein, a "nickase" is an enzyme that creates a single-strand break (also known as a "nick") in double strand DNA, i.e., cuts one strand but not the other of the DNA double helix. As used herein, an "RNA-guided DNA nickase" means a polypeptide or complex of polypeptides having DNA nickase activity, wherein the DNA nickase activity is sequence-specific and depends on the sequence of the RNA. Exemplary RNA-guided DNA nickases include Cas nickases. Cas nickases include nickase forms of a Csm or Cmr complex of a type III CRISPR system, the Cas10, Csm1, or Cmr2 subunit thereof, a Cascade complex of a type I CRISPR system, the Cas3 subunit thereof, and Class 2 Cas nucleases. Class 2 Cas nickases include variants in which only one of the two catalytic domains is inactivated, which have RNA-guided DNA nickase activity. Class 2 Cas nickases include, for example, Cas9 (e.g., H840A, D10A, or N863A variants of SpyCas9), Cpf1, C2c1, C2c2, C2c3, HF Cas9 (e.g., N497A, R661A, Q695A, Q926A variants), HypaCas9 (e.g., N692A, M694A, Q695A, H698A variants), eSPCas9(1.0) (e.g, K810A, K1003A, R1060A variants), and eSPCas9(1.1)

(e.g., K848A, K1003A, R1060A variants) proteins and modifications thereof. Cpf1 protein, Zetsche et al., Cell, 163: 1-13 (2015), is homologous to Cas9, and contains a RuvC-like protein domain. Cpf1 sequences of Zetsche are incorporated by reference in their entirety. See, e.g., Zetsche, Tables S1 and S3. “Cas9” encompasses S. pyogenes (Spy) Cas9, the variants of Cas9 listed herein, and equivalents thereof. See, e.g., Makarova et al., Nat Rev Microbiol, 13(11): 722-36 (2015); Shmakov et al., Molecular Cell, 60:385-397 (2015).

[0060] As used herein, the term “fusion protein” refers to a hybrid polypeptide which comprises protein domains from at least two different proteins. One protein may be located at the amino-terminal (N-terminal) portion of the fusion protein or at the carboxy-terminal (C-terminal) protein thus forming an “amino-terminal fusion protein” or a “carboxy-terminal fusion protein,” respectively. Any of the proteins provided herein may be produced by any method known in the art. For example, the proteins provided herein may be produced via recombinant protein expression and purification, which is especially suited for fusion proteins comprising a peptide linker. Methods for recombinant protein expression and purification are well known, and include those described by Green and Sambrook, Molecular Cloning: A Laboratory Manual (4th ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2012)), the entire contents of which are incorporated herein by reference.

[0061] The term “linker,” as used herein, refers to a chemical group or a molecule linking two adjacent molecules or moieties. Typically, the linker is positioned between, or flanked by, two groups, molecules, or other moieties and connected to each one via a covalent bond. In some embodiments, the linker is an amino acid or a plurality of amino acids (e.g., a peptide or protein) such as a 16-amino acid residue “XTEN” linker, or a variant thereof (See, e.g., the Examples; and Schellenberger et al. A recombinant polypeptide extends the in vivo half-life of peptides and proteins in a tunable manner. Nat. Biotechnol. 27, 1186-1190 (2009)). In some embodiments, the XTEN linker comprises the sequence SGSETPGTSESATPES (SEQ ID NO: 900), SGSETPGTSESA (SEQ ID NO: 901), or SGSETPGTSESATPEGGSGGS (SEQ ID NO: 902).

[0062] As used herein, the term “uracil glycosylase inhibitor” or “UGI” refers to a protein that is capable of inhibiting a uracil-DNA glycosylase (UDG) base-excision repair enzyme.

[0063] As used herein, “open reading frame” or “ORF” of a gene refers to a sequence consisting of a series of codons that specify the amino acid sequence of the protein that the gene codes for. The ORF begins with a start codon (e.g., ATG in DNA or AUG in RNA) and ends with a stop codon, e.g., TAA, TAG or TGA in DNA or UAA, UAG, or UGA in RNA.

[0064] As used herein, "ribonucleoprotein" (RNP) or "RNP complex" refers to a guide RNA together with an RNA-guided DNA binding agent, such as a Cas nuclease, e.g., a Cas cleavase, Cas nickase, or dCas DNA binding agent (e.g., Cas9). In some embodiments, the guide RNA guides the RNA-guided DNA binding agent such as Cas9 to a target sequence, and the guide RNA hybridizes with and the agent binds to the target sequence; in cases where the agent is a cleavase or nickase, binding can be followed by cleaving or nicking.

[0065] As used herein, a first sequence is considered to "comprise a sequence with at least X% identity to" a second sequence if an alignment of the first sequence to the second sequence shows that X% or more of the positions of the second sequence in its entirety are matched by the first sequence. For example, the sequence AAGA comprises a sequence with 100% identity to the sequence AAG because an alignment would give 100% identity in that there are matches to all three positions of the second sequence. The differences between RNA and DNA (generally the exchange of uridine for thymidine or vice versa) and the presence of nucleoside analogs such as modified uridines do not contribute to differences in identity or complementarity among polynucleotides as long as the relevant nucleotides (such as thymidine, uridine, or modified uridine) have the same complement (e.g., adenosine for all of thymidine, uridine, or modified uridine; another example is cytosine and 5-methylcytosine, both of which have guanosine or modified guanosine as a complement). Thus, for example, the sequence 5'-AXG where X is any modified uridine, such as pseudouridine, N1-methyl pseudouridine, or 5-methoxyuridine, is considered 100% identical to AUG in that both are perfectly complementary to the same sequence (5'-CAU). Exemplary alignment algorithms are the Smith-Waterman and Needleman-Wunsch algorithms, which are well-known in the art. One skilled in the art will understand what choice of algorithm and parameter settings are appropriate for a given pair of sequences to be aligned; for sequences of generally similar length and expected identity >50% for amino acids or >75% for nucleotides, the Needleman-Wunsch algorithm with default settings of the Needleman-Wunsch algorithm interface provided by the EBI at the www.ebi.ac.uk web server is generally appropriate.

[0066] "mRNA" is used herein to refer to a polynucleotide and comprises an open reading frame that can be translated into a polypeptide (*i.e.*, can serve as a substrate for translation by a ribosome and amino-acylated tRNAs). mRNA can comprise a phosphate-sugar backbone including ribose residues or analogs thereof, e.g., 2'-methoxy ribose residues. In some embodiments, the sugars of an mRNA phosphate-sugar backbone consist essentially of ribose residues, 2'-methoxy ribose residues, or a combination thereof.

[0067] As used herein, “indels” refer to insertion/deletion mutations consisting of a number of nucleotides that are either inserted or deleted, e.g. at the site of double-stranded breaks (DSBs), in a target nucleic acid.

[0068] As used herein, “reduced or eliminated” expression of a protein on a cell refers to a partial or complete loss of expression of the protein relative to an unmodified cell. In some embodiments, the surface expression of a protein on a cell is measured by flow cytometry and has “reduced or eliminated” surface expression relative to an unmodified cell as evidenced by a reduction in fluorescence signal upon staining with the same antibody against the protein. A cell that has “reduced or eliminated” surface expression of a protein by flow cytometry relative to an unmodified cell may be referred to as “negative” for expression of that protein as evidenced by a fluorescence signal similar to a cell stained with an isotype control antibody. The “reduction or elimination” of protein expression can be measured by other known techniques in the field with appropriate controls known to those skilled in the art.

[0069] As used herein, “knockdown” refers to a decrease in expression of a particular gene product (e.g., protein, mRNA, or both), e.g., as compared to expression of an unedited target sequence. Knockdown of a protein can be measured by detecting total cellular amount of the protein from a sample, such as a tissue, fluid, or cell population of interest. It can also be measured by measuring a surrogate, marker, or activity for the protein. Methods for measuring knockdown of mRNA are known and include analyzing mRNA isolated from a sample of interest. In some embodiments, “knockdown” may refer to some loss of expression of a particular gene product, for example a decrease in the amount of mRNA transcribed or a decrease in the amount of protein expressed by a cell or population of cells (including *in vivo* populations such as those found in tissues).

[0070] As used herein, “knockout” refers to a loss of expression from a particular gene or of a particular protein in a cell. Knockout can result in a decrease in expression below the level of detection of the assay. Knockout can be measured either by detecting total cellular amount of a protein in a cell, a tissue or a population of cells.

[0071] As used herein, a “target sequence” or “genomic target sequence” refers to a sequence of nucleic acid in a target gene that has complementarity to the guide sequence of the gRNA. The interaction of the target sequence and the guide sequence directs an RNA-guided DNA binding agent to bind, and potentially nick or cleave (depending on the activity of the agent), within the target sequence.

[0072] As used herein, “treatment” refers to any administration or application of a therapeutic for disease or disorder in a subject, and includes inhibiting the disease, arresting

its development, relieving one or more symptoms of the disease, curing the disease, or preventing one or more symptoms of the disease, including recurrence of the symptom.

[0073] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying drawings. While the invention is described in conjunction with the illustrated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the invention as defined by the appended claims and included embodiments.

[0074] Before describing the present teachings in detail, it is to be understood that the disclosure is not limited to specific compositions or process steps, as such may vary. It should be noted that, as used in this specification and the appended claims, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a conjugate" includes a plurality of conjugates and reference to "a cell" includes a plurality of cells and the like.

[0075] Numeric ranges are inclusive of the numbers defining the range. Measured and measurable values are understood to be approximate, taking into account significant digits and the error associated with the measurement. Also, the use of "comprise", "comprises", "comprising", "contain", "contains", "containing", "include", "includes", and "including" are not intended to be limiting. It is to be understood that both the foregoing general description and detailed description are exemplary and explanatory only and are not restrictive of the teachings.

[0076] Unless specifically noted in the specification, embodiments in the specification that recite "comprising" various components are also contemplated as "consisting of" or "consisting essentially of" the recited components; embodiments in the specification that recite "consisting of" various components are also contemplated as "comprising" or "consisting essentially of" the recited components; and embodiments in the specification that recite "consisting essentially of" various components are also contemplated as "consisting of" or "comprising" the recited components (this interchangeability does not apply to the use of these terms in the claims). The term "or" is used in an inclusive sense, *i.e.*, equivalent to "and/or," unless the context clearly indicates otherwise.

[0077] The section headings used herein are for organizational purposes only and are not to be construed as limiting the desired subject matter in any way. In the event that any material incorporated by reference contradicts any term defined in this specification or any other express content of this specification, this specification controls. While the present teachings

are described in conjunction with various embodiments, it is not intended that the present teachings be limited to such embodiments. On the contrary, the present teachings encompass various alternatives, modifications, and equivalents, as will be appreciated by those of skill in the art.

B. Genetically Modified Cells

1. Engineered Human Cell Compositions

[0078] The present disclosure provides engineered human cell compositions which have reduced or eliminated surface expression of HLA-A relative to an unmodified cell, comprising a genetic modification in the HLA-A gene, wherein the cell is homozygous for HLA-B and homozygous for HLA-C. In some embodiments, the engineered human cell is an allogeneic cell. In some embodiments, the engineered human cell with reduced HLA-A expression is useful for adoptive cell transfer therapies. In some embodiments, the engineered human cell comprises additional genetic modifications in the genome of the cell (*e.g.*, reducing or elimination of MHC class II proteins, and/or reducing or eliminating endogenous T cell receptor (TCR) proteins, and/or introduction of an exogenous nucleic acid for expression) to yield a cell that is desirable for allogeneic transplant purposes.

[0079] In some embodiments, the engineered human cell is an allogeneic cell therapy. In some embodiments, the engineered human cell is transferred to a recipient that has the same HLA-B allele as the engineered human cell. In some embodiments, the engineered human cell is transferred to a recipient that has the same HLA-C allele as the engineered human cell. In some embodiments, the engineered human cell is transferred to a recipient that has the same HLA-B and HLA-C alleles as the engineered human cell. Thus, the engineered human cells disclosed herein provide a partial HLA match to a recipient, thereby reducing the risk of an adverse immune response.

[0080] In some embodiments, an engineered human cell is provided 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 the cell is homozygous for HLA-B and homozygous for HLA-C.

[0081] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from: chr6:29942854-chr6:29942913 and

chr6:29943518- chr6: 29943619; wherein the cell is homozygous for HLA-B and homozygous for HLA-C.

[0082] In some embodiments, for each given range of genomic coordinates, a range may encompass +/- 10 nucleotides on either end of the specified coordinates. For example, if chr6:29942854- chr6:29942913 is given, in some embodiments the genomic target sequence or genetic modification may fall within chr6:29942844- chr6:29942923. In some embodiments, for each given range of genomic coordinates, the range may encompass +/- 5 nucleotides on either end of the range.

[0083] In some embodiments, a given range of genomic coordinates may comprise a target sequence on both strands of the DNA (*i.e.*, the plus (+) strand and the minus (-) strand).

[0084] Genetic modifications in the HLA-A gene are described further herein. In some embodiments, a genetic modification in the HLA-a gene comprises any one or more of an insertion, deletion, substitution, or deamination of at least one nucleotide in a target sequence.

[0085] The engineered human cells described herein may comprise a genetic modification in any HLA-A allele of the HLA-A gene. The HLA gene is located in chromosome 6 in a genomic region referred to as the HLA superlocus; hundreds of HLA-A alleles have been reported in the art (*see e.g.,* Shiina et al., Nature 54:15-39 (2009). Sequences for HLA-A alleles are available in the art (*see e.g.*, IPD-IMGT/HLA database for retrieving sequences of specific HLA-A alleles https://www.ebi.ac.uk/ipd/imgt/hla/allele.html).

[0086] In some embodiments, 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. In some embodiments, the cell has reduced or eliminated expression of HLA-A1. In some embodiments, the cell has reduced or eliminated expression of HLA-A2. In some embodiments, the cell has reduced or eliminated expression of HLA-A3. In some embodiments, the cell has reduced or eliminated expression of HLA-A11. In some embodiments, the cell has reduced or eliminated expression of HLA-A24.

[0087] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942864 to chr6: 29942903.

[0088] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528 to chr6:29943609.

[0089] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942864-29942884; chr6:29942868-29942888; chr6:29942876-29942896; chr6:29942877-29942897; and chr6:29942883-29942903.

[0090] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557; chr6:29943549-29943569; and chr6:29943589-29943609.

[0091] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942876-29942897.

[0092] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-chr629943550.

[0093] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942864-29942884, chr6:29942868-29942888, chr6:29942876-29942896, chr6:29942877-29942897.

[0094] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-29943548, chr6:29943529-29943549, chr6:29943530-29943550.

[0095] In some embodiments, an engineered human cell is provided 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 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.

[0096] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942864-29942884.

[0097] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942868-29942888.

[0098] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942876-29942896.

[0099] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942877-29942897.

[00100] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942883-29942903.

[00101] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943126-29943146.

[00102] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-29943548.

[00103] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943529-29943549.

[00104] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943530-29943550.

[00105] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943537-29943557.

[00106] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943549-29943569.

[00107] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943589-29943609.

[00108] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29944026-29944046.

[00109] In some embodiments, an engineered human cell is provided which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell, comprising a genetic modification in an HLA-A gene, wherein the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates chosen from: chr6:29942854-chr6:29942913 and chr6:29943518- chr6: 29943619. In some embodiments, the cell is homozygous for HLA-B. In some embodiments, the cell is homozygous for HLA-C. In some embodiments, the cell is homozygous for HLA-B and homozygous for HLA-C.

[00110] In some embodiments, an engineered human cell is provided which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell, comprising a genetic modification in an HLA-A gene, 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. In some embodiments, the cell is homozygous for HLA-B. In some embodiments, the cell is homozygous for HLA-C. In some embodiments, the cell is homozygous for HLA-B and homozygous for HLA-C.

[00111] In some embodiments, an engineered human cell is provided which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell, comprising a genetic modification in an HLA-A gene, 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, wherein the genetic modification comprises at least 2, at least 3, at least 4, 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. In some embodiments, the cell is homozygous for HLA-B. In some embodiments, the cell is homozygous for HLA-C. In some embodiments, the cell is homozygous for HLA-B and homozygous for HLA-C.

[00112] In some embodiments, an engineered human cell is provided which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell, comprising a genetic modification in an HLA-A gene, 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, wherein the genetic modification comprises at least 5 contiguous nucleotides within the genomic coordinates. In some embodiments, the cell is homozygous for HLA-B. In some embodiments, the cell is homozygous for HLA-C. In some embodiments, the cell is homozygous for HLA-B and homozygous for HLA-C.

[00113] In some embodiments, an engineered human cell is provided which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell, comprising a genetic modification in an HLA-A gene, 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, wherein the genetic modification comprises at least 6, 7, 8, 9, or 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the genetic modification comprises at least 6 contiguous nucleotides within the genomic coordinates. In some embodiments, the genetic modification comprises at least 7 contiguous nucleotides within the genomic coordinates. In some embodiments, the genetic modification comprises at least 8 contiguous nucleotides within the genomic coordinates. In some embodiments, the genetic modification comprises at least 9 contiguous nucleotides within the genomic coordinates. In some embodiments, the genetic modification comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the cell is homozygous for HLA-B. In some embodiments, the cell is homozygous for HLA-C. In some embodiments, the cell is homozygous for HLA-B and homozygous for HLA-C.

[00114] In some embodiments, an engineered human cell is provided which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell, comprising a genetic modification in an HLA-A gene, 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, wherein the genetic modification comprises at least one C to T substitution or at least one A to G substitution within the genomic coordinates. In some embodiments, the cell is homozygous for HLA-B. In some embodiments, the cell is homozygous for HLA-C. In some embodiments, the cell is homozygous for HLA-B and homozygous for HLA-C.

[00115] In some embodiments, an engineered human cell is provided 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, 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. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00116] In some embodiments, an engineered human cell is provided 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. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00117] In some embodiments, an engineered human cell is provided 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; chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557; chr6:29943549-29943569; and chr6:29943589-29943609. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00118] In some embodiments, an engineered human cell is provided 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; and chr6:29942883-29942903. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00119] In some embodiments, an engineered human cell is provided 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: chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557; chr6:29943549-29943569; and chr6:29943589-29943609. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00120] In some embodiments, an engineered human cell is provided 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. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00121] In some embodiments, an engineered human cell is provided 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: chr6:29943528-29943548, chr6:29943529-29943549, chr6:29943530-29943550. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00122] In some embodiments, an engineered human cell is provided 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: chr6:29945290-29945310, chr6:29945296-29945316, chr6:29945297-29945317, and chr6:29945300-29945320. Due to allelic polymorphism, in some embodiments, the target sequences may comprise 1, 2, or 3 mismatches from the genomic sequence of hg38. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00123] In some embodiments, an engineered human cell is provided 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: chr6:29890117-29890137, 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. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates. In some embodiments, the gene editing system comprises an RNA-guided DNA binding agent, such as an *S. pyogenes* Cas9 or a base editor that comprises an *S. pyogenes* Cas9 nickase.

[00124] In some embodiments, an engineered human cell is provided 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: chr6:29942815-29942835, 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. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates. In some embodiments, the gene editing system comprises an RNA-guided DNA binding agent, such as an *S. pyogenes* Cas9.

[00125] In some embodiments, an engineered human cell is provided 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: chr6:29942884-29942904, chr6:29943519-29943539, chr6:29942863-29942883. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates. In some embodiments, the gene editing system comprises an RNA-guided DNA binding agent, such as an *S. aureus* Cas9.

[00126] In some embodiments, an engineered human cell is provided 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: chr6:29943517-29943537, and chr6:29943523-29943543. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates. In some embodiments, the gene editing system comprises an RNA-guided DNA binding agent, such as a CasX.

[00127] In some embodiments, an engineered human cell is provided 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: chr6:29942845-29942869, 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. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

In some embodiments, the gene editing system comprises an RNA-guided DNA binding agent, such as an Nme2 Cas9.

[00128] In some embodiments, an engineered human cell is provided 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: chr6:29942885-29942905, 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. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates. In some embodiments, the gene editing system comprises an RNA-guided DNA binding agent, such as a base editor comprising a deaminase and an *S. pyogenes* Cas9 nickase.

[00129] In some embodiments, an engineered human cell is provided 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: chr6:29942469-29942489, 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, chr6:29945341-29945361, and chr6:29945526-29945546. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00130] In some embodiments, an engineered human cell is provided 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 to chr6:29942913 and chr6:29943518 to chr6: 29943619. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A

genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00131] In some embodiments, an engineered human cell is provided 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. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00132] In some embodiments, an engineered human cell is provided 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-chr629943550. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00133] In some embodiments, an engineered human cell is provided 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 chr6:29942864-29942884. In some embodiments, an engineered human cell is provided 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 chr6:29942868-29942888. In some embodiments, an engineered human cell is provided 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 chr6:29942876-29942896. In some embodiments, an engineered human cell is provided 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 chr6:29942877-29942897. In some embodiments, an engineered human cell is provided 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 chr6:29942883-29942903. In some embodiments, an engineered human cell is provided 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 chr6:29943126-29943146. In some embodiments, an engineered human cell is provided 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 chr6:29943528-29943548. In some embodiments, an engineered human cell is provided 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 chr6:29943529-29943549. In some embodiments, an engineered human cell is provided 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 chr6:29943530-29943550. In some embodiments, an engineered human cell is provided 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 chr6:29943537-29943557. In some embodiments, an engineered human cell is provided 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 chr6:29943549-29943569. In some embodiments, an engineered human cell is provided 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 chr6:29943589-29943609. In some embodiments, an engineered human cell is provided 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 chr6:29944026-29944046. In some embodiments, the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates. In some embodiments, the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00134] In some embodiments, the HLA-A genomic target sequence comprises at least 17, 19, 18, or 20 contiguous nucleotides within the genomic coordinates.

[00135] In some embodiments, the gene editing system comprises a transcription activator-like effector nuclease (TALEN). In some embodiments, the gene editing system comprises a zinc finger nuclease. In some embodiments, the gene editing system comprises a

CRISPR/Cas system, such as a class 2 system. In some embodiments, the gene editing system comprises an RNA-guided DNA-binding agent or a nucleic acid encoding an RNA-guided DNA binding agent.

[00136] Exemplary RNA-guided DNA binding agents are shown in **Table 1A** below.

[00137] Table 1A. Exemplary RNA-guided DNA binding agents.

RNA-guided DNA binding agent	**PAM**	**Guide Length**
Cas9 nuclease from *S. pyogenes*	NGG	20 bp
Cas9 nuclease from *Neisseria meningitidis*	NNNNG[A/C]TT	20bp
Cas9 nuclease from *Streptococcus thermophilus*	NNAGAAW	20bp
Cas9 nuclease is from *Staphylococcus aureus*	NNG(A/G)(A/G)T	20bp
Cpf1 nuclease from *Francisella novicida*	TTTN	23bp
Cpf1 nuclease from *Acidaminococcus sp.*	TTTV	23bp
Cpf1 nuclease from *Lachnospiraceae bacterium*	TTTV	23bp
C-to-T base editor*	NGG	20bp
A-to-G base editor*	NGG	20bp
Cas12a	same as Cpf1	
CasX	TTCN	20bp
NME2	NNNNCC	24bp

*Exemplary base editor based on deaminase-SpyCas9 nickase. As is apparent, the base editor specificity, including PAM, will vary with its nickase.

[00138] In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent comprises a Cas9 protein. In some embodiments, the RNA-guided DNA binding agent is selected from one of: *S. pyogenes* Cas9, *Neisseria meningitidis* Cas9, e.g. an Nme2Cas9, *S. thermophilus* Cas9, *S. aureus* Cas9, *Francisella novicida* Cpf1, *Acidaminococcus sp.* Cpf1, *Lachnospiraceae bacterium* Cpf1, C-to-T base editor, A-to-G base editor, Cas12a, Mad7 nuclease, ARCUS nucleases, and CasX. In some embodiments, the RNA-guided DNA binding agent comprises a polypeptide selected

from one of: *S. pyogenes* Cas9, *Neisseria meningitidis* Cas9, e.g. an Nme2Cas9, *S. thermophilus* Cas9, *S. aureus* Cas9, *Francisella novicida* Cpf1, *Acidaminococcus sp.* Cpf1, *Lachnospiraceae bacterium* Cpf1, C-to-T base editor, A-to-G base editor, Cas12a, and CasX.

[00139] In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is *S. pyogenes* Cas9. In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is *N. meningitidis* Cas9, e.g. Nme2Cas9. In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is *S. thermophilus* Cas9. In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is *S. aureus* Cas9. In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is Cpf1 from *F. novicida.* In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is Cpf1 from *Acidaminococcus sp.* In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is Cpf1 from *Lachnospiraceae bacterium ND2006.* In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is a C to T base editor. In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is a A to G base editor. In some embodiments, the base editor comprises a deaminase and an RNA-guided nickase. In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent comprises a APOBEC3A deaminase (A3A) and an RNA-guided nickase. In some embodiments, the RNA-guided nickase is a SpyCas9 nickase. In some embodiments, the RNA-guided nickase comprises an NmeCas9 nickase. In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is Cas12a. In some embodiments, the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is CasX.

[00140] In any of the above embodiments, the gene editing system comprises an RNA-guided DNA binding agent, or a nucleic acid encoding an RNA-guided DNA binding agent. In some embodiments, the RNA-guided DNA binding agent comprises a Cas9. In some embodiments, the RNA-guided DNA binding agent is an *S. pyogenes* Cas9. In some embodiments, the RNA-guided DNA binding agent is a base editor. In some embodiments the base editor comprises a C to T deaminase and an RNA-guided nickase such as an *S. pyogenes* Cas9 nickase. In some embodiments the base editor comprises a A to G deaminase and an RNA-guided nickase such as an *S. pyogenes* Cas9 nickase.

[00141] In some embodiments, when the engineered cell is homozygous for HLA-B, 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.

[00142] In some embodiments, when the engineered cell is homozygous for HLA-C, 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.

[00143] In some embodiments, 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.

[00144] In some embodiments, the engineered cell is homozygous for HLA-B and homozygous for HLA-C. In some embodiments, the HLA-B and HLA-C alleles of the engineered human cell 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. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*07:02 and HLA-C*07:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*08:01 and HLA-C*07:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*44:02 and HLA-C*05:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*35:01 and HLA-C*04:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*40:01 and HLA-C*03:04. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*57:01 and HLA-C*06:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*14:02 and HLA-C*08:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*15:01 and HLA-C*03:03. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*13:02 and HLA-C*06:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*44:03 and HLA-C*16:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*38:01 and HLA-C*12:03. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*18:01 and HLA-C*07:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*44:03 and HLA-C*04:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*51:01 and HLA-C*15:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*49:01 and HLA-C*07:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*15:01 and HLA-C*03:04. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*18:01 and HLA-C*12:03. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*27:05 and HLA-C*02:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*35:03 and HLA-C*04:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*18:01 and HLA-C*05:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*52:01 and HLA-C*12:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*51:01 and HLA-C*14:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*37:01 and HLA-C*06:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*53:01 and HLA-C*04:01. In some

embodiments, the HLA-B and HLA-C alleles are HLA-B*55:01 and HLA-C*03:03. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*44:02 and HLA-C*07:04. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*44:03 and HLA-C*07:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*35:02 and HLA-C*04:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*15:01 and HLA-C*04:01. In some embodiments, the HLA-B and HLA-C alleles are and HLA-B*40:02 and HLA-C*02:02.

[00145] The HLA-B and HLA-C allele combinations disclosed herein cumulatively cover about 88% of the population. The cumulative frequency of HLA-B and HLA-C allele pairs is shown in **Table 1B** below.

[00146] Table 1B. Cumulative Frequency of HLA-A and HLA-C Alleles in the Population.

Cumulative Frequency	Alleles
0.194	HLA-B*07:02 and HLA-C*07:02
0.33	HLA-B*08:01 and HLA-C*07:01
0.413	HLA-B*44:02 and HLA-C*05:01
0.483	HLA-B*35:01 and HLA-C*04:01
0.534	HLA-B*40:01 and HLA-C*03:04
0.594	HLA-B*57:01 and HLA-C*06:02
0.62	HLA-B*14:02 and HLA-C*08:02
0.648	HLA-B*15:01 and HLA-C*03:03
0.671	HLA-B*13:02 and HLA-C*06:02
0.696	HLA-B*44:03 and HLA-C*16:01
0.717	HLA-B*38:01 and HLA-C*12:03
0.734	HLA-B*18:01 and HLA-C*07:01
0.751	HLA-B*44:03 and HLA-C*04:01
0.766	HLA-B*51:01 and HLA-C*15:02
0.776	HLA-B*49:01 and HLA-C*07:01
0.787	HLA-B*15:01 and HLA-C*03:04
0.798	HLA-B*18:01 and HLA-C*12:03
0.809	HLA-B*27:05 and HLA-C*02:02
0.815	HLA-B*35:03 and HLA-C*04:01
0.827	HLA-B*18:01 and HLA-C*05:01
0.838	HLA-B*52:01 and HLA-C*12:02
0.845	HLA-B*51:01 and HLA-C*14:02
0.856	HLA-B*37:01 and HLA-C*06:02
0.865	HLA-B*53:01 and HLA-C*04:01
0.872	HLA-B*55:01 and HLA-C*03:03
0.876	HLA-B*44:02 and HLA-C*07:04
0.881	HLA-B*44:03 and HLA-C*07:01
0.884	HLA-B*35:02 and HLA-C*04:01
0.888	HLA-B*15:01 and HLA-C*04:01

[00147] In some embodiments, an engineered human cell which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell is provided, that is homozygous for HLA-B and homozygous for HLA-C, further has reduced or eliminated surface expression of MHC class II protein. In some embodiments, the engineered human cell has a genetic modification in a gene that reduces or eliminates surface expression of MHC class II. In some embodiments, the engineered human cell has a genetic modification in the CIITA gene. In some embodiments, the engineered human cell has a genetic modification in the HLA-DR gene. In some embodiments, the engineered human cell has a genetic modification in the HLA-DQ gene. In some embodiments, the engineered human cell has a genetic modification in the HLA-DP gene. In some embodiments, the engineered human cell has a genetic modification in the RFX gene. In some embodiments, the engineered human cell has a genetic modification in the CREB gene. In some embodiments, the engineered human cell has a genetic modification in the Nuclear Factor (NF)-gamma gene.

[00148] In some embodiments, an engineered human cell which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell is provided, that is homozygous for HLA-B and homozygous for HLA-C, further has reduced or eliminated surface expression of TRAC protein. In some embodiments, an engineered human cell which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell is provided, that is homozygous for HLA-B and homozygous for HLA-C, further has reduced or eliminated surface expression of TRBC protein.

[00149] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528 to chr6:29943609, and wherein the engineered cell further comprises a genetic modification in a gene that reduces or eliminates the surface expression of MHC class II. In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528 to chr6:29943609, and wherein the engineered cell further comprises a genetic modification in the CIITA gene.

[00150] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one

nucleotide within the genomic coordinates chr6:29943528 to chr6:29943609, and wherein the engineered cell further comprises a genetic modification in the TRAC gene. In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528 to chr6:29943609, and wherein the engineered cell further comprises a genetic modification in the TRBC gene.

[00151] In some embodiments, an engineered human cell is provided 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 the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528 to chr6:29943609, and wherein the engineered cell further comprises an exogenous nucleic acid. In some embodiments, the engineered cell comprises an exogenous nucleic acid encoding a targeting receptor that is expressed on the surface of the engineered cell. In some embodiments, the targeting receptor is a CAR or a universal CAR. In some embodiments, the targeting receptor is a TCR. In some embodiments, the targeting receptor is a WT1 TCR. In some embodiments, the targeting receptor is a ligand for the receptor. In some embodiments, the targeting receptor is a hybrid CAR/TCR. In some embodiments, the targeting receptor comprises an antigen recognition domain (e.g., a cancer antigen recognition domain) and a subunit of a TCR). In some embodiments, the targeting receptor is a cytokine receptor. In some embodiments, the targeting receptor is a chemokine receptor. In some embodiments, the targeting receptor is a B cell receptor (BCR). In some embodiments, the engineered cell further comprises an exogenous nucleic acid encoding a polypeptide that is secreted by the engineered cell (i.e., a soluble polypeptide). In some embodiments, the exogenous nucleic acid encodes a therapeutic polypeptide. In some embodiments, the secreted polypeptide is an antibody. In some embodiments, the secreted polypeptide is an enzyme. In some embodiments, the exogenous nucleic acid encodes an antibody encodes a cytokine. In some embodiments, the exogenous nucleic acid encodes a chemokine. In some embodiments, the exogenous nucleic acid encodes a fusion protein.

[00152] The engineered human cell may be any of the exemplary cell types disclosed herein. Further, because MHC class I molecules are expressed on all nucleated cells, the engineered human cell may be any nucleated cell. In some embodiments, the engineered cell is an immune cell. In some embodiments, the engineered cell is a stem cell such as a hematopoetic stem cell (HSC). In some embodiments, the engineered cell is an induced

pluripotent stem cell (iPSC). In some embodiments, the engineered cell is a mesenchymal stem cell (MSC). In some embodiments, the engineered cell is a neural stem cell (NSC). In some embodiments, the engineered cell is a limbal stem cell (LSC). In some embodiments, the engineered cell is a progenitor cell, e.g. an endothelial progenitor cell or a neural progenitor cell. In some embodiments, the engineered cell is a tissue-specific primary cell. In some embodiments, the engineered cell is a chosen from: chondrocyte, myocyte, and keratinocyte. In some embodiments, the engineered cell is a monocyte, macrophage, mast cell, dendritic cell, or granulocyte. In some embodiments, the engineered cell is monocyte. In some embodiments, the engineered cell is a macrophage. In some embodiments, the engineered cell is a mast cell. In some embodiments, the engineered cell is a dendritic cell. In some embodiments, the engineered cell is a granulocyte. In some embodiments, the engineered cell is a lymphocyte. In some embodiments, the engineered cell is a T cell. In some embodiments, the engineered cell is a CD4+ T cell. In some embodiments, the engineered cell is a CD8+ T cell. In some embodiments, the engineered cell is a memory T cell. In some embodiments, the engineered cell is a B cell. In some embodiments, the engineered cell is a plasma B cell. In some embodiments, the engineered cell is a memory B cell. In some embodiments, the engineered cell is a macrophage.

[00153] In some embodiments, the disclosure provides a pharmaceutical composition comprising any one of the engineered human cells disclosed herein. In some embodiments, the pharmaceutical composition comprises a population of any one of the engineered cells disclosed herein. In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 65% HLA-A negative as measured by flow cytometry. In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 70% HLA-A negative as measured by flow cytometry. In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 80% HLA-A negative as measured by flow cytometry. In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 90% HLA-A negative as measured by flow cytometry. In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 91% negative as measured by flow cytometry. In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 92% HLA-A negative as measured by flow cytometry. In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 93% HLA-A negative as measured by flow cytometry. In some embodiments, the pharmaceutical composition comprises a

population of engineered cells that is at least 94% HLA-A negative as measured by flow cytometry.

[00154] In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 95% endogenous TCR protein negative as measured by flow cytometry. In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 97% endogenous TCR protein negative as measured by flow cytometry. In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 98% endogenous TCR protein negative as measured by flow cytometry. In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 99% endogenous TCR protein negative as measured by flow cytometry. In some embodiments, the pharmaceutical composition comprises a population of engineered cells that is at least 99.5% endogenous TCR protein negative as measured by flow cytometry.

[00155] In some embodiments, methods are provided for administering the engineered human cells or pharmaceutical compositions disclosed herein to a subject in need thereof. In some embodiments, methods are provided for administering the engineered human cells or pharmaceutical compositions disclosed herein to a subject as an ACT therapy. In some embodiments, methods are provided for administering the engineered human cells or pharmaceutical compositions disclosed herein to a subject as a treatment for cancer. In some embodiments, methods are provided for administering the engineered human cells or pharmaceutical compositions disclosed herein to a subject as a treatment for an autoimmune disease. In some embodiments, methods are provided for administering the engineered human cells or pharmaceutical compositions disclosed herein to a subject as a treatment for an infectious disease.

C. Methods and Compositions for Reducing or Eliminating Surface Expression of HLA-A

[00156] The present disclosure provides methods and compositions for reducing or eliminating surface expression of HLA-A protein relative to an unmodified cell by genetically modifying the HLA-A gene. The resultant genetically modified cell may also be referred to herein as an engineered cell. In some embodiments, an already-genetically modified (or engineered) cell may be the starting cell for further genetic modification using the methods or compositions provided herein. In some embodiments, the cell is an allogeneic cell. In some embodiments, a cell with reduced HLA-A expression is useful for adoptive cell

transfer therapies. In some embodiments, editing of the HLA-A gene is combined with additional genetic modifications to yield a cell that is desirable for allogeneic transplant purposes.

[00157] In some embodiments, the methods comprise 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. In some embodiments, the methods further comprise contacting the cell with an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent. In some embodiments, the RNA-guided DNA binding agent comprises a Cas9 protein. In some embodiments, the RNA-guided DNA binding agent is selected from one of: *S. pyogenes* Cas9, *Neisseria meningitidis* Cas9, e.g. an Nme2Cas9, *S. thermophilus* Cas9, *S. aureus* Cas9, *Francisella novicida* Cpf1, *Acidaminococcus sp.* Cpf1, *Lachnospiraceae bacterium* Cpf1, C-to-T base editor, A-to-G base editor, Cas12a, and CasX. In some embodiments, the RNA-guided DNA binding agent comprises a polypeptide selected from one of: *S. pyogenes* Cas9, *Neisseria meningitidis* Cas9, e.g. an Nme2Cas9, *S. thermophilus* Cas9, *S. aureus* Cas9, *Francisella novicida* Cpf1, *Acidaminococcus sp.* Cpf1, *Lachnospiraceae bacterium* Cpf1, C-to-T base editor, A-to-G base editor, Cas12a, and CasX. In some embodiments, the RNA-guided DNA binding agent is *S. pyogenes* Cas9. In some embodiments, the CIITA guide RNA is a *S. pyogenes* Cas9 guide RNA. In some embodiments, the RNA-guided DNA binding agent comprises a deaminase domain. In some embodiments the RNA-guided DNA binding agent comprises an APOBEC3A deaminase (A3A) and an RNA-guided nickase. In some embodiments the RNA-guided DNA binding agent is *N. meningitidis* Cas9, e.g., Nme2Cas9. In some embodiments the RNA-guided DNA binding agent is *S. thermophilus* Cas9. In some embodiments the RNA-guided DNA binding agent is *S. aureus* Cas9. In some embodiments the RNA-guided DNA binding agent is Cpf1

from *F. novicida*. In some embodiments the RNA-guided DNA binding agent is Cpf1 from *Acidaminococcus sp.* In some embodiments the RNA-guided DNA binding agent is Cpf1 from *Lachnospiraceae bacterium ND2006*. In some embodiments the RNA-guided DNA binding agent is a C to T base editor. In some embodiments the RNA-guided DNA binding agent is a A to G base editor. In some embodiments, the base editor comprises a deaminase and an RNA-guided nickase. In some embodiments the RNA-guided DNA binding agent comprises a APOBEC3A deaminase (A3A) and an RNA-guided nickase. In some embodiments, the RNA-guided nickase is a SpyCas9 nickase. In some embodiments, the RNA-guided nickase comprises an NmeCas9 nickase. In some embodiments the RNA-guided DNA binding agent is Cas12a. In some embodiments the RNA-guided DNA binding agent is CasX. In some embodiments, the expression of HLA-A protein on the surface of the cell (*i.e.*, engineered cell) is thereby reduced.

[00158] In some embodiments, the methods comprise 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. In some embodiments, the methods further comprise contacting the cell with an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent. In some embodiments, the RNA-guided DNA binding agent is Cas9. In some embodiments, the RNA-guided DNA binding agent is *S. pyogenes* Cas9. In some embodiments, the CIITA guide RNA is a *S. pyogenes* Cas9 guide RNA. In some embodiments, the RNA-guided DNA binding agent comprises a deaminase domain. In some embodiments the RNA-guided DNA binding agent comprises an APOBEC3A deaminase (A3A) and an RNA-guided nickase. In some

embodiments, the expression of HLA-A protein on the surface of the cell (*i.e.*, engineered cell) is thereby reduced.

[00159] In some embodiments, the methods of reducing or eliminating expression HLA-A protein on the surface of a cell comprise contacting a cell with any one or more of the HLA-A guide RNAs disclosed herein. In some embodiments, the CIITA guide RNA comprises a guide sequence selected from SEQ ID NO: 1-211.

[00160] In some embodiments, compositions are provided 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. In some embodiments, the composition further comprises an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent. In some embodiments, the composition comprises an RNA-guided DNA binding agent that is Cas9. In some embodiments, the RNA-guided DNA binding agent is *S. pyogenes* Cas9. In some embodiments, the CIITA guide RNA is a *S. pyogenes* Cas9 guide RNA. In some embodiments, the RNA-guided DNA binding agent comprises a deaminase domain. In some embodiments the RNA-guided DNA binding agent comprises an APOBEC3A deaminase (A3A) and an RNA-guided nickase.

[00161] In some embodiments, the composition further comprises a uracil glycosylase inhibitor (UGI). In some embodiments, the composition comprises an RNA-guided DNA binding agent that the RNA-guided DNA binding agent generates a cytosine (C) to thymine (T) conversion with the HLA-A genomic target sequence. In some embodiments, the composition comprises an RNA-guided DNA binding agent that generates an adenosine (A) to guanine (G) conversion with the HLA-A genomic target sequence.

[00162] In some embodiments, an engineered human cell produced by the methods described herein is provided. In some embodiments, the engineered human cell produced by the methods and compositions described herein is an allogeneic cell. In some embodiments, the methods produce a composition comprising an engineered human cell having reduced or

eliminated HLA-A expression. In some embodiments, the engineered human cell produced by the methods disclosed herein elicits a reduced response from CD8+ T cells as compared to an unmodified cell as measured in an *in vitro* cell culture assay containing CD8+ T cells.

[00163] In some embodiments, the compositions disclosed herein further comprise a pharmaceutically acceptable carrier. In some embodiments, a cell produced by the compositions disclosed herein comprising a pharmaceutically acceptable carrier is provided. In some embodiments, compositions comprising the cells disclosed herein are provided.

1. HLA-A guide RNAs

[00164] The methods and compositions provided herein disclose guide RNAs useful for reducing or eliminating the expression of HLA-A protein on the surface of a human cell. In some embodiments, such guide RNAs direct an RNA-guided DNA binding agent to an HLA-A genomic target sequence and may be referred to herein as "HLA-A guide RNAs." In some embodiments, the HLA-A guide RNA directs an RNA-guided DNA binding agent to a human HLA-A genomic target sequence. In some embodiments, the HLA-A guide RNA comprises a guide sequence selected from SEQ ID NO: 1-211.

[00165] In some embodiments, a composition is provided comprising an HLA-A guide RNA described herein and an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent.

[00166] In some embodiments, a composition is provided comprising an HLA-A single-guide RNA (sgRNA) comprising a guide sequence selected from SEQ ID NO: 1-211. In some embodiments, a composition is provided comprising HLA-A sgRNA described herein and an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent.

[00167] In some embodiments, a composition is provided comprising an HLA-A dual-guide RNA (dgRNA) comprising a guide sequence selected from SEQ ID NO: 1-211. In some embodiments, a composition is provided comprising a HLA-a dgRNA described herein and an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent.

[00168] In some embodiments, the HLA-A gRNA comprises a guide sequence selected from any one of SEQ ID NOs: 1-211. Exemplary HLA-A guide sequences are shown below in **Table 2** (SEQ ID NOs: 1-95 with corresponding guide RNA sequences SEQ ID NOs: 249-343 and 344-438), **Table 3** (SEQ ID NOs: 96-128 with corresponding guide RNA sequences SEQ ID NOs: 439-471 and 472-504), **Table 4** (SEQ ID NOs:129-182), and **Table 5** (SEQ ID

NOs: 183-211 with corresponding guide RNA sequences SEQ ID NOs: 505-532 and 533-560).

[00169] **Table 2. Exemplary HLA-A guide RNAs**

Guide ID	**SEQ ID NO to the Guide Sequence**	**Guide Sequence**	**Exemplary Guide RNA Full Sequence** (SEQ ID NOS: 249-343)	**Exemplary Guide RNA Modified Sequence** (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	**Genomic Coordinates (hg38)**
G018983	1	UGGAGGGCCUGAUGUGUGUU	UGGAGGGCCUGAUGUGUGUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mG*mG*AGGGCCUGAUGUGUGUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945290-29945310 (mismatch to hg38=2)
G018984	2	GCCUGAUGUGUGUUGGGUGU	GCCUGAUGUGUGUUGGGUGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mC*UGAUGUGUGUUGGGUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945296-29945316 (mismatch to hg38=2)
G018985	3	CCUGAUGUGUGUUGGG	CCUGAUGUGUGUUGGG	mC*mC*mU*GAUGUGUGUUGG	chr6:29945297-29945317

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
		UGUU	UGUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	GUGUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	(mismatch to hg38=1)
G018986	4	CCCAACACCCAACACACAUC	CCCAACACCCAACACACAUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mC*mC*AACACCCAACACACAUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945300-29945320 (mismatch to hg38=1)
G018965	5	UCAGGAAACAUGAAGAAAGC	UCAGGAAACAUGAAGAAAGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUU	mU*mC*mA*GGAAACAUGAAGAAAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmA	chr6:29890117-29890137

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			GAAAAAGU GGCACCGA GUCGGUGC UUUU	mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	
G019018	6	AGGCGCCU GGGCCUCU CCCG	AGGCGCCU GGGCCUCU CCCGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mA*mG*mG*C GCCUGGGCCU CUCCCGGUUU UAGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29927058 -29927078
G018937	7	CGGGCUGG CCUCCCAC AAGG	CGGGCUGG CCUCCCAC AAGGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mG*mG*GC UGGCCUCCCA CAAGGGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29934330 -29934350

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
G018990	8	ACGGCCAUCCUCGGCGUCUG	ACGGCCAUCCUCGGCGUCUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mC*mG*GCCAUCCUCGGCGUCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942541-29942561
G018991	9	GACGGCCAUCCUCGGCGUCU	GACGGCCAUCCUCGGCGUCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mA*mC*GGCCAUCCUCGGCGUCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942542-29942562
G018992	10	GACGCCGAGGAUGGCCGUCA	GACGCCGAGGAUGGCCGUCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU	mG*mA*mC*GCCGAGGAUGGCCGUCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAU	chr6:29942543-29942563

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	AAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018993	11	UGACGGCCAUCCUCGGCGUC	UGACGGCCAUCCUCGGCGUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mG*mA*CGGCCAUCCUCGGCGUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942543-29942563
G018994	12	GGCGCCAUGACGGCCAUCCU	GGCGCCAUGACGGCCAUCCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mC*GCCAUGACGGCCAUCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmG	chr6:29942550-29942570

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
				mGmUmGmCmU*mU*mU*mU	
G018995	13	ACAGCGACGCCGCGAGCCAG	ACAGCGACGCCGCGAGCCAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mC*mA*GCGACGCCGCGAGCCAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942864-29942884
G018996	14	CGACGCCGCGAGCCAGAGGA	CGACGCCGCGAGCCAGAGGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mG*mA*CGCCGCGAGCCAGAGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942868-29942888
G018997	15	CGAGCCAGAGGAUGGAGCCG	CGAGCCAGAGGAUGGAGCCGGUUUUAGAGCUAGAAAUAGC	mC*mG*mA*GCCAGAGGAUGGAGCCGGUUUUAGAmGmCmUmAmGmAmAm	chr6:29942876-29942896

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	
G018998	16	CGGCUCCA UCCUCUGG CUCG	CGGCUCCA UCCUCUGG CUCGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mG*mG*CU CCAUCCUCUG GCUCGGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29942876 -29942896
G018999	17	GAGCCAGA GGAUGGAG CCGC	GAGCCAGA GGAUGGAG CCGCGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC	mG*mA*mG*CC AGAGGAUGGA GCCGCGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm	chr6:29942877 -29942897

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			UUUU	CmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G019000	18	GCGCCCGCGGCUCCAUCCUC	GCGCCCGCGGCUCCAUCCUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mG*CCCGCGGCUCCAUCCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942883-29942903
G019001	19	GCCCGUCCGUGGGGAUGAG	GCCCGUCCGUGGGGAUGAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mC*CGUCCGUGGGGAUGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943062-29943082
G019002	20	UCAUCCCCCACGGACGGGCC	UCAUCCCCCACGGACGGGCCGUUU	mU*mC*mA*UCCCCCACGGACGGGCCGUUUU	chr6:29943063-29943083

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			UAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	AGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G019003	21	AUCUCGGACCCGGAGACUGU	AUCUCGGACCCGGAGACUGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mU*mC*UCGGACCCGGAGACUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943092-29943112
G019004	22	GGGGUCCCGCGGCUUCGGGG	GGGGUCCCGCGGCUUCGGGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGU	mG*mG*mG*GUCCCGCGGCUUCGGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGm	chr6:29943115-29943135

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			GGCACCGA GUCGGUGC UUUU	AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	
G019005	23	CUCGGGGU CCCGCGGC UUCG	CUCGGGGU CCCGCGGC UUCGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mU*mC*GG GGUCCCGCGG CUUCGGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29943118 -29943138
G019006	24	UCUCGGGG UCCCGCGG CUUC	UCUCGGGG UCCCGCGG CUUCGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mU*mC*mU*CG GGGUCCCGCG GCUUCGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29943119 -29943139
G019007	25	GUCUCGGG	GUCUCGGG	mG*mU*mC*UC	chr6:29943120

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
		GUCCCGCGGCUU	GUCCCGCGGCUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	GGGGUCCCGCGGCUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	-29943140
G019008	26	GCAAGGGUCUCGGGGUCCCG	GCAAGGGUCUCGGGGUCCCGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mA*AGGGUCUCGGGGUCCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943126-29943146
G019009	27	GGACCCCGAGACCCUUGCCC	GGACCCCGAGACCCUUGCCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUU	mG*mG*mA*CCCCGAGACCCUUGCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUC	chr6:29943128-29943148

Guide ID	**SEQ ID NO to the Guide Sequence**	**Guide Sequence**	**Exemplary Guide RNA Full Sequence** (SEQ ID NOS: 249-343)	**Exemplary Guide RNA Modified Sequence** (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	**Genomic Coordinates (hg38)**
			AUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	CGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G019010	28	GACCCCGAGACCCUUGCCCC	GACCCCGAGACCCUUGCCCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mA*mC*CCCGAGACCCUUGCCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943129-29943149
G019011	29	CGAGACCCUUGCCCCGGGAG	CGAGACCCUUGCCCCGGGAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mG*mA*GACCCUUGCCCCGGGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCm	chr6:29943134-29943154

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
				U*mU*mU*mU	
G019012	30	CUCCCGGG GCAAGGGU CUCG	CUCCCGGG GCAAGGGU CUCGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mU*mC*CC GGGGCAAGGG UCUCGGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29943134 -29943154
G019013	31	UCUCCCGG GGCAAGGG UCUC	UCUCCCGG GGCAAGGG UCUCGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mU*mC*mU*CC CGGGGCAAGG GUCUCGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29943135 -29943155
G019014	32	CUCUCCCG GGGCAAGG GUCU	CUCUCCCG GGGCAAGG GUCUGUUU UAGAGCUA GAAAUAGC AAGUUAAA	mC*mU*mC*UC CCGGGGCAAG GGUCUGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC	chr6:29943136 -29943156

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	
G019015	33	CCUUGCCC CGGGAGAG GCCC	CCUUGCCC CGGGAGAG GCCCGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mC*mU*UG CCCCGGGAGA GGCCCGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29943140 -29943160
G019016	34	CUGGGCCU CUCCCGGG GCAA	CUGGGCCU CUCCCGGG GCAAGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mU*mG*G GCCUCUCCCG GGGCAAGUUU UAGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm	chr6:29943142 -29943162

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
				AmGmUmCmG mGmUmGmCm U*mU*mU*mU	
G019017	35	CCUGGGCC UCUCCCGG GGCA	CCUGGGCC UCUCCCGG GGCAGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mC*mU*GG GCCUCUCCCG GGGCAGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29943143 -29943163
G019019	36	UUUAGGCC AAAAAUCC CCCC	UUUAGGCC AAAAAUCC CCCCGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mU*mU*mU*A GGCCAAAAAU CCCCCCGUUU UAGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29943188 -29943208
G021208	37	CGCUGCAG CGCACGGG UACC	CGCUGCAG CGCACGGG UACCGUUU UAGAGCUA	mC*mG*mC*UG CAGCGCACGG GUACCGUUUU AGAmGmCmU	chr6:29943528 -29943548

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			GAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G021209	38	GCUGCAGCGCACGGGUACCA	GCUGCAGCGCACGGGUACCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mU*GCAGCGCACGGGUACCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943529-29943549
G021210	39	CUGCAGCGCACGGGUACCAG	CUGCAGCGCACGGGUACCAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGA	mC*mU*mG*CAGCGCACGGGUACCAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmA	chr6:29943530-29943550

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			GUCGGUGC UUUU	mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	
G018932	40	CGCACGGG UACCAGGG GCCA	CGCACGGG UACCAGGG GCCAGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mG*mC*AC GGGUACCAGG GGCCAGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29943536 -29943556
G018933	41	GCACGGGU ACCAGGGG CCAC	GCACGGGU ACCAGGGG CCACGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mG*mC*mA*CG GGUACCAGGG GCCACGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29943537 -29943557
G018934	42	CACGGGUA CCAGGGGC	CACGGGUA CCAGGGGC	mC*mA*mC*GG GUACCAGGGG	chr6:29943538 -29943558

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
		CACG	CACGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	CCACGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018935	43	GGGAGGCGCCCCGUGGCCCC	GGGAGGCGCCCCGUGGCCCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mG*AGGCGCCCCGUGGCCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943549-29943569
G018936	44	GCGAUCAGGGAGGCGCCCCG	GCGAUCAGGGAGGCGCCCCGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUU	mG*mC*mG*AUCAGGGAGGCGCCCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmA	chr6:29943556-29943576

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			GAAAAAGUGGCACCGAGUCGGUGCUUUU	mCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G021211	45	UCCUUGUGGGAGGCCAGCCC	UCCUUGUGGGAGGCCAGCCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mC*mC*UUGUGGGAGGCCAGCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943589-29943609
G018938	46	CUCCUUGUGGGAGGCCAGCC	CUCCUUGUGGGAGGCCAGCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mC*CUUGUGGGAGGCCAGCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943590-29943610

Guide ID	**SEQ ID NO to the Guide Sequence**	**Guide Sequence**	**Exemplary Guide RNA Full Sequence** (SEQ ID NOS: 249-343)	**Exemplary Guide RNA Modified Sequence** (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	**Genomic Coordinates (hg38)**
G018939	47	GGCUGGCCUCCCACAAGGAG	GGCUGGCCUCCCACAAGGAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mC*UGGCCUCCCACAAGGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943590-29943610
G018940	48	UUGUCUCCCCUCCUUGUGGG	UUGUCUCCCCUCCUUGUGGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mU*mG*UCUCCCCUCCUUGUGGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943599-29943619
G018941	49	CCACAAGGAGGGGAGACAAU	CCACAAGGAGGGGAGACAAUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU	mC*mC*mA*CAAGGAGGGGAGACAAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAU	chr6:29943600-29943620

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	AAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018942	50	CACAAGGAGGGGAGACAAUU	CACAAGGAGGGGAGACAAUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mA*mC*AAGGAGGGGAGACAAUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943601-29943621
G018943	51	CAAUUGUCUCCCCUCCUUGU	CAAUUGUCUCCCCUCCUUGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mA*mA*UUGUCUCCCCUCCUUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmG	chr6:29943602-29943622

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
				mGmUmGmCm U*mU*mU*mU	
G018944	52	CCAAUUGU CUCCCCUC CUUG	CCAAUUGU CUCCCCUC CUUGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mC*mA*AU UGUCUCCCCU CCUUGGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29943603 -29943623
G018945	53	AUCCCUCG AAUACUGA UGAG	AUCCCUCG AAUACUGA UGAGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mA*mU*mC*CC UCGAAUACUG AUGAGGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29943774 -29943794
G018946	54	AACCACUC AUCAGUAU UCGA	AACCACUC AUCAGUAU UCGAGUUU UAGAGCUA GAAAUAGC	mA*mA*mC*CA CUCAUCAGUA UUCGAGUUUU AGAmGmCmU mAmGmAmAm	chr6:29943779 -29943799

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			AAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	AmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018947	55	GAACCACUCAUCAGUAUUCG	GAACCACUCAUCAGUAUUCGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mA*mA*CCACUCAUCAGUAUUCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943780-29943800
G018948	56	GAGGAAAAGUCACGGGCCCA	GAGGAAAAGUCACGGGCCCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC	mG*mA*mG*GAAAAGUCACGGGCCCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGm	chr6:29943822-29943842

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			UUUU	CmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018949	57	GGCCCGUGACUUUUCCUCUC	GGCCCGUGACUUUUCCUCUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mC*CCGUGACUUUUCCUCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943824-29943844
G018950	58	UGCUUCACACUCAAUGUGUG	UGCUUCACACUCAAUGUGUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mG*mC*UUCACACUCAAUGUGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943857-29943877
G018951	59	GCUUCACACUCAAUGUGUGU	GCUUCACACUCAAUGUGUGUGUUU	mG*mC*mU*UCACACUCAAUGUGUGUGUUUU	chr6:29943858-29943878

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			UAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	AGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018952	60	CUUCACACUCAAUGUGUGUG	CUUCACACUCAAUGUGUGUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mU*CACACUCAAUGUGUGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943859-29943879
G018953	61	UUCACACUCAAUGUGUGUGG	UUCACACUCAAUGUGUGUGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGU	mU*mU*mC*ACACUCAAUGUGUGUGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGm	chr6:29943860-29943880

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			GGCACCGAGUCGGUGCUUUU	AmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018954	62	UUGAGAAUGGACAGGACACC	UUGAGAAUGGACAGGACACCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mU*mG*AGAAUGGACAGGACACCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29944026-29944046
G021205	63	AGGCAUUUUGCAUCUGUCAU	AGGCAUUUUGCAUCUGUCAUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mG*mG*CAUUUUGCAUCUGUCAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29944077-29944097
G021206	64	CAGGCAUU	CAGGCAUU	mC*mA*mG*GC	chr6:29944078

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
		UUGCAUCUGUCA	UUGCAUCUGUCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	AUUUUGCAUCUGUCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	-29944098
G018955	65	AGGGGCCCUGACCCUGCUAA	AGGGGCCCUGACCCUGCUAAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mG*mG*GGCCCUGACCCUGCUAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29944458-29944478
G018956	66	UGGGAAAAGAGGGGAAGGUG	UGGGAAAAGAGGGGAAGGUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUU	mU*mG*mG*GAAAAGAGGGGAAGGUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUC	chr6:29944478-29944498

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			AUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	CGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018957	67	UGGAGGAGGAAGAGCUCAGG	UGGAGGAGGAAGAGCUCAGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mG*mG*AGGAGGAAGAGCUCAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29944597-29944617
G018958	68	UGAGAUUUCUUGUCUCACUG	UGAGAUUUCUUGUCUCACUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mG*mA*GAUUUCUUGUCUCACUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCm	chr6:29944642-29944662

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
				U*mU*mU*mU	
G018959	69	GAGAUUUC UUGUCUCA CUGA	GAGAUUUC UUGUCUCA CUGAGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mG*mA*mG*A UUUCUUGUCU CACUGAGUUU UAGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29944643 -29944663
G018960	70	UAAAGCAC CUGUUAAA AUGA	UAAAGCAC CUGUUAAA AUGAGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mU*mA*mA*A GCACCUGUUA AAAUGAGUUU UAGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29944772 -29944792
G018961	71	AAUCUGUC CUUCAUUU UAAC	AAUCUGUC CUUCAUUU UAACGUUU UAGAGCUA GAAAUAGC AAGUUAAA	mA*mA*mU*C UGUCCUUCAU UUUAACGUUU UAGAmGmCmU mAmGmAmAm AmUmAmGmC	chr6:29944782 -29944802

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			AUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	AAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018962	72	GUCACAGGGGAAGGUCCCUG	GUCACAGGGGAAGGUCCCUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mU*mC*ACAGGGGAAGGUCCCUGGUUUUAGAmGmCmUmAmGmAmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29944850-29944870
G018964	73	AAACAUGAAGAAAGCAGGUG	AAACAUGAAGAAAGCAGGUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mA*mA*CAUGAAGAAAGCAGGUGGUUUUAGAmGmCmUmAmGmAmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGm	chr6:29944907-29944927

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
				AmGmUmCmG mGmUmGmCm U*mU*mU*mU	
G018966	74	UGUCCUGU GAGAUACC AGAA	UGUCCUGU GAGAUACC AGAAGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mU*mG*mU*CC UGUGAGAUAC CAGAAGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29945024 -29945044
G018967	75	AUGAAGGA GGCUGAUG CCUG	AUGAAGGA GGCUGAUG CCUGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mA*mU*mG*A AGGAGGCUGA UGCCUGGUUU UAGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29945097 -29945117
G018968	76	AGGCUGAU GCCUGAGG UCCU	AGGCUGAU GCCUGAGG UCCUGUUU UAGAGCUA	mA*mG*mG*C UGAUGCCUGA GGUCCUGUUU UAGAmGmCmU	chr6:29945104 -29945124

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			GAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018969	77	GGCUGAUGCCUGAGGUCCUU	GGCUGAUGCCUGAGGUCCUUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mC*UGAUGCCUGAGGUCCUUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945105-29945125
G018970	78	CACAAUAUCCCAAGGACCUC	CACAAUAUCCCAAGGACCUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGA	mC*mA*mC*AAUAUCCCAAGGACCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmA	chr6:29945116-29945136

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			GUCGGUGC UUUU	mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	
G018971	79	GGUCCUUG GGAUAUUG UGUU	GGUCCUUG GGAUAUUG UGUUGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mG*mG*mU*CC UUGGGAUAUU GUGUUGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29945118 -29945138
G018972	80	GUCCUUGG GAUAUUGU GUUU	GUCCUUGG GAUAUUGU GUUUGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mG*mU*mC*CU UGGGAUAUUG UGUUUGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29945119 -29945139
G018973	81	CUCCCAAA CACAAUAU	CUCCCAAA CACAAUAU	mC*mU*mC*CC AAACACAAUA	chr6:29945124 -29945144

Guide ID	**SEQ ID NO to the Guide Sequence**	**Guide Sequence**	**Exemplary Guide RNA Full Sequence** (SEQ ID NOS: 249-343)	**Exemplary Guide RNA Modified Sequence** (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	**Genomic Coordinates (hg38)**
		CCCA	CCCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	UCCCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018974	82	UCCUCUAGCCACAUCUUCUG	UCCUCUAGCCACAUCUUCUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mC*mC*UCUAGCCACAUCUUCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945176-29945196
G018975	83	ACAGAAGAUGUGGCUAGAGG	ACAGAAGAUGUGGCUAGAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUU	mA*mC*mA*GAAGAUGUGGCUAGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmA	chr6:29945177-29945197

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			GAAAAAGUGGCACCGAGUCGGUGCUUUU	mCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018976	84	CCUCUAGCCACAUCUUCUGU	CCUCUAGCCACAUCUUCUGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mC*mU*CUAGCCACAUCUUCUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945177-29945197
G018977	85	CCCACAGAAGAUGUGGCUAG	CCCACAGAAGAUGUGGCUAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mC*mC*ACAGAAGAUGUGGCUAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945180-29945200

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
G018978	86	GUCAGAUCCCACAGAAGAUG	GUCAGAUCCCACAGAAGAUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mU*mC*AGAUCCCACAGAAGAUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945187-29945207
G018979	87	AUCUUCUGUGGGAUCUGACC	AUCUUCUGUGGGAUCUGACCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mU*mC*UUCUGUGGGAUCUGACCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945188-29945208
G018980	88	CCCAGGCAGUGACAGUGCCC	CCCAGGCAGUGACAGUGCCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCU	mC*mC*mC*AGGCAGUGACAGUGCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAU	chr6:29945228-29945248

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			AGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	AAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018981	89	CUGGGCACUGUCACUGCCUG	CUGGGCACUGUCACUGCCUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mG*GGCACUGUCACUGCCUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945230-29945250
G018982	90	CCUGGGCACUGUCACUGCCU	CCUGGGCACUGUCACUGCCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mC*mU*GGGCACUGUCACUGCCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmG	chr6:29945231-29945251

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
				mGmUmGmCm U*mU*mU*mU	
G021207	91	CCCUGGGC ACUGUCAC UGCC	CCCUGGGC ACUGUCAC UGCCGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mC*mC*UG GGCACUGUCA CUGCCGUUUU AGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29945232 -29945252
G018987	92	UUGGGUGU UGGGCGGA ACAG	UUGGGUGU UGGGCGGA ACAGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mU*mU*mG*G GUGUUGGGCG GAACAGGUUU UAGAmGmCmU mAmGmAmAm AmUmAmGmC AAGUUAAAAU AAGGCUAGUC CGUUAUCAmA mCmUmUmGm AmAmAmAmA mGmUmGmGm CmAmCmCmGm AmGmUmCmG mGmUmGmCm U*mU*mU*mU	chr6:29945308 -29945328
G018988	93	UGGAUGUA UUGAGCAU GCGA	UGGAUGUA UUGAGCAU GCGAGUUU UAGAGCUA GAAAUAGC	mU*mG*mG*A UGUAUUGAGC AUGCGAGUUU UAGAmGmCmU mAmGmAmAm	chr6:29945361 -29945381

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			AAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	AmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G018989	94	GGAUGUAUUGAGCAUGCGAU	GGAUGUAUUGAGCAUGCGAUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mA*UGUAUUGAGCAUGCGAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945362-29945382
G018963	95	AACAUGAAGAAAGCAGGUGU	AACAUGAAGAAAGCAGGUGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC	mA*mA*mC*AUGAAGAAAGCAGGUGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGm	chr6:31382543-31382563

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence (SEQ ID NOS: 249-343)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 344-438)	Genomic Coordinates (hg38)
			UUUU	CmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	

[00170] **Table 3. Additional Exemplary *S. pyogenes* HLA-A guide RNAs**

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence with PAM (SEQ ID NOS: 439-471)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 472-504)	Genomic Coordinates
G021885	96	UAGCCCACGGCGAUGAAGCG	UAGCCCACGGCGAUGAAGCGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mA*mG*CCCACGGCGAUGAAGCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942815-29942835
G021886	97	GUAGCCCACGGCGAUGAAGC	GUAGCCCACGGCGAUGAAGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mU*mA*GCCCACGGCGAUGAAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCm	chr6:29942816-29942836

				U*mU*mU*mU	
G021887	98	CGUAGCCCACGGCGAUGAAG	CGUAGCCCACGGCGAUGAAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mG*mU*AGCCCACGGCGAUGAAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942817-29942837
G021888	99	CUUCAUCGCCGUGGGCUACG	CUUCAUCGCCGUGGGCUACGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mU*CAUCGCCGUGGGCUACGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942817-29942837
G021889	100	CGUGUCGUCCACGUAGCCCA	CGUGUCGUCCACGUAGCCCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGU	mC*mG*mU*GUCGUCCACGUAGCCCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAm	chr6:29942828-29942848

			GGCACCGA GUCGGUGC UUUU	AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	
G021890	101	UGGACGAC ACGCAGUU CGUG	UGGACGAC ACGCAGUU CGUGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mU*mG*mG* ACGACACGC AGUUCGUGG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	chr6:2994283 7-29942857
G021891	102	GGAUGGAG CCGCGGGC GCCG	GGAUGGAG CCGCGGGC GCCGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mG*mG*mA* UGGAGCCGC GGGCGCCGG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	chr6:2994288 5-29942905
G021892	103	GCGGGCGC CGUGGAUA GAGC	GCGGGCGC CGUGGAUA GAGCGUUU	mG*mC*mG* GGCGCCGUG GAUAGAGCG	chr6:2994289 5-29942915

			UAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	UUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G021893	104	UGCUCUAUCCACGGCGCCCG	UGCUCUAUCCACGGCGCCCGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mG*mC*UCUAUCCACGGCGCCCGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942896-29942916
G021894	105	GGCGCCGUGGAUAGAGCAGG	GGCGCCGUGGAUAGAGCAGGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mC*GCCGUGGAUAGAGCAGGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAm	chr6:29942898-29942918

				GmUmCmGmGmUmGmCmU*mU*mU*mU	
G021895	106	GCGCCGUGGAUAGAGCAGGA	GCGCCGUGGAUAGAGCAGGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mG*CCGUGGAUAGAGCAGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942899-29942919
G021896	107	CGCCGUGGAUAGAGCAGGAG	CGCCGUGGAUAGAGCAGGAGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mG*mC*CGUGGAUAGAGCAGGAGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942900-29942920
G021897	108	GUGGAUAGAGCAGGAGGGGC	GUGGAUAGAGCAGGAGGGGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUU	mG*mU*mG*GAUAGAGCAGGAGGGGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUA	chr6:29942904-29942924

			AUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	AGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G021898	109	GGCCCCUCCUGCUCUAUCCA	GGCCCCUCCUGCUCUAUCCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mC*CCCUCCUGCUCUAUCCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942905-29942925
G021899	110	AGCAGGAGGGGCCGGAGUAU	AGCAGGAGGGGCCGGAGUAUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mG*mC*AGGAGGGGCCGGAGUAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942912-29942932
G021900	111	GCAGGAGG	GCAGGAGG	mG*mC*mA*	chr6:2994291

		GGCCGGAG UAUU	GGCCGGAG UAUUGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	GGAGGGGCC GGAGUAUUG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	3-29942933
G021901	112	GGAGUGGC UCCGCAGA UACC	GGAGUGGC UCCGCAGA UACCGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mG*mG*mA* GUGGCUCCG CAGAUACCG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	chr6:2994349 0-29943510
G021902	113	CUCCGCAG AUACCUGG AGAA	CUCCGCAG AUACCUGG AGAAGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mU*mC*C GCAGAUACC UGGAGAAGU UUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm	chr6:2994349 7-29943517

				GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	
G021903	114	UCCGCAGA UACCUGGA GAAC	UCCGCAGA UACCUGGA GAACGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mU*mC*mC* GCAGAUACC UGGAGAACG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	chr6:2994349 8-29943518
G021904	115	CAGAUACC UGGAGAAC GGGA	CAGAUACC UGGAGAAC GGGAGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mA*mG* AUACCUGGA GAACGGGAG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	chr6:2994350 2-29943522
G021905	116	UCCCGUUC UCCAGGUA UCUG	UCCCGUUC UCCAGGUA UCUGGUUU UAGAGCUA GAAAUAGC AAGUUAAA	mU*mC*mC*C GUUCUCCAG GUAUCUGGU UUUAGAmG mCmUmAmG mAmAmAmU	chr6:2994350 2-29943522

			AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	
G021906	117	GCGUCUCC UUCCCGUU CUCC	GCGUCUCC UUCCCGUU CUCCGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mG*mC*mG* UCUCCUUCC CGUUCUCCG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	chr6:2994351 1-29943531
G021907	118	GAAGGAGA CGCUGCAG CGCA	GAAGGAGA CGCUGCAG CGCAGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mG*mA*mA* GGAGACGCU GCAGCGCAG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m	chr6:2994352 0-29943540

				U	
G021908	119	AAGGAGAC GCUGCAGC GCAC	AAGGAGAC GCUGCAGC GCACGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mA*mA*mG* GAGACGCUG CAGCGCACG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	chr6:2994352 1-29943541
G021909	120	AGAUCUAC AGGCGAUC AGGG	AGAUCUAC AGGCGAUC AGGGGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mA*mG*mA* UCUACAGGC GAUCAGGGG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	chr6:2994356 6-29943586
G021910	121	UGAUCGCC UGUAGAUC UCCC	UGAUCGCC UGUAGAUC UCCCGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA	mU*mG*mA* UCGCCUGUA GAUCUCCCG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm	chr6:2994356 9-29943589

			GUCGGUGCUUUU	GmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G021911	122	GGGAGAUCUACAGGCGAUCA	GGGAGAUCUACAGGCGAUCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mG*AGAUCUACAGGCGAUCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943569-29943589
G021912	123	CGGGAGAUCUACAGGCGAUC	CGGGAGAUCUACAGGCGAUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mG*mG*GAGAUCUACAGGCGAUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943570-29943590
G021913	124	CGCCUGUAGAUCUCCCGGGC	CGCCUGUAGAUCUCCCGGGCGUUUUAGAGCUA	mC*mG*mC*CUGUAGAUCUCCCGGGCGUUUUAGAmG	chr6:29943573-29943593

			GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	
G021914	125	GGCCAGCC CGGGAGAU CUAC	GGCCAGCC CGGGAGAU CUACGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mG*mG*mC* CAGCCCGGG AGAUCUACG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	chr6:2994357 8-29943598
G021915	126	UCCCGGGC UGGCCUCC CACA	UCCCGGGC UGGCCUCC CACAGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mU*mC*mC*C GGGCUGGCC UCCCACAGU UUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm	chr6:2994358 5-29943605

				GmUmGmCm U*mU*mU*m U	
G021916	127	GGGCUGGC CUCCCACA AGGA	GGGCUGGC CUCCCACA AGGAGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mG*mG*mG* CUGGCCUCC CACAAGGAG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	chr6:2994358 9-29943609
G021917	128	CUGAUCGC CUGUAGAU CUCC	CUGAUCGC CUGUAGAU CUCCGUUU UAGAGCUA GAAAUAGC AAGUUAAA AUAAGGCU AGUCCGUU AUCAACUU GAAAAAGU GGCACCGA GUCGGUGC UUUU	mC*mU*mG* AUCGCCUGU AGAUCUCCG UUUUAGAmG mCmUmAmG mAmAmAmU mAmGmCAA GUUAAAAUA AGGCUAGUC CGUUAUCAm AmCmUmUm GmAmAmAm AmAmGmUm GmGmCmAm CmCmGmAm GmUmCmGm GmUmGmCm U*mU*mU*m U	chr6:2994356 8-29943588

* The guide sequence disclosed in this Table may be unmodified, modified with the exemplary modification pattern shown in the Table, or modified with a different modification pattern disclosed herein or available in the art.

[00171] **Table 4. Exemplary HLA-A guide sequences**

SEQ ID	Guide Sequence	PAM	RNA-guided DNA binding agent	Genomic Coordinates

NO				(hg38)
129	AGGAUGGAGCCGCGGGCGCC	GTGGAT	*S. aureus* Cas9	chr6:29942884-29942904
130	GGAAGGAGACGCUGCAGCGC	ACGGGT	*S. aureus* Cas9	chr6:29943519-29943539
131	GACAGCGACGCCGCGAGCCA	GAGGAT	*S. aureus* Cas9	chr6:29942863-29942883
132	CGGGAAGGAGACGCUGCAGC	TTCT	CasX	chr6:29943517-29943537
133	CCGUGCGCUGCAGCGUCUCC	TTCC	CasX	chr6:29943523-29943543
134	ACGCAGUUCGUGCGGUUCGACAGC	NNNNCC	NME2	chr6:29942845-29942869
135	UCGUGCGGUUCGACAGCGACGCCG	NNNNCC	NME2	chr6:29942852-29942876
136	CAGCGACGCCGCGAGCCAGAGGAU	NNNNCC	NME2	chr6:29942865-29942889
137	GCUCUAUCCACGGCGCCCGCGGCU	NNNNCC	NME2	chr6:29942891-29942915
138	UCCUGCUCUAUCCACGGCGCCCGC	NNNNCC	NME2	chr6:29942895-29942919
139	CCGGCCCCUCCUGCUCUAUCCACG	NNNNCC	NME2	chr6:29942903-29942927
140	UCCGGCCCCUCCUGCUCUAUCCAC	NNNNCC	NME2	chr6:29942904-29942928
141	GGGAAGGAGACGCUGCAGCGCACG	NNNNCC	NME2	chr6:29943518-29943542
142	AGACGCUGCAGCGCACGGGUACCA	NNNNCC	NME2	chr6:29943525-29943549
143	GCGCACGGGUACCAGGGGCCACGG	NNNNCC	NME2	chr6:29943535-29943559
144	CACGGGUACCAGGGGCCACGGGGC	NNNNCC	NME2	chr6:29943538-29943562
145	ACGGGUACCAGGGGCCACGGGGCG	NNNNCC	NME2	chr6:29943539-29943563
146	CAGGGGCCACGGGGCGCCUCCCUG	NNNNCC	NME2	chr6:29943547-29943571
147	CAGGGAGGCGCCCCGUGGCCCCUG	NNNNCC	NME2	chr6:29943547-29943571
148	UCAGGGAGGCGCCCCGUGGCCCCU	NNNNCC	NME2	chr6:29943548-29943572
149	CAGGCGAUCAGGGAGGCGCCCCGU	NNNNCC	NME2	chr6:29943555-29943579
150	ACAGGCGAUCAGGGAGGCGCCCCG	NNNNCC	NME2	chr6:29943556-29943580
151	UACAGGCGAUCAGGGAGGCGCCCC	NNNNCC	NME2	chr6:29943557-29943581
152	GGGCGCCUCCCUGAUCGCCUGUAG	NNNNCC	NME2	chr6:29943558-29943582

153	GGCGCCUCCCUGAUCGC CUGUAGA	NNNN CC	NME2	chr6:29943559-29943583
154	GAGAUCUACAGGCGAUC AGGGAGG	NNNN CC	NME2	chr6:29943563-29943587
155	GGAGAUCUACAGGCGA UCAGGGAG	NNNN CC	NME2	chr6:29943564-29943588
156	GGGAGAUCUACAGGCG AUCAGGGA	NNNN CC	NME2	chr6:29943565-29943589
157	CUGAUCGCCUGUAGAUC UCCCGGG	NNNN CC	NME2	chr6:29943568-29943592
158	AUCGCCUGUAGAUCUCC CGGGCUG	NNNN CC	NME2	chr6:29943571-29943595
159	UCGCCUGUAGAUCUCCC GGGCUGG	NNNN CC	NME2	chr6:29943572-29943596
160	UUGUCUCCCCUCCUUGU GGGAGGC	NNNN CC	NME2	chr6:29943595-29943619
161	AUUGUCUCCCCUCCUUG UGGGAGG	NNNN CC	NME2	chr6:29943596-29943620
162	CCCAAUUGUCUCCCCUC CUUGUGG	NNNN CC	NME2	chr6:29943600-29943624
163	GGAUGGAGCCGCGGGCG CCG	NGG	Spy+Base_Editor	chr6:29942885-29942905
164	GCGGGCGCCGUGGAUAG AGC	NGG	Spy+Base_Editor	chr6:29942895-29942915
165	UGCUCUAUCCACGGCGC CCG	NGG	Spy+Base_Editor	chr6:29942896-29942916
166	GGCGCCGUGGAUAGAGC AGG	NGG	Spy+Base_Editor	chr6:29942898-29942918
167	GCGCCGUGGAUAGAGCA GGA	NGG	Spy+Base_Editor	chr6:29942899-29942919
168	CGCCGUGGAUAGAGCAG GAG	NGG	Spy+Base_Editor	chr6:29942900-29942920
169	GUGGAUAGAGCAGGAG GGGC	NGG	Spy+Base_Editor	chr6:29942904-29942924
170	GCGUCUCCUUCCCGUUC UCC	NGG	Spy+Base_Editor	chr6:29943511-29943531
171	GAAGGAGACGCUGCAGC GCA	NGG	Spy+Base_Editor	chr6:29943520-29943540
172	AAGGAGACGCUGCAGCG CAC	NGG	Spy+Base_Editor	chr6:29943521-29943541
173	GCUGCAGCGCACGGGUA CCA	NGG	Spy+Base_Editor	chr6:29943529-29943549
174	AGAUCUACAGGCGAUCA GGG	NGG	Spy+Base_Editor	chr6:29943566-29943586
175	CUGAUCGCCUGUAGAUC UCC	NGG	Spy+Base_Editor	chr6:29943568-29943588
176	UGAUCGCCUGUAGAUCU CCC	NGG	Spy+Base_Editor	chr6:29943569-29943589
177	GGGAGAUCUACAGGCG	NGG	Spy+Base_Editor	chr6:29943569-

	AUCA			29943589
178	CGGGAGAUCUACAGGCG AUC	NGG	Spy+Base_Editor	chr6:29943570-29943590
179	CGCCUGUAGAUCUCCCG GGC	NGG	Spy+Base_Editor	chr6:29943573-29943593
180	GGCCAGCCCGGGAGAUC UAC	NGG	Spy+Base_Editor	chr6:29943578-29943598
181	UCCCGGGCUGGCCUCCC ACA	NGG	Spy+Base_Editor	chr6:29943585-29943605
182	GGGCUGGCCUCCCACAA GGA	NGG	Spy+Base_Editor	chr6:29943589-29943609

* The guide sequence disclosed in this Table may be unmodified, or modified with a modification pattern disclosed herein or available in the art.

[00172] **Table 5. Additional Exemplary HLA-A guide sequences.**

Guide ID	SEQ ID NO to the Guide Sequence	Guide Sequence	Exemplary Guide RNA Full Sequence with PAM (SEQ ID NOS: 505-532)	Exemplary Guide RNA Modified Sequence (four terminal U residues are optional and may include 0, 1, 2, 3, 4, or more Us) (SEQ ID NOS: 533-560)	Genomic Coordinates (hg38)
G021857	183	ACGACACUGAUUGGCUUCUC	ACGACACUGAUUGGCUUCUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mC*mG*ACACUGAUUGGCUUCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29942469-29942489
G021858	184	ACCCCUCAUCCCCCACGGAC	ACCCCUCAUCCCCCACGGACGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mC*mC*CCUCAUCCCCCACGGACGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943058-29943078
G0218	185	GGCCCG	GGCCCGUCCG	mG*mG*mC*CCGUC	chr6:299430

59		UCCGUGGGGGAUGA	UGGGGGAUGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	CGUGGGGGAUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	63-29943083
G021860	186	GCCAGGUCGCCCACAGUCUC	GCCAGGUCGCCCACAGUCUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mC*AGGUCGCCCACAGUCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943080-29943100
G021861	187	GUUUAGGCCAAAAAUCCCCC	GUUUAGGCCAAAAAUCCCCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mU*mU*UAGGCCAAAAAUCCCCCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943187-29943207
G021862	188	GGCCAAAAAUCCCCCCGGGU	GGCCAAAAAUCCCCCCGGGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mG*mC*CAAAAAUCCCCCCGGGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29943192-29943212
G021863	189	GACCAACCCGGGGGAUU	GACCAACCCGGGGGGAUUUUGUUUUAGAGC	mG*mA*mC*CAACCCGGGGGGAUUUUGUUUUAGAmGmCmU	chr6:29943197-29943217

		UU	UAGAAAUAGC AAGUUAAAAU AAGGCUAGUC CGUUAUCAAC UUGAAAAAGU GGCACCGAGU CGGUGCUUUU	mAmGmAmAmAmUm AmGmCAAGUUAAA AUAAGGCUAGUCCG UUAUCAmAmCmUm UmGmAmAmAmAmA mGmUmGmGmCmAm CmCmGmAmGmUmC mGmGmUmGmCmU* mU*mU*mU	
G021864	190	CACGGGCCCAAGGCUGCUGC	CACGGGCCCA AGGCUGCUGC GUUUUAGAGC UAGAAAUAGC AAGUUAAAAU AAGGCUAGUC CGUUAUCAAC UUGAAAAAGU GGCACCGAGU CGGUGCUUUU	mC*mA*mC*GGGCC CAAGGCUGCUGCGU UUUAGAmGmCmUm AmGmAmAmAmUmA mGmCAAGUUAAAA UAAGGCUAGUCCGU UAUCAmAmCmUmU mGmAmAmAmAmAm GmUmGmGmCmAmC mCmGmAmGmUmCm GmGmUmGmCmU*m U*mU*mU	chr6:29943812-29943832
G021865	191	ACCCUCAUGCUGCACAUGGC	ACCCUCAUGC UGCACAUGGC GUUUUAGAGC UAGAAAUAGC AAGUUAAAAU AAGGCUAGUC CGUUAUCAAC UUGAAAAAGU GGCACCGAGU CGGUGCUUUU	mA*mC*mC*CUCAU GCUGCACAUGGCGU UUUAGAmGmCmUm AmGmAmAmAmUmA mGmCAAGUUAAAA UAAGGCUAGUCCGU UAUCAmAmCmUmU mGmAmAmAmAmAm GmUmGmGmCmAmC mCmGmAmGmUmCm GmGmUmGmCmU*m U*mU*mU	chr6:29944349-29944369
G021866	192	CCUCUAGGACCUUAAGGCCC	CCUCUAGGAC CUUAAGGCCC GUUUUAGAGC UAGAAAUAGC AAGUUAAAAU AAGGCUAGUC CGUUAUCAAC UUGAAAAAGU GGCACCGAGU CGGUGCUUUU	mC*mC*mU*CUAGG ACCUUAAGGCCCGU UUUAGAmGmCmUm AmGmAmAmAmUmA mGmCAAGUUAAAA UAAGGCUAGUCCGU UAUCAmAmCmUmU mGmAmAmAmAmAm GmUmGmGmCmAmC mCmGmAmGmUmCm GmGmUmGmCmU*m U*mU*mU	chr6:29944996-29945016
G021867	193	GCUCCUUUCUGGUAUCUCAC	GCUCCUUUCU GGUAUCUCAC GUUUUAGAGC UAGAAAUAGC AAGUUAAAAU	mG*mC*mU*CCUUU CUGGUAUCUCACGU UUUAGAmGmCmUm AmGmAmAmAmUmA mGmCAAGUUAAAA	chr6:29945018-29945038

			AAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	UAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G021868	194	GCUAUGGGGUUUCUUUGCAU	GCUAUGGGGUUUCUUUGCAUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mU*AUGGGGUUUCUUUGCAUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945341-29945361
G021869	195	GCCUUUGCAGAAACAAAGUC	GCCUUUGCAGAAACAAAGUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mC*UUUGCAGAAACAAAGUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945526-29945546
G021870	196	UGGACCAACCGCCCUCCUGA	UGGACCAACCGCCCUCCUGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mG*mG*ACCAACCGCCCUCCUGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29944880-29944900 (mismatch to hg38=2)
G021871	197	AGCCUCUCUGACCUUUAGCA	AGCCUCUCUGACCUUUAGCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAAC	mA*mG*mC*CUCUCUGACCUUUAGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmU	Na

			UUGAAAAAGU GGCACCGAGU CGGUGCUUUU	mGmAmAmAmAmAm GmUmGmGmCmAmC mCmGmAmGmUmCm GmGmUmGmCmU*m U*mU*mU	
G021872	198	CGCCCUCCUGAAGGUCCUCA	CGCCCUCCUG AAGGUCCUCA GUUUUAGAGC UAGAAAUAGC AAGUUAAAAU AAGGCUAGUC CGUUAUCAAC UUGAAAAAGU GGCACCGAGU CGGUGCUUUU	mC*mG*mC*CCUCC UGAAGGUCCUCAGU UUUAGAmGmCmUm AmGmAmAmAmUmA mGmCAAGUUAAAA UAAGGCUAGUCCGU UAUCAmAmCmUmU mGmAmAmAmAmAm GmUmGmGmCmAmC mCmGmAmGmUmCm GmGmUmGmCmU*m U*mU*mU	Na
G021873	200	CCGCCCUCCUGAAGGUCCUC	CCGCCCUCCU GAAGGUCCUC GUUUUAGAGC UAGAAAUAGC AAGUUAAAAU AAGGCUAGUC CGUUAUCAAC UUGAAAAAGU GGCACCGAGU CGGUGCUUUU	mC*mC*mG*CCCUCC UGAAGGUCCUCGUU UUAGAmGmCmUmA mGmAmAmAmUmAm GmCAAGUUAAAAU AAGGCUAGUCCGUU AUCAmAmCmUmUm GmAmAmAmAmAmG mUmGmGmCmAmCm CmGmAmGmUmCmG mGmUmGmCmU*mU* mU*mU	Na
G021874	201	UGGUUCCCUUUGACACACAC	UGGUUCCCUU UGACACACAC GUUUUAGAGC UAGAAAUAGC AAGUUAAAAU AAGGCUAGUC CGUUAUCAAC UUGAAAAAGU GGCACCGAGU CGGUGCUUUU	mU*mG*mG*UUCCC UUUGACACACACGU UUUAGAmGmCmUm AmGmAmAmAmUmA mGmCAAGUUAAAA UAAGGCUAGUCCGU UAUCAmAmCmUmU mGmAmAmAmAmAm GmUmGmGmCmAmC mCmGmAmGmUmCm GmGmUmGmCmU*m U*mU*mU	chr6:29943794-29943814 (mismatch to hg38=3)
G021875	202	GACCCUGCUAAAGGUCAGAG	GACCCUGCUA AAGGUCAGAG GUUUUAGAGC UAGAAAUAGC AAGUUAAAAU AAGGCUAGUC CGUUAUCAAC UUGAAAAAGU GGCACCGAGU	mG*mA*mC*CCUGC UAAAGGUCAGAGG UUUUAGAmGmCmU mAmGmAmAmAmUm AmGmCAAGUUAAA AUAAGGCUAGUCCG UUAUCAmAmCmUm UmGmAmAmAmAmA mGmUmGmGmCmAm	na

			CGGUGCUUUU	CmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	
G021876	203	AGGACCUUCAGGAGGGCGGU	AGGACCUUCAGGAGGGCGGUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mG*mG*ACCUUCAGGAGGGCGGUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	na
G021877	204	GCACACUUCUACCUGGGUCU	GCACACUUCUACCUGGGUCUGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mC*mA*CACUUCUACCUGGGUCUGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29944671-29944691 (mismatch to hg38=3)
G021878	205	GAGCCUCUCUGACCUUUAGC	GAGCCUCUCUGACCUUUAGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mG*mA*mG*CCUCUCUGACCUUUAGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	na
G021879	206	ACACUCCUCCAGCACACAUG	ACACUCCUCCAGCACACAUGGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mA*mC*mA*CUCCUCCAGCACACAUGGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*m	chr6:29944054-29944074 (mismatch to hg38=2)

				U*mU*mU	
G021880	207	CUCUGACCUUUAGCAGGGUC	CUCUGACCUUUAGCAGGGUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mU*mC*UGACCUUUAGCAGGGUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	na
G021881	208	CAAGAUAGCCACAUGUGUGC	CAAGAUAGCCACAUGUGUGCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mC*mA*mA*GAUAGCCACAUGUGUGCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29944043-29944063 (mismatch to hg38=2)
G021882	209	UCUGACCUUUAGCAGGGUCA	UCUGACCUUUAGCAGGGUCAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mC*mU*GACCUUUAGCAGGGUCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29944450-29944470 (mismatch to hg38=3)
G021883	210	UGUAAAGGUGAGAGCCUGGA	UGUAAAGGUGAGAGCCUGGAGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	mU*mG*mU*AAAGGUGAGAGCCUGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	chr6:29945274-29945294 (mismatch to hg38=1)
G0218	211	GAAGGU	GAAGGUCCCU	mG*mA*mA*GGUCC	chr6:299448

84		CCCUGAGGACCUUC	GAGGACCUUCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUUUU	CUGAGGACCUUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU	59-29944879 (mismatch to hg38=3)

* The guide sequence disclosed in this Table may be unmodified, modified with the exemplary modification pattern shown in the Table, or modified with a different modification pattern disclosed herein or available in the art.

[00173] In some embodiments, the HLA-A gRNA comprises a guide sequence selected from any one of SEQ ID NOs: 1-95. In some embodiments, the HLA-A gRNA comprises a guide sequence selected from any one of SEQ ID NOs: 7, 13-18, 22, 26, 31, 33, 37-41, 43, 45, 47, 57, 59, 62, 66, 87. In some embodiments, the HLA-A gRNA comprises a guide sequence selected from any one of SEQ ID NOs: 13-18, 26, 37-39, 41, 43, 45, 62. In some embodiments, the HLA-A gRNA comprises a guide sequence selected from any one of SEQ ID NOs: 13-18. In some embodiments, the HLA-A gRNA comprises a guide sequence selected from any one of SEQ ID NOs: 13-17. n some embodiments, the HLA-A gRNA comprises a guide sequence selected from any one of SEQ ID NOs: 37-39, 41, 43, and 45. In some embodiments, the HLA-A gRNA comprises a guide sequence selected from any one of SEQ ID NOs: 37-39.

[00174] In some embodiments, the gRNA comprises a guide sequence selected from any one of SEQ ID NOs: 1-211. In some embodiments, the HLA-A guide RNA comprises a guide sequence that is at least 17, 18, 19, or 20 contiguous nucleotides of a sequence selected from SEQ ID NOs: 1-211. In some embodiments, the HLA-A guide RNA comprises a guide sequence that is at least 95%, 90%, or 85% identical to a sequence selected from SEQ ID NOs: 1-211. In some embodiments, the HLA-A guide RNA comprises a guide sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 1-211.

[00175] In some embodiments, the HLA-A guide RNA comprises a guide sequence that comprises at least 10 contiguous nucleotides ± 10 nucleotides of a genomic coordinate listed in **Tables 2-5**. As used herein, at least 10 contiguous nucleotides ± 10 nucleotides of a genomic coordinate means, for example, at least 10 contiguous nucleotides within the genomic coordinates wherein the genomic coordinates include 10 nucleotides in the 5'

direction and 10 nucleotides in the 3' direction from the ranges listed in **Tables 2-5**. For example, an HLA-A guide RNA may comprise 10 contiguous nucleotides within the genomic coordinates chr6:29942864 to chr6: 29942903 or chr6:29943528 to chr6:29943609, including the boundary nucleotides of these ranges. In some embodiments, the HLA-A guide RNA comprises a guide sequence that is at least 17, 18, 19, or 20 contiguous nucleotides of a sequence that comprises 10 contiguous nucleotides ± 10 nucleotides of a genomic coordinate 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 sequence that comprises 10 contiguous nucleotides ± 10 nucleotides of a genomic coordinate listed in **Table 4**. In some embodiments, the HLA-A guide RNA comprises a guide sequence that is at least 95%, 90%, or 85% identical to a sequence selected from a sequence that is 17, 18, 19, or 20 contiguous nucleotides of a sequence that comprises 10 contiguous nucleotides ± 10 nucleotides of a genomic coordinate 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 sequence that comprises 10 contiguous nucleotides ± 10 nucleotides of a genomic coordinate listed in **Table 4**.

[00176] In some embodiments, the **Tables 2-5** guide RNA comprises a guide sequence that comprises at least 15 contiguous nucleotides ± 10 nucleotides of a genomic coordinate listed in **Tables 2-5**. In some embodiments, the HLA-A guide RNA comprises a guide sequence that comprises at least 20 contiguous nucleotides ± 10 nucleotides of a genomic coordinate listed in **Tables 2-5**.

[00177] In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 1. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 2. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 3. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 4. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 5. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 6. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 7. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 8. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 9. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 10. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 11. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 12. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 13. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 14. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 15. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 16. In some embodiments, the HLA-A guide RNA comprises

SEQ ID NO: 17. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 18. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 19. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 20. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 21. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 22. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 23. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 24. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 25. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 26. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 27. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 28. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 29. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 30. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 31. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 32. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 33. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 34. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 35. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 36. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 37. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 38. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 39. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 40. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 41. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 42. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 43. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 44. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 45. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 46. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 47. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 48. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 49. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 50. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 51. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 52. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 53. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 54. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 55. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 56. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 57. In some embodiments, the HLA-A guide

RNA comprises SEQ ID NO: 58. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 59. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 60. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 61. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 62. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 63. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 64. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 65. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 66. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 67. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 68. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 69. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 70. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 71. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 72. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 73. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 74. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 75. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 76. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 77. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 78. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 79. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 80. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 81. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 82. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 83. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 84. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 85. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 86. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 87. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 88. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 89. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 90. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 91. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 92. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 93. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 94. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 95. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 96. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 97. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 98. In some embodiments, the

HLA-A guide RNA comprises SEQ ID NO: 99. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 100. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 101. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 102. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 103. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 104. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 105. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 106. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 107. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 108. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 109. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 110. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 111. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 112. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 113. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 114. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 115. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 116. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 117. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 118. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 119. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 120. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 121. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 122. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 123. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 124. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 125. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 126. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 127. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 128. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 129. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 130. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 131. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 132. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 133. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 134. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 135. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 136. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 137. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 138. In some

embodiments, the HLA-A guide RNA comprises SEQ ID NO: 139. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 140. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 141. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 142. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 143. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 144. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 145. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 146. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 147. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 148. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 149. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 150. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 151. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 152. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 153. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 154. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 155. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 156. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 157. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 158. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 159. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 160. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 161. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 162. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 163. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 164. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 165. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 166. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 167. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 168. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 169. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 170. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 171. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 172. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 173. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 174. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 175. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 176. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 177. In some embodiments, the HLA-A guide RNA comprises SEQ

ID NO: 178. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 179. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 180. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 181. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 182. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 183. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 184. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 185. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 186. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 187. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 188. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 189. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 190. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 191. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 192. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 193. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 194. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 195. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 196. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 197. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 198. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 199. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 200. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 201. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 202. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 203. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 204. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 205. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 206. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 207. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 208. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 209. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 210. In some embodiments, the HLA-A guide RNA comprises SEQ ID NO: 211.

[00178] Additional embodiments of HLA-A guide RNAs are provided herein, including *e.g.*, exemplary modifications to the guide RNA.

2. *Genetic modifications to HLA-A*

[00179] In some embodiments, the methods and compositions disclosed herein genetically modify at least one nucleotide in the HLA-A gene in a cell. Genetic modifications encompass the population of modifications that results from contact with a gene editing system (*e.g.*, the population of edits that result from Cas9 and an HLA-A guide RNA, or the population of edits that result from BC22 and an HLA-A guide RNA).

[00180] In some embodiments, the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from: chr6:29942854- chr6:29942913 and chr6:29943518- chr6: 29943619.

[00181] In some embodiments, the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942864-chr6: 29942903.

[00182] In some embodiments, the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-chr6:29943609.

[00183] In some embodiments, the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942864-29942884; chr6:29942868-29942888; chr6:29942876-29942896; chr6:29942877-29942897; and chr6:29942883-29942903.

[00184] In some embodiments, the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557; chr6:29943549-29943569; and chr6:29943589-29943609.

[00185] In some embodiments, the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942876-29942897.

[00186] In some embodiments, the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-chr629943550.

[00187] In some embodiments, 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.

[00188] In some embodiments, the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from: chr6:29943528-29943548, chr6:29943529-29943549, and chr6:29943530-29943550.

[00189] In some embodiments, the genetic modification comprises at least one nucleotide within the genomic coordinates 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.

[00190] In some embodiments, 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.

[00191] In some embodiments, 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, 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.

[00192] In some embodiments, 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.

[00193] In some embodiments, 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; chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557; chr6:29943549-29943569; and chr6:29943589-29943609.

[00194] In some embodiments, 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; and chr6:29942883-29942903.

[00195] In some embodiments, the genetic modification comprises an indel, a C to T substitution, or an A to G substitution 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.

[00196] In some embodiments, the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates chosen from: 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.

[00197] In some embodiments, the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates chosen from: 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.

[00198] In some embodiments, the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates chosen from: chr6:29942884-29942904, chr6:29943519-29943539, chr6:29942863-29942883.

[00199] In some embodiments, the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates chosen from: chr6:29943517-29943537, and chr6:29943523-29943543.

[00200] In some embodiments, the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates chosen from: 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, chr6:29943600-29943624.

[00201] In some embodiments, the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates chosen from: 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.

[00202] In some embodiments, the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates chosen from: 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, chr6:29945341-29945361, chr6:29945526-29945546.

[00203] In some embodiments, the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates: chr6:29942876-29942897.

[00204] In some embodiments, 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, and chr6:29942877-29942897.

[00205] In some embodiments, the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates: chr6:29943528-chr629943550.

[00206] In some embodiments, the genetic modification comprises an indel, a C to T substitution, or an A to G substitution within the genomic coordinates chosen from: chr6:29943528-29943548, chr6:29943529-29943549, and chr6:29943530-29943550.

[00207] In some embodiments, the modification to HLA-A comprises any one or more of an insertion, deletion, substitution or deamination of at least one nucleotide in a target sequence. In some embodiments, the modification to HLA-A comprises an insertion of 1, 2, 3, 4 or 5 or more nucleotides in a target sequence. In some embodiments, the modification to HLA-A comprises a deletion of 1, 2, 3, 4 or 5 or more nucleotides in a target sequence. In other embodiments, the modification to HLA-A comprises an insertion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 25 or more nucleotides in a target sequence. In other embodiments, the modification to HLA-A comprises a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 25 or more nucleotides in a target sequence. In some embodiments, the modification to HLA-A comprises an indel, which is generally defined in the art as an insertion or deletion of less than 1000 base pairs (bp). In some embodiments, the modification to HLA-A comprises an indel which results in a frameshift mutation in a target sequence. In some embodiments, the modification to HLA-A comprises a substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 25 or more nucleotides in a target sequence. In some embodiments, the modification to HLA-A comprises one or more of an insertion, deletion, or substitution of nucleotides resulting from the incorporation of a template nucleic acid. In some embodiments, the modification to HLA-A comprises an insertion of a donor nucleic acid in a target sequence. In some embodiments, the modification to HLA-A is not transient.

3. *Efficacy of HLA-A guide RNAs*

[00208] The efficacy of an HLA-A guide RNA may be determined by techniques available in the art that assess the editing efficiency of a guide RNA, and the expression of HLA-A protein on the surface of a cell. In some embodiments, the reduction or elimination of HLA-A protein on the surface of a cell may be determined by comparison to an unmodified cell (or "relative to an unmodified cell"). An engineered cell or cell population may also be compared to a population of unmodified cells.

[00209] An "unmodified cell" (or "unmodified cells") refers to a control cell (or cells) of the same type of cell in an experiment or test, wherein the "unmodified" control cell has not been contacted with an HLA-A guide. Therefore, an unmodified cell (or cells) may be a cell that has not been contacted with a guide RNA, or a cell that has been contacted with a guide RNA that does not target HLA-A.

[00210] In some embodiments, the efficacy of an HLA-A guide RNA is determined by measuring levels of HLA-A protein on the surface of a cell. In some embodiments, HLA-A protein levels are measured by flow cytometry (*e.g.*, with an antibody against HLA-A2/HLA-

A3). In some embodiments, the population of cells is enriched (e.g., by FACS or MACS) and is at least 65%, 70%, 80%, 90%, 91%, 92%, 93%, or 94% HLA-A negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is not enriched (e.g., by FACS or MACS) and is at least 65%, 70%, 80%, 90%, 91%, 92%, 93%, or 94% HLA-A negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 65% HLA-A negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 70% HLA-A negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 80% HLA-A negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 90% HLA-A negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 95% MHC I negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 100% HLA-A negative as measured by flow cytometry relative to a population of unmodified cells.

[00211] In some embodiments, an effective HLA-A guide RNA may be determined by measuring the response of immune cells *in vitro* or *in vivo* (*e.g.*, CD8+ T cells) to the genetically modified target cell. For example, a reduced response from CD8+ T cells is indicative of an effective HLA-A guide RNA. A CD8+ T cell response may be evaluated by an assay that measures CD8+ T cell activation responses, *e.g.*, CD8+ T cell proliferation, expression of activation markers, and/or cytokine production (IL-2, IFN-γ, TNF-α) (*e.g.*, flow cytometry, ELISA). The CD8+ T cell response may be assessed *in vitro* or *in vivo*. In some embodiments, the CD8+ T cell response may be evaluated by co-culturing the genetically modified cell with CD8+ T cells *in vitro*. In some embodiments, CD8+ T cell activity may be evaluated in an *in vivo* model, *e.g.*, a rodent model. In an *in vivo* model, *e.g.*, genetically modified cells may be administered with CD8+ T cell; survival of the genetically modified cells is indicative of the ability to avoid CD8+ T cell lysis. In some embodiments, the methods produce a composition comprising a cell that survives *in vivo* in the presence of CD8+ T cells for greater than 1, 2, 3, 4, 5, or 6 weeks or more. In some embodiments, the methods produce a composition comprising a cell that survives *in vivo* in the presence of CD8+ T cells for at least one week to six weeks. In some embodiments, the methods produce a composition comprising a cell that survives *in vivo* in the presence of CD8+ T cells for at least two to four weeks. In some embodiments, the methods produce a composition

comprising a cell that survives *in vivo* in the presence of CD8+ T cells for at least four to six weeks. In some embodiments, the methods produce a composition comprising a cell that survives *in vivo* in the presence of CD8+ T cells for more than six weeks.

[00212] The efficacy of an HLA-A guide RNA may also be assessed by the survival of the cell post-editing. In some embodiments, the cell survives post editing for at least one week to six weeks. In some embodiments, the cell survives post editing for at least two weeks. In some embodiments, the cell survives post editing for at least three weeks. In some embodiments, the cell survives post editing for at least four weeks. In some embodiments, the cell survives post editing for at least five weeks. In some embodiments, the cell survives post editing for at least six weeks. In some embodiments, the cell survives post editing for at least one week to twelve weeks. The viability of a genetically modified cell may be measured using standard techniques, including *e.g.*, by measures of cell death, by flow cytometry live/dead staining, or cell proliferation.

[00213] In some embodiments, the engineered cell is assessed by the persistence of the engineered human cell which has reduced or eliminated HLA-A expression and is homozygous for HLA-B and homozygous for HLA-C. As used herein, "persistence" refers to the ability of the engineered cell to exist in an *in vitro* and/or *in vivo* environment with reactive or responding T cells and/or NK cells present, *e.g.*, the ability to exist *in vivo* after transfer into a recipient. In some embodiments, the engineered human T cells are protective against NK-mediated rejection. In some embodiments, the ratio of viable engineered cells in vivo in the presence of NK cells relative to viable engineered cells in vivo in the absence of NK cells is at least 0.3:1 or greater, at least 20 days, at least 30 days, at least 40 days, at least 50 days, at least 60 days, at least 70 days, at least 80 days, or at least 90 days after transfer into a recipient, as demonstrated herein. In some embodiments, at least 90 days after transfer into a recipient, the ratio of viable engineered cells in vivo in the presence of NK cells relative to viable engineered cells in vivo in the absence of NK cells is at least 0.4:1 or greater, 0.5:1 or greater, 0.6:1 or greater, 0.7:1 or greater, 0.8:1 or greater, or 0.9:1 or greater, as demonstrated herein. In some embodiments, the engineered human T cells are protective against CD8+ T cell-mediated rejection.

[00214] In some embodiments, the engineered cells may be assessed using a mixed lymphocyte reaction (MLR). (*See e.g.*, DeWolf et al., Transplantation 100:1639-1649 (2017). In some embodiments, engineered human cells are mixed with labeled unedited (non-engineered) responding T cells, and the MLR assay measures proliferation of

responding T cells activated by allorecognition (*i.e.*, through mismatched HLA molecules on the surface of the engineered human cell).

D. Methods and Compositions for Reducing or Eliminating MHC Class II and Additional Modifications

[00215] In some embodiments, multiplex gene editing may be performed in a cell. In some embodiments, the methods comprise reducing or eliminating expression of HLA-A protein on the surface of a cell comprising genetically modifying the HLA-A gene comprising contacting the cell with a composition comprising a HLA-A guide RNA disclosed herein; and optionally an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent, the method further comprising contacting with one or more compositions selected from: (a) a guide RNA that directs an RNA-guided DNA binding agent to the CIITA gene; (b) a guide RNA that directs an RNA-guided DNA binding agent to a locus in the genome of the cell other than HLA-A or CIITA; and (c) a donor nucleic acid for insertion in the genome of the cell.

1. MHC class II knock out

[00216] In some embodiments, methods for reducing or eliminating expression of HLA-A protein on the surface of a cell by genetically modifying HLA-A as disclosed herein are provided, wherein the methods and compositions further provide for reducing or eliminating expression of MHC class II protein on the surface of the cell relative to an unmodified cell. In some embodiments, MHC class II protein expression is reduced or eliminated by contacting the cell with a CIITA guide RNA. In some embodiments, the cell is an allogeneic cell. In some embodiments, the cell is homozygous for HLA-B and homozygous for HLA-C.

[00217] In some embodiments, methods are provided for reducing surface expression of MHC class II on the engineered human cell. MHC class II expression is impacted by a variety of proteins. (*See e.g.*, Crivello *et al.*, Journal Immunology 202:1895-1903 (2019).) For example, the CIITA protein functions as a transcriptional activator (activating the MHC class II promoter) and is essential for MHC class II protein expression. In some embodiments, MHC class II protein expression is reduced or eliminated by genetically modifying a gene selected from: CIITA, HLA-DR, HLA-DQ, HLA-DP, RFX5, RFXB/ANK, RFXAP, CREB, NF-YA, NF-YB, and NF-YC. In some embodiments, MHC class II protein expression is reduced or eliminated by genetically modifying the CIITA gene. In some embodiments, MHC class II protein expression is reduced or eliminated by genetically modifying the HLA-DR gene. In some embodiments, MHC class II protein expression is

reduced or eliminated by genetically modifying the HLA-DQ gene. In some embodiments, MHC class II protein expression is reduced or eliminated by genetically modifying the HLA-DP gene. In some embodiments, MHC class II protein expression is reduced or eliminated by genetically modifying the RFX5 gene. In some embodiments, MHC class II protein expression is reduced or eliminated by genetically modifying the RFXB/ANK gene. In some embodiments, MHC class II protein expression is reduced or eliminated by genetically modifying the RFXAP gene. In some embodiments, MHC class II protein expression is reduced or eliminated by genetically modifying the CREB gene. In some embodiments, MHC class II protein expression is reduced or eliminated by genetically modifying the NK-YA gene. In some embodiments, MHC class II protein expression is reduced or eliminated by genetically modifying the NK-YB gene. In some embodiments, MHC class II protein expression is reduced or eliminated by genetically modifying the NK-YC gene.

[00218] In some embodiments, methods are provided for making an engineered human cell which has reduced or eliminated expression of HLA-A protein relative to an unmodified cell, wherein the cell is homozygous for HLA-B and homozygous for HLA-C, further comprising reducing or eliminating the surface expression of MHC class II protein in the cell relative to an unmodified cell. In some embodiments, the methods comprise contacting the cell with a CIITA guide RNA.

[00219] In some embodiments, the efficacy of a CIITA guide RNA is determined by measuring levels of CIITA protein in a cell. The levels of CIITA protein may be detected by, *e.g.*, cell lysate and western blot with an anti-CIITA antibody. In some embodiments, the efficacy of a CIITA guide RNA is determined by measuring levels of CIITA protein in the cell nucleus. In some embodiments, the efficacy of a CIITA guide RNA is determined by measuring levels of CIITA mRNA in a cell. The levels of CIITA mRNA may be detected by *e.g.*, RT-PCR. In some embodiments, a decrease in the levels CIITA protein and/or CIITA mRNA in the target cell as compared to an unmodified cell is indicative of an effective CIITA guide RNA.

[00220] In some embodiments, the efficacy of a CIITA guide RNA is determined by measuring the reduction or elimination of MHC class II protein expression by the target cells. The CIITA protein functions as a transactivator, activating the MHC class II promoter, and is essential for the expression of MHC class II protein. In some embodiments, MHC class II protein expression may be detected on the surface of the target cells. In some embodiments, MHC class II protein expression is measured by flow cytometry. In some embodiments, an antibody against MHC class II protein (*e.g.*, anti-HLA-DR, -DQ, -DP) may be used to detect

MHC class II protein expression *e.g.*, by flow cytometry. In some embodiments, a reduction or elimination in MHC class II protein on the surface of a cell (or population of cells) as compared to an unmodified cell (or population of unmodified cells) is indicative of an effective CIITA guide RNA. In some embodiments, a cell (or population of cells) that has been contacted with a particular CIITA guide RNA and RNA-guided DNA binding agent that is negative for MHC class II protein by flow cytometry is indicative of an effective CIITA guide RNA.

[00221] In some embodiments, the MHC class II protein expression is reduced or eliminated in a population of cells using the methods and compositions disclosed herein. In some embodiments, the population of cells is enriched (e.g., by FACS or MACS) and is at least 65%, 70%, 80%, 90%, 91%, 92%, 93%, or 94% MHC class II negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is not enriched (e.g., by FACS or MACS) and is at least 65%, 70%, 80%, 90%, 91%, 92%, 93%, or 94% MHC class II negative as measured by flow cytometry relative to a population of unmodified cells.

[00222] In some embodiments, the population of cells is at least 65% MHC II negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 70% MHC class II negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 80% MHC II negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 90% MHC class II negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 91% MHC class II negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 92% MHC II negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 93% MHC class II negative as measured by flow cytometry relative to a population of unmodified cells. In some embodiments, the population of cells is at least 94% MHC class II negative as measured by flow cytometry relative to a population of unmodified cells.

[00223] In some embodiments, the population of cells elicits a reduced response from immune cells *in vitro* or *in vivo* (*e.g.*, CD4+ T cells). A CD4+ T cell response may be evaluated by an assay that measures the activation response of CD4+ T cells *e.g.*, CD4+ T cell proliferation, expression of activation markers, and/or cytokine production (IL-2, IL-12,

IFN-γ) (*e.g.*, flow cytometry, ELISA). The response of CD4+ T cells may be evaluated in *in vitro* cell culture assays in which the genetically modified cell is co-cultured with cells comprising CD4+ T cells. For example, the engineered cell may be co-cultured *e.g.*, with PBMCs, purified CD3+ T cells comprising CD4+ T cells, purified CD4+ T cells, or a CD4+ T cell line. The CD4+ T cell response elicited from the engineered cell may be compared to the response elicited from an unmodified cell.

[00224] In some embodiments, an engineered human cell is provided wherein the cell has reduced or eliminated expression of HLA-A and MHC class II protein on the cell surface, wherein the cell comprises a genetic modification in the HLA-A gene, wherein the cell is homozygous for HLA-B and homozygous for HLA-C, and wherein the cell comprises a modification in the CIITA gene. In some embodiments, the engineered cell elicits a reduced response from CD4+ T cells and elicits a reduced response from CD8+ T cells.

2. *Exogenous nucleic acids knock in*

[00225] In some embodiments, the present disclosure provides methods and compositions for reducing or eliminating expression of HLA-A protein on the surface of a cell by genetically modifying HLA-A as disclosed herein, wherein the methods and compositions further provide for expression of a protein encoded by an exogenous nucleic acid (*e.g.*, an antibody, chimeric antigen receptor (CAR), T cell receptor (TCR), cytokine or cytokine receptor, chemokine or chemokine receptor, enzyme, fusion protein, or other type of cell-surface bound or soluble polypeptide). In some embodiments, the exogenous nucleic acid encodes a protein that is expressed on the cell surface. For example, in some embodiments, the exogenous nucleic acid encodes a targeting receptor expressed on the cell surface (described further herein). In some embodiments, the genetically modified cell may function as a "cell factory" for the expression of a secreted polypeptide encoded by an exogenous nucleic acid, including *e.g.*, as a source for continuous production of a polypeptide *in vivo* (as described further herein). In some embodiments, the cell is an allogeneic cell. In some embodiments, the cell is homozygous for HLA-B and homozygous for HLA-C.

[00226] In some embodiments, the methods comprise reducing expression of HLA-A protein on the surface of a cell comprising genetically modifying the HLA-A gene comprising contacting the cell with a composition comprising an HLA-A guide RNA disclosed herein, the method further comprising contacting the cell with an exogenous nucleic acid.

[00227] In some embodiments, the methods comprise reducing or eliminating expression of HLA-A protein on the surface of a cell, comprising genetically modifying the cell with one or more compositions comprising a HLA-A guide RNA as disclosed herein, an exogenous nucleic acid encoding a polypeptide (*e.g.*, a targeting receptor), and an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent.

[00228] In some embodiments, the methods comprise reducing or eliminating expression of HLA-A protein and MHC class II protein on the surface of a cell, comprising genetically modifying the cell with one or more compositions comprising a HLA-A guide RNA as disclosed herein, a CIITA guide RNA, an exogenous nucleic acid encoding a polypeptide (*e.g.*, a targeting receptor), and an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent.

[00229] In some embodiments, the exogenous nucleic acid encodes a polypeptide that is expressed on the surface of the cell. In some embodiments, the exogenous nucleic acid encodes a soluble polypeptide. As used herein, “soluble” polypeptide refers to a polypeptide that is secreted by the cell. In some embodiments, the soluble polypeptide is a therapeutic polypeptide. In some embodiments, the soluble polypeptide is an antibody. In some embodiments, the soluble polypeptide is an enzyme. In some embodiments, the soluble polypeptide is a cytokine. In some embodiments, the soluble polypeptide is a chemokine. In some embodiments, the soluble polypeptide is a fusion protein.

[00230] In some embodiments, the exogenous nucleic acid encodes an antibody. In some embodiments, the exogenous nucleic acid encodes an antibody fragment (*e.g.*, Fab, Fab2). In some embodiments, the exogenous nucleic acid encodes is a full-length antibody. In some embodiments, the exogenous nucleic acid encodes is a single-chain antibody (*e.g.*, scFv). In some embodiments, the antibody is an IgG, IgM, IgD, IgA, or IgE. In some embodiments, the antibody is an IgG antibody. In some embodiments, the antibody is an IgG1 antibody. In some embodiments, the antibody is an IgG4 antibody. In some embodiments, the heavy chain constant region contains mutations known to reduce effector functions. In some embodiments, the heavy chain constant region contains mutations known to enhance effector functions. In some embodiments, the antibody is a bispecific antibody. In some embodiments, the antibody is a single-domain antibody (*e.g.*, VH domain-only antibody).

[00231] In some embodiments, the exogenous nucleic acid encodes a neutralizing antibody. A neutralizing antibody neutralizes the activity of its target antigen. In some embodiments, the antibody is a neutralizing antibody against a virus antigen. In some embodiments, the antibody neutralizes a target viral antigen, blocking the ability of the virus

to infect a cell. In some embodiments, a cell-based neutralization assay may be used to measure the neutralizing activity of an antibody. The particular cells and readout will depend on the target antigen of the neutralizing antibody. The half maximal effective concentration (EC_{50}) of the antibody can be measured in a cell-based neutralization assay, wherein a lower EC_{50} is indicative of more potent neutralizing antibody.

[00232] In some embodiments, the exogenous nucleic acid encodes an antibody that binds to an antigen associated with a disease or disorder (*see e.g.*, diseases and disorders described in Section IV).

[00233] In some embodiments, the exogenous nucleic acid encodes a polypeptide that is expressed on the surface of the cell (*i.e.*, a cell-surface bound protein). In some embodiments, the exogenous nucleic acid encodes a targeting receptor. A "targeting receptor" is a receptor present on the surface of a cell, e.g., a T cell, to permit binding of the cell to a target site, e.g., a specific cell or tissue in an organism. In some embodiments, the targeting receptor is a CAR. In some embodiments, the targeting receptor is a universal CAR (UniCAR). In some embodiments, the targeting receptor is a proliferation-inducing ligand (APRIL). In some embodiments, the targeting receptor is a TCR. In some embodiments, the targeting receptor is a TRuC. In some embodiments, the targeting receptor is a B cell receptor (BCR) (e.g., expressed on a B cell). In some embodiments, the targeting receptor is chemokine receptor. In some embodiments, the targeting receptor is a cytokine receptor.

[00234] In some embodiments, targeting receptors include a chimeric antigen receptor (CAR), a T-cell receptor (TCR), and a receptor for a cell surface molecule operably linked through at least a transmembrane domain in an internal signaling domain capable of activating a T cell upon binding of the extracellular receptor portion. In some embodiments, a CAR refers to an extracellular antigen recognition domain, e.g., an scFv, VHH, nanobody; operably linked to an intracellular signaling domain, which activates the T cell when an antigen is bound. CARs are composed of four regions: an antigen recognition domain, an extracellular hinge region, a transmembrane domain, and an intracellular T-cell signaling domain. Such receptors are well known in the art (see, e.g., WO2020092057, WO2019191114, WO2019147805, WO2018208837). A universal CAR (UniCAR) for recognizing various antigens (see, e.g., EP 2 990 416 A1) and a reversed universal CAR (RevCAR) that promotes binding of an immune cell to a target cell through an adaptor molecule (see, e.g., WO2019238722) are also contemplated. CARs can be targeted to any antigen to which an antibody can be developed and are typically directed to molecules displayed on the surface of a cell or tissue to be targeted. In some embodiments, the targeting

receptor comprises an antigen recognition domain (e.g., a cancer antigen recognition domain and a subunit of a TCR (e.g., a TRuC). (*See* Baeuerle et al. Nature Communications 2087 (2019).)

[00235] In some embodiments, the exogenous nucleic acid encodes a TCR. In some embodiments, the exogenous nucleic acid encodes a genetically modified TCR. In some embodiments, the exogenous nucleic acid encodes is a genetically modified TCR with specificity for a polypeptide expressed by cancer cells. In some embodiments, the exogenous nucleic acid encodes a targeting receptor specific for Wilms' tumor gene (WT1) antigen. In some embodiments, the exogenous nucleic acid encodes the WT1-specific TCR (*see e.g.*, WO2020/081613A1).

[00236] In some embodiments, an exogenous nucleic acid is inserted into the genome of the target cell. In some embodiments, the exogenous nucleic acid is integrated into the genome of the target cell. In some embodiments, the exogenous nucleic acid is integrated into the genome of the target cell by homologous recombination (HR). In some embodiments, the exogenous nucleic acid is integrated into the genome of the target cell by blunt end insertion. In some embodiments, the exogenous nucleic acid is integrated into the genome of the target cell by non-homologous end joining. In some embodiments, the exogenous nucleic acid is integrated into a safe harbor locus in the genome of the cell. In some embodiments, the exogenous nucleic acid is integrated into one of the TRAC locus, B2M locus, AAVS1 locus, and/or CIITA locus. In some embodiments, the exogenous nucleic acid is provided to the cell in a lipid nucleic acid assembly composition. In some embodiments, the lipid nucleic acid assembly composition is a lipid nanoparticle (LNP).

[00237] In some embodiments, the methods produce a composition comprising an engineered cell having reduced or eliminated HLA-A expression and comprising an exogenous nucleic acid. In some embodiments, the methods produce a composition comprising an engineered cell having reduced or eliminated HLA-A expression and that secretes and/or expresses a polypeptide encoded by an exogenous nucleic acid integrated into the genome of the cell. In some embodiments, the methods produce a composition comprising an engineered cell having reduced or eliminated HLA-A protein expression, and/or reduced or eliminated HLA-A levels in the cell nucleus, and having reduced MHC class II protein expression, and secreting and/or expressing a polypeptide encoded by an exogenous nucleic acid integrated into the genome of the cell. In some embodiments, the engineered cell elicits a reduced response from CD4+ T cells, and/or CD8+ T cells.

[00238] In some embodiments, an allogeneic cell is provided wherein the cell has reduced or eliminated expression of MHC class II and HLA-A protein on the cell surface, wherein the cell comprises a modification in the HLA-A gene as disclosed herein, wherein the cell comprises a modification in the CIITA gene, and wherein the cell further comprises an exogenous nucleic acid encoding a polypeptide (e.g., a targeting receptor).

[00239] In some embodiments, the present disclosure provides methods for reducing or eliminating expression of HLA-A protein on the surface of a cell by genetically modifying HLA-A as disclosed herein, wherein the methods further provide for reducing expression of one or more additional target genes (*e.g.*, TRAC, TRBC). In some embodiments, the additional genetic modifications provide further advantages for use of the genetically modified cells for adoptive cell transfer applications. In some embodiments, the cell is an allogeneic cell. In some embodiments, the cell is homozygous for HLA-B and homozygous for HLA-C.

[00240] In some embodiments, the methods comprise reducing or eliminating expression of HLA-A protein on the surface of a cell, comprising genetically modifying the cell with one or more compositions comprising a HLA-A guide RNA as disclosed herein, a CIITA guide RNA, an exogenous nucleic acid encoding polypeptide (e.g., a targeting receptor), a guide RNA that directs an RNA-guided DNA binding agent to a target sequence located in an another gene, thereby reducing or eliminating expression of the other gene, and an RNA-guided DNA binding agent or a nucleic acid encoding an RNA-guided DNA binding agent. In some embodiments, the additional target gene is TRAC. In some embodiments, the additional target gene is TRBC.

E. Exemplary Cell Types

[00241] In some embodiments, methods and compositions disclosed herein genetically modify a human cell. In some embodiments, the cell is an allogeneic cell. In some embodiments the genetically modified cell is referred to as an engineered cell. An engineered cell refers to a cell (or progeny of a cell) comprising an engineered genetic modification, *e.g.* that has been contacted with a gene editing system and genetically modified by the gene editing system. The terms "engineered cell" and "genetically modified cell" are used interchangeably throughout. The engineered human cell may be any of the exemplary cell types disclosed herein. Further, because MHC class I molecules are expressed on all nucleated cells, the engineered human cell may be any nucleated cell.

[00242] In some embodiments, when the cell is homozygous for HLA-B, 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.

[00243] In some embodiments, when the cell is homozygous for HLA-C, 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.

[00244] In some embodiments, the cell is homozygous for HLA-B and homozygous for HLA-C and 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.

[00245] In some embodiments, the cell is homozygous for HLA-B and homozygous for HLA-C. In some embodiments, the HLA-B and HLA-C alleles of the engineered human cell 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. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*07:02 and HLA-C*07:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*08:01 and HLA-C*07:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*44:02 and HLA-C*05:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*35:01 and HLA-C*04:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*40:01 and HLA-C*03:04. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*57:01 and HLA-C*06:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*14:02 and HLA-C*08:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*15:01 and HLA-C*03:03. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*13:02 and HLA-C*06:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*44:03 and HLA-C*16:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*38:01 and HLA-C*12:03. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*18:01 and HLA-C*07:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*44:03 and HLA-C*04:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*51:01 and HLA-C*15:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*49:01 and HLA-C*07:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*15:01 and HLA-C*03:04. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*18:01 and HLA-C*12:03. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*27:05 and HLA-C*02:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*35:03 and HLA-C*04:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*18:01 and HLA-C*05:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*52:01 and HLA-C*12:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*51:01 and HLA-C*14:02. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*37:01 and HLA-C*06:02. In some embodiments,

the HLA-B and HLA-C alleles are HLA-B*53:01 and HLA-C*04:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*55:01 and HLA-C*03:03. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*44:02 and HLA-C*07:04. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*44:03 and HLA-C*07:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*35:02 and HLA-C*04:01. In some embodiments, the HLA-B and HLA-C alleles are HLA-B*15:01 and HLA-C*04:01. In some embodiments, the HLA-B and HLA-C alleles are and HLA-B*40:02 and HLA-C*02:02.

[00246] In some embodiments, the cell is an immune cell. As used herein, "immune cell" refers to a cell of the immune system, including *e.g.*, a lymphocyte (*e.g.*, T cell, B cell, natural killer cell ("NK cell", and NKT cell, or iNKT cell)), monocyte, macrophage, mast cell, dendritic cell, or granulocyte (*e.g.*, neutrophil, eosinophil, and basophil). In some embodiments, the cell is a primary immune cell. In some embodiments, the immune system cell may be selected from $CD3^+$, $CD4^+$ and $CD8^+$ T cells, regulatory T cells (Tregs), B cells, NK cells, and dendritic cells (DC). In some embodiments, the immune cell is allogeneic.

[00247] In some embodiments, the cell is a lymphocyte. In some embodiments, the cell is an adaptive immune cell. In some embodiments, the cell is a T cell. In some embodiments, the cell is a B cell. In some embodiments, the cell is a NK cell. In some embodiments, the cell is a macrophage. In some embodiments, the lymphocyte is allogeneic.

[00248] As used herein, a T cell can be defined as a cell that expresses a T cell receptor ("TCR" or "αβ TCR" or "γδ TCR"), however in some embodiments, the TCR of a T cell may be genetically modified to reduce its expression (*e.g.*, by genetic modification to the TRAC or TRBC genes), therefore expression of the protein CD3 may be used as a marker to identify a T cell by standard flow cytometry methods. CD3 is a multi-subunit signaling complex that associates with the TCR. Thus, a T cell may be referred to as CD3+. In some embodiments, a T cell is a cell that expresses a CD3+ marker and either a CD4+ or CD8+ marker. In some embodiments, the T cell is allogeneic.

[00249] In some embodiments, the T cell expresses the glycoprotein CD8 and therefore is CD8+ by standard flow cytometry methods and may be referred to as a "cytotoxic" T cell. In some embodiments, the T cell expresses the glycoprotein CD4 and therefore is CD4+ by standard flow cytometry methods and may be referred to as a "helper" T cell. CD4+ T cells can differentiate into subsets and may be referred to as a Th1 cell, Th2 cell, Th9 cell, Th17 cell, Th22 cell, T regulatory ("Treg") cell, or T follicular helper cells ("Tfh"). Each CD4+ subset releases specific cytokines that can have either proinflammatory or anti-inflammatory

functions, survival or protective functions. A T cell may be isolated from a subject by CD4+ or CD8+ selection methods.

[00250] In some embodiments, the T cell is a memory T cell. In the body, a memory T cell has encountered antigen. A memory T cell can be located in the secondary lymphoid organs (central memory T cells) or in recently infected tissue (effector memory T cells). A memory T cell may be a CD8+ T cell. A memory T cell may be a CD4+ T cell.

[00251] As used herein, a "central memory T cell" can be defined as an antigen-experienced T cell, and for example, may expresses CD62L and CD45RO. A central memory T cell may be detected as CD62L+ and CD45RO+ by Central memory T cells also express CCR7, therefore may be detected as CCR7+ by standard flow cytometry methods.

[00252] As used herein, an "early stem-cell memory T cell" (or "Tscm") can be defined as a T cell that expresses CD27 and CD45RA, and therefore is CD27+ and CD45RA+ by standard flow cytometry methods. A Tscm does not express the CD45 isoform CD45RO, therefore a Tscm will further be CD45RO- if stained for this isoform by standard flow cytometry methods. A CD45RO- CD27+ cell is therefore also an early stem-cell memory T cell. Tscm cells further express CD62L and CCR7, therefore may be detected as CD62L+ and CCR7+ by standard flow cytometry methods. Early stem-cell memory T cells have been shown to correlate with increased persistence and therapeutic efficacy of cell therapy products.

[00253] In some embodiments, the cell is a B cell. As used herein, a "B cell" can be defined as a cell that expresses CD19 and/or CD20, and/or B cell mature antigen ("BCMA"), and therefore a B cell is CD19+, and/or CD20+, and/or BCMA+ by standard flow cytometry methods. A B cell is further negative for CD3 and CD56 by standard flow cytometry methods. The B cell may be a plasma cell. The B cell may be a memory B cell. The B cell may be a naïve B cell. The B cell may be IgM+, or has a class-switched B cell receptor (*e.g.*, IgG+, or IgA+). In some embodiments, the B cell is allogeneic.

[00254] In some embodiments, the cell is a mononuclear cell, such as from bone marrow or peripheral blood. In some embodiments, the cell is a peripheral blood mononuclear cell ("PBMC"). In some embodiments, the cell is a PBMC, *e.g.* a lymphocyte or monocyte. In some embodiments, the cell is a peripheral blood lymphocyte ("PBL"). In some embodiments, the mononuclear cell is allogeneic.

[00255] Cells used in ACT and/or tissue regenerative therapy are included, such as stem cells, progenitor cells, and primary cells. Stem cells, for example, include pluripotent stem cells (PSCs); induced pluripotent stem cells (iPSCs); embryonic stem cells (ESCs);

mesenchymal stem cells (MSCs, *e.g.*, isolated from bone marrow (BM), peripheral blood (PB), placenta, umbilical cord (UC) or adipose); hematopoietic stem cells (HSCs; *e.g.* isolated from BM or UC); neural stem cells (NSCs); tissue specific progenitor stem cells (TSPSCs); and limbal stem cells (LSCs). Progenitor and primary cells include mononuclear cells (MNCs, *e.g.*, isolated from BM or PB); endothelial progenitor cells (EPCs, *e.g.* isolated from BM, PB, and UC); neural progenitor cells (NPCs); and tissue-specific primary cells or cells derived therefrom (TSCs) including chondrocytes, myocytes, and keratinocytes. Cells for organ or tissue transplantations such as islet cells, cardiomyocytes, thyroid cells, thymocytes, neuronal cells, skin cells, and retinal cells are also included.

[00256] In some embodiments, the human cell is isolated from a human subject. In some embodiments, the cell is isolated from human donor PBMCs or leukopaks. In some embodiments, the cell is from a subject with a condition, disorder, or disease. In some embodiments, the cell is from a human donor with Epstein Barr Virus ("EBV").

[00257] In some embodiments, the methods are carried out *ex vivo*. As used herein, "*ex vivo*" refers to an *in vitro* method wherein the cell is capable of being transferred into a subject, *e.g.* as an ACT therapy. In some embodiments, an *ex vivo* method is an *in vitro* method involving an ACT therapy cell or cell population.

[00258] In some embodiments, the cell is from a cell line. In some embodiments, the cell line is derived from a human subject. In some embodiments, the cell line is a lymphoblastoid cell line ("LCL"). The cell may be cryopreserved and thawed. The cell may not have been previously cryopreserved.

[00259] In some embodiments, the cell is from a cell bank. In some embodiments, the cell is genetically modified and then transferred into a cell bank. In some embodiments the cell is removed from a subject, genetically modified *ex vivo*, and transferred into a cell bank. In some embodiments, a genetically modified population of cells is transferred into a cell bank. In some embodiments, a genetically modified population of immune cells is transferred into a cell bank. In some embodiments, a genetically modified population of immune cells comprising a first and second subpopulations, wherein the first and second sub-populations have at least one common genetic modification and at least one different genetic modification are transferred into a cell bank.

F. Exemplary Gene Editing Systems

[00260] Various suitable gene editing systems may be used to make the engineered cells disclosed herein, including but not limited to the CRISPR/Cas system; zinc finger nuclease

(ZFN) system; and the transcription activator-like effector nuclease (TALEN) system. Generally, the gene editing systems involve the use of engineered cleavage systems to induce a double strand break (DSB) or a nick (e.g., a single strand break, or SSB) in a target DNA sequence. Cleavage or nicking can occur through the use of specific nucleases such as engineered ZFN, TALENs, or using the CRISPR/Cas system with an engineered guide RNA to guide specific cleavage or nicking of a target DNA sequence. Further, targeted nucleases are being developed based on the Argonaute system (e.g., from T. thermophilus, known as 'TtAgo', see Swarts et al (2014) Nature 507(7491): 258-261), which also may have the potential for uses in gene editing and gene therapy.

[00261] In some embodiments, the gene editing system is a TALEN system. Transcription activator-like effector nucleases (TALEN) are restriction enzymes that can be engineered to cut specific sequences of DNA. They are made by fusing a TAL effector DNA-binding domain to a DNA cleavage domain (a nuclease which cuts DNA strands). Transcription activator-like effectors (TALEs) can be engineered to bind to a desired DNA sequence, to promote DNA cleavage at specific locations (see, e.g., Boch, 2011, Nature Biotech). The restriction enzymes can be introduced into cells, for use in gene editing or for gene editing in situ, a technique known as gene editing with engineered nucleases. Such methods and compositions for use therein are known in the art. See, e.g., WO2019147805, WO2014040370, WO2018073393, the contents of which are hereby incorporated in their entireties.

[00262] In some embodiments, the gene editing system is a zinc-finger system. Zinc-finger nucleases (ZFNs) are artificial restriction enzymes generated by fusing a zinc finger DNA-binding domain to a DNA-cleavage domain. Zinc finger domains can be engineered to target specific desired DNA sequences to enables zinc-finger nucleases to target unique sequences within complex genomes. The non-specific cleavage domain from the type IIs restriction endonuclease FokI is typically used as the cleavage domain in ZFNs. Cleavage is repaired by endogenous DNA repair machinery, allowing ZFN to precisely alter the genomes of higher organisms. Such methods and compositions for use therein are known in the art. See, e.g., WO2011091324, the contents of which are hereby incorporated in their entireties.

[00263] In some embodiments, the gene editing system is a CRISPR/Cas system, including e.g., a CRISPR guide RNA comprising a guide sequence and RNA-guided DNA binding agent, and described further herein.

G. CRISPR Guide RNA

[00264] Provided herein are guide sequences useful for modifying a target sequence, *e.g.*, using a guide RNA comprising a disclosed guide sequence with an RNA-guided DNA binding agent (*e.g.*, a CRISPR/Cas system).

[00265] Each of the guide sequences disclosed herein may further comprise additional nucleotides to form a crRNA, e.g., with the following exemplary nucleotide sequence following the guide sequence at its 3' end: GUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 213) in 5' to 3' orientation. In the case of a sgRNA, the above guide sequences may further comprise additional nucleotides (scaffold sequence) to form a sgRNA, e.g., with the following exemplary nucleotide sequence following the 3' end of the guide sequence: GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUU GAAAAAGUGGCACCGAGUCGGUGCUUUU (SEQ ID NO: 214) or GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUU GAAAAAGUGGCACCGAGUCGGUGC (SEQ ID NO: 215, which is SEQ ID NO: 214 without the four terminal U's) in 5' to 3' orientation. In some embodiments, the four terminal U's of SEQ ID NO: 214 are not present. In some embodiments, only 1, 2, or 3 of the four terminal U's of SEQ ID NO: 214 are present.

[00266] In some embodiments, the sgRNA comprises any one of the guide sequences of SEQ ID Nos: 1-211 and additional nucleotides to form a crRNA, e.g., with the following exemplary scaffold nucleotide sequence following the guide sequence at its 3' end: GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUU GGCACCGAGUCGGUGC (SEQ ID NO: 216) in 5' to 3' orientation. SEQ ID NO: 216 lacks 8 nucleotides with reference to a wild-type guide RNA conserved sequence: GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUU GAAAAAGUGGCACCGAGUCGGUGC (SEQ ID NO: 215). Other exemplary scaffold nucleotide sequences are provided in Table 6. In some embodiments, the sgRNA comprises any one of the guide sequences of SEQ ID NOs: 1-211 and additional guide scaffold sequences, in 5' to 3' orientation, in Table 6, including modified versions of the scaffold sequences, as shown.

[00267] In some embodiments, the guide RNA is a sgRNA comprising any one of the sequences shown in **Table 2** (SEQ ID NOs: 249-343 and 344-438), **Table 3** (SEQ ID NOs: 439-471 and 472-504), and **Table 5** (SEQ ID NOs: 505-532 and 533-560). In some embodiments, the guide RNA is a chemically modified guide RNA. In some embodiments,

the guide RNA is a chemically modified single guide RNA. The chemically modified guide RNAs may comprise one or more of the modifications as shown in **Tables 2, 3, 5, and 6**. The chemically modified guide RNAs may comprise one or more of modified nucleotides of any one of SEQ ID NOs: 1003, 1007-1009 and 1011-1014.

[00268] In some embodiments, the guide RNA is a sgRNA comprising any one of SEQ ID NOs: 249-343, 439-471, and 505-532 with at least one chemical modification disclosed herein. In some embodiments, the guide RNA is a sgRNA comprising a sequence that is at least 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, or 90% identical to any one of SEQ ID NOs: 249-343, 439-471, and 505-532 with at least one chemical modification disclosed herein.

[00269] In some embodiments, the guide RNA is a sgRNA comprising the modification pattern shown in SEQ ID NO: 1013 or 1014. In some embodiments, the guide RNA is a sgRNA comprising a sequence that is at least 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, or 90% identical to any of the nucleic acids of SEQ ID NOs: 344-438, 472-504, and 533-560.

[00270] In some embodiments, the guide RNA comprises a sgRNA comprising the modification pattern shown in SEQ ID NO: 1003. In some embodiments, the guide RNA comprises a sgRNA comprising the modified nucleotides of SEQ ID NO: 1003, including a guide sequence comprises a sequence selected from SEQ ID NOs: 1-211. In some embodiments, the guide RNA is a sgRNA comprising a sequence of SEQ ID NO: 1016 or a sequence that is at least 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, or 90% identical to SEQ ID NO: 1016.

[00271] In some embodiments, the guide RNA comprises a single guide RNA comprising any one of the sequences of SEQ ID NOs: 344-438, 472-504, and 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.

[00272] In some embodiments, the guide RNA comprises a guide sequence comprising any one of SEQ ID NOs: 13-18, 26, 37-39, 41, 43, 45, and 62. In some embodiments, the guide RNA comprises a single guide RNA comprising any one of the sequences 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 SEQ ID NOs: 356-361, 369, 380-382, 384, 386, 388, and 405.

[00273] The guide RNA may further comprise a trRNA. In each composition and method embodiment described herein, the crRNA and trRNA may be associated as a single RNA

(sgRNA) or may be on separate RNAs (dgRNA). In the context of sgRNAs, the crRNA and trRNA components may be covalently linked, e.g., via a phosphodiester bond or other covalent bond. In some embodiments, a crRNA and/or trRNA sequence may be referred to as a "scaffold" or "conserved portion" of a guide RNA.

[00274] In each of the compositions, use, and method embodiments described herein, the guide RNA may comprise two RNA molecules as a "dual guide RNA" or "dgRNA." The dgRNA comprises a first RNA molecule comprising a crRNA comprising, *e.g.*, a guide sequence shown in **Tables 2-5**, and a second RNA molecule comprising a trRNA. The first and second RNA molecules may not be covalently linked, but may form an RNA duplex via the base pairing between portions of the crRNA and the trRNA.

[00275] In each of the composition, use, and method embodiments described herein, the guide RNA may comprise a single RNA molecule as a "single guide RNA" or "sgRNA". The sgRNA may comprise a crRNA (or a portion thereof) comprising a guide sequence shown in **Tables 2- 5**, covalently linked to a trRNA. The sgRNA may comprise 17, 18, 19, or 20 contiguous nucleotides of a guide sequence shown in **Tables 2-5**. In some embodiments, the crRNA and the trRNA are covalently linked via a linker. In some embodiments, the sgRNA forms a stem-loop structure via the base pairing between portions of the crRNA and the trRNA. In some embodiments, the crRNA and the trRNA are covalently linked via one or more bonds that are not a phosphodiester bond.

[00276] In some embodiments, the trRNA may comprise all or a portion of a trRNA sequence derived from a naturally-occurring CRISPR/Cas system. In some embodiments, the trRNA comprises a truncated or modified wild type trRNA. The length of the trRNA depends on the CRISPR/Cas system used. In some embodiments, the trRNA comprises or consists of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or more than 100 nucleotides. In some embodiments, the trRNA may comprise certain secondary structures, such as, for example, one or more hairpin or stem-loop structures, or one or more bulge structures.

[00277] In some embodiments, a composition comprising one or more guide RNAs comprising a guide sequence of any one in **Tables 2-5** is provided. In some embodiments, a composition comprising one or more guide RNAs comprising a guide sequence of any one in **Tables 2-5** is provided, wherein the nucleotides of SEQ ID NO: 213-216 follow the guide sequence at its 3' end. In some embodiments, the one or more guide RNAs comprising a guide sequence of any one in **Tables 2-5**, wherein the nucleotides of SEQ ID NO: 213-216

follow the guide sequence at its 3' end, is modified according to the modification pattern of any one of SEQ ID NOs: 1003, 1007-1009, and 1011-1014.

[00278] In some embodiments, a composition comprising one or more guide RNAs comprising a guide sequence of any one in **Tables 2-5** is provided. In one aspect, a composition comprising one or more gRNAs is provided, comprising a guide sequence that is at least 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, or 90% identical to any of the nucleic acids of SEQ ID NOs: 1-211.

[00279] In other embodiments, a composition is provided that comprises at least one, e.g., at least two gRNA's comprising guide sequences selected from any two or more of the guide sequences shown in **Tables 2-5**. In some embodiments, the composition comprises at least two gRNA's that each comprise a guide sequence at least 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, or 90% identical to any of the guide sequences shown in **Tables 2-5**.

[00280] In some embodiments, the guide RNA compositions of the present invention are designed to recognize (*e.g.*, hybridize to) a target sequence in HLA-A. For example, the HLA-A target sequence may be recognized and cleaved by a provided Cas cleavase comprising a guide RNA. In some embodiments, an RNA-guided DNA binding agent, such as a Cas cleavase, may be directed by a guide RNA to a target sequence in HLA-A, where the guide sequence of the guide RNA hybridizes with the target sequence and the RNA-guided DNA binding agent, such as a Cas cleavase, cleaves the target sequence.

[00281] In some embodiments, the selection of the one or more guide RNAs is determined based on target sequences within HLA-A. In some embodiments, the compositions comprising one or more guide sequences comprise a guide sequence that is complementary to the corresponding genomic region shown in **Tables 2-5**, according to coordinates from human reference genome hg38. Guide sequences of further embodiments may be complementary to sequences in the close vicinity of the genomic coordinate listed in any of the **Tables 2-5** within HLA-A. For example, guide sequences of further embodiments may be complementary to sequences that comprise 10 contiguous nucleotides ± 10 nucleotides of a genomic coordinate listed in **Tables 2-5**.

[00282] Without being bound by any particular theory, modifications (e.g., frameshift mutations resulting from indels occurring as a result of a nuclease-mediated DSB) in certain regions of the target gene may be less tolerable than mutations in other regions, thus the location of a DSB is an important factor in the amount or type of protein knockdown that may result. In some embodiments, a gRNA complementary or having complementarity to a

target sequence within the target gene used to direct an RNA-guided DNA binding agent to a particular location in the target gene.

[00283] In some embodiments, the guide sequence is at least 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, or 80% identical to a target sequence present in the target gene. In some embodiments, the guide sequence is at least 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, or 80% identical to a target sequence present in the human *HLA-A* gene.

[00284] In some embodiments, the target sequence may be complementary to the guide sequence of the guide RNA. In some embodiments, the degree of complementarity or identity between a guide sequence of a guide RNA and its corresponding target sequence may be at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, the target sequence and the guide sequence of the gRNA may be 100% complementary or identical. In other embodiments, the target sequence and the guide sequence of the gRNA may contain at least one mismatch. For example, the target sequence and the guide sequence of the gRNA may contain 1, 2, 3, or 4 mismatches, where the total length of the guide sequence is 20. In some embodiments, the target sequence and the guide sequence of the gRNA may contain 1-4 mismatches where the guide sequence is 20 nucleotides.

[00285] In some embodiments, a composition or formulation disclosed herein comprises an mRNA comprising an open reading frame (ORF) encoding an RNA-guided DNA binding agent, such as a Cas nuclease as described herein. In some embodiments, an mRNA comprising an ORF encoding an RNA-guided DNA binding agent, such as a Cas nuclease, is provided, used, or administered.

H. Modified gRNAs and mRNAs

[00286] In some embodiments, the gRNA (e.g., sgRNA, short-sgRNA, dgRNA, or crRNA) is modified. The term "modified" or "modification" in the context of a gRNA described herein includes, the modifications described above, including, for example, (a) end modifications, e.g., 5′ end modifications or 3′ end modifications, including 5' or 3' protective end modifications, (b) nucleobase (or "base") modifications, including replacement or removal of bases, (c) sugar modifications, including modifications at the 2′, 3′, and/or 4′ positions, (d) internucleoside linkage modifications, and (e) backbone modifications, which can include modification or replacement of the phosphodiester linkages and/or the ribose sugar. A modification of a nucleotide at a given position includes a modification or replacement of the phosphodiester linkage immediately 3' of the sugar of the nucleotide.

Thus, for example, a nucleic acid comprising a phosphorothioate between the first and second sugars from the 5' end is considered to comprise a modification at position 1. The term "modified gRNA" generally refers to a gRNA having a modification to the chemical structure of one or more of the base, the sugar, and the phosphodiester linkage or backbone portions, including nucleotide phosphates, all as detailed and exemplified herein.

[00287] Further description and exemplary patterns of modifications are provided in Table 1 of WO2019/237069 published December 12, 2019, the entire contents of which are incorporated herein by reference.

[00288] In some embodiments, a gRNA comprises modifications at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or more YA sites. In some embodiments, the pyrimidine of the YA site comprises a modification (which includes a modification altering the internucleoside linkage immediately 3' of the sugar of the pyrimidine). In some embodiments, the adenine of the YA site comprises a modification (which includes a modification altering the internucleoside linkage immediately 3' of the sugar of the adenine). In some embodiments, the pyrimidine and the adenine of the YA site comprise modifications, such as sugar, base, or internucleoside linkage modifications. The YA modifications can be any of the types of modifications set forth herein. In some embodiments, the YA modifications comprise one or more of phosphorothioate, 2'-OMe, or 2'-fluoro. In some embodiments, the YA modifications comprise pyrimidine modifications comprising one or more of phosphorothioate, 2'-OMe, 2'-H, inosine, or 2'-fluoro. In some embodiments, the YA modification comprises a bicyclic ribose analog (e.g., an LNA, BNA, or ENA) within an RNA duplex region that contains one or more YA sites. In some embodiments, the YA modification comprises a bicyclic ribose analog (e.g., an LNA, BNA, or ENA) within an RNA duplex region that contains a YA site, wherein the YA modification is distal to the YA site.

[00289] In some embodiments, the guide sequence (or guide region) of a gRNA comprises 1, 2, 3, 4, 5, or more YA sites ("guide region YA sites") that may comprise YA modifications. In some embodiments, one or more YA sites located at 5-end, 6-end, 7-end, 8-end, 9-end, or 10-end from the 5' end of the 5' terminus (where "5-end", etc., refers to position 5 to the 3' end of the guide region, i.e., the most 3' nucleotide in the guide region) comprise YA modifications.. A modified guide region YA site comprises a YA modification.

[00290] In some embodiments, a modified guide region YA site is within 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, or 9 nucleotides of the 3' terminal nucleotide of the guide region. For example, if a modified guide region YA site is within 10 nucleotides of the 3' terminal

nucleotide of the guide region and the guide region is 20 nucleotides long, then the modified nucleotide of the modified guide region YA site is located at any of positions 11-20. In some embodiments, a modified guide region YA site is at or after nucleotide 4, 5, 6, 7, 8, 9, 10, or 11 from the 5' end of the 5' terminus.

[00291] In some embodiments, a modified guide region YA site is other than a 5' end modification. For example, a sgRNA can comprise a 5' end modification as described herein and further comprise a modified guide region YA site. Alternatively, a sgRNA can comprise an unmodified 5' end and a modified guide region YA site. Alternatively, a short-sgRNA can comprise a modified 5' end and an unmodified guide region YA site.

[00292] In some embodiments, a modified guide region YA site comprises a modification that at least one nucleotide located 5' of the guide region YA site does not comprise. For example, if nucleotides 1-3 comprise phosphorothioates, nucleotide 4 comprises only a 2'-OMe modification, and nucleotide 5 is the pyrimidine of a YA site and comprises a phosphorothioate, then the modified guide region YA site comprises a modification (phosphorothioate) that at least one nucleotide located 5' of the guide region YA site (nucleotide 4) does not comprise. In another example, if nucleotides 1-3 comprise phosphorothioates, and nucleotide 4 is the pyrimidine of a YA site and comprises a 2'-OMe, then the modified guide region YA site comprises a modification (2'-OMe) that at least one nucleotide located 5' of the guide region YA site (any of nucleotides 1-3) does not comprise. This condition is also always satisfied if an unmodified nucleotide is located 5' of the modified guide region YA site.

[00293] In some embodiments, the modified guide region YA sites comprise modifications as described for YA sites above. The guide region of a gRNA may be modified according to any embodiment comprising a modified guide region set forth herein. Any embodiments set forth elsewhere in this disclosure may be combined to the extent feasible with any of the foregoing embodiments.

[00294] In some embodiments, the 5' and/or 3' terminus regions of a gRNA are modified.

[00295] In some embodiments, the terminal (i.e., last) 1, 2, 3, 4, 5, 6, or 7 nucleotides in the 3' terminus region are modified. Throughout, this modification may be referred to as a "3' end modification". In some embodiments, the terminal (i.e., last) 1, 2, 3, 4, 5, 6, or 7 nucleotides in the 3' terminus region comprise more than one modification. In some embodiments, the 3' end modification comprises or further comprises any one or more of the following: a modified nucleotide selected from 2'-O-methyl (2'-O-Me) modified nucleotide, 2'-O-(2-methoxyethyl) (2'-O-moe) modified nucleotide, a 2'-fluoro (2'-F) modified

nucleotide, a phosphorothioate (PS) linkage between nucleotides, an inverted abasic modified nucleotide, or combinations thereof. In some embodiments, the 3' end modification comprises or further comprises modifications of 1, 2, 3, 4, 5, 6, or 7 nucleotides at the 3' end of the gRNA. In some embodiments, the 3' end modification comprises or further comprises one PS linkage, wherein the linkage is between the last and second to last nucleotide. In some embodiments, the 3' end modification comprises or further comprises two PS linkages between the last three nucleotides. In some embodiments, the 3' end modification comprises or further comprises four PS linkages between the last four nucleotides. In some embodiments, the 3' end modification comprises or further comprises PS linkages between any one or more of the last 2, 3, 4, 5, 6, or 7 nucleotides. In some embodiments, the gRNA comprising a 3' end modification comprises or further comprises a 3' tail, wherein the 3' tail comprises a modification of any one or more of the nucleotides present in the 3' tail. In some embodiments, the 3' tail is fully modified. In some embodiments, the 3' tail comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, or 1-10 nucleotides, optionally where any one or more of these nucleotides are modified. In some embodiments, a gRNA is provided comprising a 3' protective end modification. In some embodiments, the 3' tail comprises between 1 and about 20 nucleotides, between 1 and about 15 nucleotides, between 1 and about 10 nucleotides, between 1 and about 5 nucleotides, between 1 and about 4 nucleotides, between 1 and about 3 nucleotides, and between 1 and about 2 nucleotides. In some embodiments, the gRNA does not comprise a 3' tail.

[00296] In some embodiments, the 5' terminus region is modified, for example, the first 1, 2, 3, 4, 5, 6, or 7 nucleotides of the gRNA are modified. Throughout, this modification may be referred to as a "5' end modification". In some embodiments, the first 1, 2, 3, 4, 5, 6, or 7 nucleotides of the 5' terminus region comprise more than one modification. In some embodiments, at least one of the terminal (i.e., first) 1, 2, 3, 4, 5, 6, or 7 nucleotides at the 5' end are modified. In some embodiments, both the 5' and 3' terminus regions (e.g., ends) of the gRNA are modified. In some embodiments, only the 5' terminus region of the gRNA is modified. In some embodiments, only the 3' terminus region (plus or minus a 3' tail) of the conserved portion of a gRNA is modified. In some embodiments, the gRNA comprises modifications at 1, 2, 3, 4, 5, 6, or 7 of the first 7 nucleotides at a 5' terminus region of the gRNA. In some embodiments, the gRNA comprises modifications at 1, 2, 3, 4, 5, 6, or 7 of the 7 terminal nucleotides at a 3' terminus region. In some embodiments, 2, 3, or 4 of the first 4 nucleotides at the 5' terminus region, and/or 2, 3, or 4 of the terminal 4 nucleotides at the 3' terminus region are modified. In some embodiments, 2, 3, or 4 of the first 4 nucleotides

at the 5' terminus region are linked with phosphorothioate (PS) bonds. In some embodiments, the modification to the 5' terminus and/or 3' terminus comprises a 2'-O-methyl (2'-O-Me) or 2'-O-(2-methoxyethyl) (2'-O-moe) modification. In some embodiments, the modification comprises a 2'-fluoro (2'-F) modification to a nucleotide. In some embodiments, the modification comprises a phosphorothioate (PS) linkage between nucleotides. In some embodiments, the modification comprises an inverted abasic nucleotide. In some embodiments, the modification comprises a protective end modification. In some embodiments, the modification comprises a more than one modification selected from protective end modification, 2'-O-Me, 2'-O-moe, 2'-fluoro (2'-F), a phosphorothioate (PS) linkage between nucleotides, and an inverted abasic nucleotide. In some embodiments, an equivalent modification is encompassed.

[00297] In some embodiments, a gRNA is provided comprising a 5' end modification and a 3' end modification. In some embodiments, the gRNA comprises modified nucleotides that are not at the 5' or 3' ends.

[00298] In some embodiments, a sgRNA is provided comprising an upper stem modification, wherein the upper stem modification comprises a modification to any one or more of US1-US12 in the upper stem region. In some embodiments, a sgRNA is provided comprising an upper stem modification, wherein the upper stem modification comprises a modification of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or all 12 nucleotides in the upper stem region. In some embodiments, an sgRNA is provided comprising an upper stem modification, wherein the upper stem modification comprises 1, 2, 3, 4, or 5 YA modifications in a YA site. In some embodiments, the upper stem modification comprises a 2'-OMe modified nucleotide, a 2'-O-moe modified nucleotide, a 2'-F modified nucleotide, and/or combinations thereof. Other modifications described herein, such as a 5' end modification and/or a 3' end modification may be combined with an upper stem modification.

[00299] In some embodiments, the sgRNA comprises a modification in the hairpin region. In some embodiments, the hairpin region modification comprises at least one modified nucleotide selected from a 2'-O-methyl (2'-OMe) modified nucleotide, a 2'-fluoro (2'-F) modified nucleotide, and/or combinations thereof. In some embodiments, the hairpin region modification is in the hairpin 1 region. In some embodiments, the hairpin region modification is in the hairpin 2 region. In some embodiments, the hairpin modification comprises 1, 2, or 3 YA modifications in a YA site. In some embodiments, the hairpin modification comprises at least 1, 2, 3, 4, 5, or 6 YA modifications. Other modifications described herein, such as an

upper stem modification, a 5' end modification, and/or a 3' end modification may be combined with a modification in the hairpin region.

[00300] In some embodiments, a gRNA comprises a substituted and optionally shortened hairpin 1 region, wherein at least one of the following pairs of nucleotides are substituted in the substituted and optionally shortened hairpin 1 with Watson-Crick pairing nucleotides: H1-1 and H1-12, H1-2 and H1-11, H1-3 and H1-10, and/or H1-4 and H1-9. "Watson-Crick pairing nucleotides" include any pair capable of forming a Watson-Crick base pair, including A-T, A-U, T-A, U-A, C-G, and G-C pairs, and pairs including modified versions of any of the foregoing nucleotides that have the same base pairing preference. In some embodiments, the hairpin 1 region lacks any one or two of H1-5 through H1-8. In some embodiments, the hairpin 1 region lacks one, two, or three of the following pairs of nucleotides: H1-1 and H1-12, H1-2 and H1-11, H1-3 and H1-10 and/or H1-4 and H1-9. In some embodiments, the hairpin 1 region lacks 1-8 nucleotides of the hairpin 1 region. In any of the foregoing embodiments, the lacking nucleotides may be such that the one or more nucleotide pairs substituted with Watson-Crick pairing nucleotides (H1-1 and H1-12, H1-2 and H1-11, H1-3 and H1-10, and/or H1-4 and H1-9) form a base pair in the gRNA.

[00301] In some embodiments, the gRNA further comprises an upper stem region lacking at least 1 nucleotide, e.g., any of the shortened upper stem regions indicated in Table 7 of U.S. Application No. 62/946,905, the contents of which are hereby incorporated by reference in its entirety, or described elsewhere herein, which may be combined with any of the shortened or substituted hairpin 1 regions described herein.

[00302] In some embodiments, an sgRNA provided herein is a short-single guide RNAs (short-sgRNAs), *e.g.*, comprising a conserved portion of an sgRNA comprising a hairpin region, wherein the hairpin region lacks at least 5-10 nucleotides or 6-10 nucleotides. In some embodiments, the 5-10 nucleotides or 6-10 nucleotides are consecutive.

[00303] In some embodiments, a short-sgRNA lacks at least nucleotides 54-58 (AAAAA) of the conserved portion of a spyCas9 sgRNA. In some embodiments, a short-sgRNA is a non-spyCas9 sgRNA that lacks nucleotides corresponding to nucleotides 54-58 (AAAAA) of the conserved portion of a spyCas9 as determined, for example, by pairwise or structural alignment.

[00304] In some embodiments, the short-sgRNA described herein comprises a conserved portion comprising a hairpin region, wherein the hairpin region lacks 5, 6, 7, 8, 9, 10, 11, or 12 nucleotides. In some embodiments, the lacking nucleotides are 5-10 lacking nucleotides or 6-10 lacking nucleotides. In some embodiments, the lacking nucleotides are consecutive. In

some embodiments, the lacking nucleotides span at least a portion of hairpin 1 and a portion of hairpin 2. In some embodiments, the 5-10 lacking nucleotides comprise or consist of nucleotides 54-58, 54-61, or 53-60 of SEQ ID NO: 215.

[00305] In some embodiments, the short-sgRNA described herein further comprises a nexus region, wherein the nexus region lacks at least one nucleotide (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in the nexus region). In some embodiments, the short-sgRNA lacks each nucleotide in the nexus region.

[00306] In some embodiments, the SpyCas9 short-sgRNA described herein comprises a sequence of NNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGUGCU (SEQ ID NO: 1002).

[00307] In some embodiments, the short-sgRNA described herein comprises a modification pattern as shown in SEQ ID NO: 1003: mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmUmGmC*mU (SEQ ID NO: 1003), where A, C, G, U, and N are adenine, cytosine, guanine, uracil, and any ribonucleotide, respectively, unless otherwise indicated. An m is indicative of a 2'O-methyl modification, and an * is indicative of a phosphorothioate linkage between the nucleotides.

[00308] In certain embodiments, using SEQ ID NO: 215 ("Exemplary SpyCas9 sgRNA-1") as an example, the Exemplary SpyCas9 sgRNA-1 further includes one or more of:

A. a shortened hairpin 1 region, or a substituted and optionally shortened hairpin 1 region, wherein

1. at least one of the following pairs of nucleotides are substituted in hairpin 1 with Watson-Crick pairing nucleotides: H1-1 and H1-12, H1-2 and H1-11, H1-3 and H1-10, or H1-4 and H1-9, and the hairpin 1 region optionally lacks
    a. any one or two of H1-5 through H1-8,
    b. one, two, or three of the following pairs of nucleotides: H1-1 and H1-12, H1-2 and H1-11, H1-3 and H1-10, and H1-4 and H1-9, or
    c. 1-8 nucleotides of hairpin 1 region; or
2. the shortened hairpin 1 region lacks 6-8 nucleotides, preferably 6 nucleotides; and

a. one or more of positions H1-1, H1-2, or H1-3 is deleted or substituted relative to Exemplary SpyCas9 sgRNA-1 (SEQ ID NO: 215) or

b. one or more of positions H1-6 through H1-10 is substituted relative to Exemplary SpyCas9 sgRNA-1 (SEQ ID NO: 215); or

3. the shortened hairpin 1 region lacks 5-10 nucleotides, preferably 5-6 nucleotides, and one or more of positions N18, H1-12, or n is substituted relative to Exemplary SpyCas9 sgRNA-1 (SEQ ID NO: 215); or

B. a shortened upper stem region, wherein the shortened upper stem region lacks 1-6 nucleotides and wherein the 6, 7, 8, 9, 10, or 11 nucleotides of the shortened upper stem region include less than or equal to 4 substitutions relative to Exemplary SpyCas9 sgRNA-1 (SEQ ID NO: 215); or

C. a substitution relative to Exemplary SpyCas9 sgRNA-1 (SEQ ID NO: 215) at any one or more of LS6, LS7, US3, US10, B3, N7, N15, N17, H2-2 and H2-14, wherein the substituent nucleotide is neither a pyrimidine that is followed by an adenine, nor an adenine that is preceded by a pyrimidine; or

D. Exemplary SpyCas9 sgRNA-1 (SEQ ID NO: 215) with an upper stem region, wherein the upper stem modification comprises a modification to any one or more of US1-US12 in the upper stem region, wherein

1. the modified nucleotide is optionally selected from a 2’-O-methyl (2’-OMe) modified nucleotide, a 2’-O-(2-methoxyethyl) (2’-O-moe) modified nucleotide, a 2’-fluoro (2’-F) modified nucleotide, a phosphorothioate (PS) linkage between nucleotides, an inverted abasic modified nucleotide, or a combination thereof; or

2. the modified nucleotide optionally includes a 2’-OMe modified nucleotide.

[00309] In certain embodiments, Exemplary SpyCas9 sgRNA-1, or an sgRNA, such as an sgRNA comprising Exemplary SpyCas9 sgRNA-1, further includes a 3’ tail, e.g., a 3’ tail of 1, 2, 3, 4, or more nucleotides. In certain embodiments, the tail includes one or more modified nucleotides. In certain embodiments, the modified nucleotide is selected from a 2’-O-methyl (2’-OMe) modified nucleotide, a 2’-O-(2-methoxyethyl) (2’-O-moe) modified nucleotide, a 2’-fluoro (2’-F) modified nucleotide, a phosphorothioate (PS) linkage between nucleotides, and an inverted abasic modified nucleotide, or a combination thereof. In certain

embodiments, the modified nucleotide includes a 2'-OMe modified nucleotide. In certain embodiments, the modified nucleotide includes a PS linkage between nucleotides. In certain embodiments, the modified nucleotide includes a 2'-OMe modified nucleotide and a PS linkage between nucleotides.

[00310] In some embodiments, the gRNA described herein further comprises a nexus region, wherein the nexus region lacks at least one nucleotide.

[00311] In some embodiments, the gRNA is chemically modified. A gRNA comprising one or more modified nucleosides or nucleotides is called a "modified" gRNA or "chemically modified" gRNA, to describe the presence of one or more non-naturally and/or naturally occurring components or configurations that are used instead of or in addition to the canonical A, G, C, and U residues. Modified nucleosides and nucleotides can include one or more of: (i) alteration, *e.g.*, replacement, of one or both of the non-linking phosphate oxygens and/or of one or more of the linking phosphate oxygens in the phosphodiester backbone linkage (an exemplary backbone modification); (ii) alteration, *e.g.*, replacement, of a constituent of the ribose sugar, *e.g.*, of the 2' hydroxyl on the ribose sugar (an exemplary sugar modification); (iii) wholesale replacement of the phosphate moiety with "dephospho" linkers (an exemplary backbone modification); (iv) modification or replacement of a naturally occurring nucleobase, including with a non-canonical nucleobase (an exemplary base modification); (v) replacement or modification of the ribose-phosphate backbone (an exemplary backbone modification); (vi) modification of the 3' end or 5' end of the oligonucleotide, *e.g.*, removal, modification or replacement of a terminal phosphate group or conjugation of a moiety, cap or linker (such 3' or 5' cap modifications may comprise a sugar and/or backbone modification); and (vii) modification or replacement of the sugar (an exemplary sugar modification).

[00312] Chemical modifications such as those listed above can be combined to provide modified gRNAs comprising nucleosides and nucleotides (collectively "residues") that can have two, three, four, or more modifications. For example, a modified residue can have a modified sugar and a modified nucleobase. In some embodiments, every base of a gRNA is modified, *e.g.*, all bases have a modified phosphate group, such as a phosphorothioate group. In certain embodiments, all, or substantially all, of the phosphate groups of an gRNA molecule are replaced with phosphorothioate groups. In some embodiments, modified gRNAs comprise at least one modified residue at or near the 5' end of the RNA. In some embodiments, modified gRNAs comprise at least one modified residue at or near the 3' end of the RNA.

[00313] In some embodiments, the gRNA comprises one, two, three or more modified residues. In some embodiments, at least 5% (*e.g.*, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or 100%) of the positions in a modified gRNA are modified nucleosides or nucleotides.

[00314] In some embodiments of a backbone modification, the phosphate group of a modified residue can be modified by replacing one or more of the oxygens with a different substituent. Further, the modified residue, *e.g.*, modified residue present in a modified nucleic acid, can include the wholesale replacement of an unmodified phosphate moiety with a modified phosphate group as described herein. In some embodiments, the backbone modification of the phosphate backbone can include alterations that result in either an uncharged linker or a charged linker with unsymmetrical charge distribution.

[00315] Examples of modified phosphate groups include phosphorothioate, phosphoroselenates, borano phosphates, borano phosphate esters, hydrogen phosphonates, phosphoroamidates, alkyl or aryl phosphonates and phosphotriesters.

[00316] Scaffolds that can mimic nucleic acids can also be constructed wherein the phosphate linker and ribose sugar are replaced by nuclease resistant nucleoside or nucleotide surrogates. Such modifications may comprise backbone and sugar modifications. In some embodiments, the nucleobases can be tethered by a surrogate backbone. Examples can include, without limitation, the morpholino, cyclobutyl, pyrrolidine and peptide nucleic acid (PNA) nucleoside surrogates.

[00317] The modified nucleosides and modified nucleotides can include one or more modifications to the sugar group, *i.e.* at sugar modification. For example, the 2' hydroxyl group (OH) can be modified, *e.g.* replaced with a number of different "oxy" or "deoxy" substituents. In some embodiments, modifications to the 2' hydroxyl group can enhance the stability of the nucleic acid since the hydroxyl can no longer be deprotonated to form a 2'-alkoxide ion. Examples of 2' hydroxyl group modifications can include alkoxy or aryloxy (OR, wherein "R" can be, *e.g.*, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or a sugar); polyethyleneglycols (PEG), $O(CH_2CH_2O)_nCH_2CH_2OR$ wherein R can be, *e.g.*, H or optionally substituted alkyl, and n can be an integer from 0 to 20. In some embodiments, the 2' hydroxyl group modification can be 2'-O-Me. In some embodiments, the 2' hydroxyl group modification can be a 2'-fluoro modification, which replaces the 2' hydroxyl group with a fluoride. In some embodiments, the 2' hydroxyl group modification can include

"locked" nucleic acids (LNA) in which the 2' hydroxyl can be connected, *e.g.*, by a C_{1-6} alkylene or C_{1-6} heteroalkylene bridge, to the 4' carbon of the same ribose sugar, where exemplary bridges can include methylene, propylene, ether, or amino bridges. In some embodiments, the 2' hydroxyl group modification can included "unlocked" nucleic acids (UNA) in which the ribose ring lacks the C2'-C3' bond. In some embodiments, the 2' hydroxyl group modification can include the methoxyethyl group (MOE), ($OCH_2CH_2OCH_3$, *e.g.*, a PEG derivative).

[00318] "Deoxy" 2' modifications can include hydrogen (*i.e.* deoxyribose sugars, *e.g.*, at the overhang portions of partially dsRNA); halo (*e.g.*, bromo, chloro, fluoro, or iodo); amino (wherein amino can be, *e.g.*, NH_2; alkylamino, dialkylamino, heterocyclyl, arylamino, diarylamino, heteroarylamino, diheteroarylamino, or amino acid); $NH(CH_2CH_2NH)_nCH2CH_2$- amino (wherein amino can be, *e.g.*, as described herein), -NHC(O)R (wherein R can be, *e.g.*, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar), cyano; mercapto; alkyl-thio-alkyl; thioalkoxy; and alkyl, cycloalkyl, aryl, alkenyl and alkynyl, which may be optionally substituted with *e.g.*, an amino as described herein.

[00319] The sugar modification can comprise a sugar group which may also contain one or more carbons that possess the opposite stereochemical configuration than that of the corresponding carbon in ribose. Thus, a modified nucleic acid can include nucleotides containing *e.g.*, arabinose, as the sugar. The modified nucleic acids can also include abasic sugars. These abasic sugars can also be further modified at one or more of the constituent sugar atoms. The modified nucleic acids can also include one or more sugars that are in the L form, *e.g.* L- nucleosides.

[00320] The modified nucleosides and modified nucleotides described herein, which can be incorporated into a modified nucleic acid, can include a modified base, also called a nucleobase. Examples of nucleobases include, but are not limited to, adenine (A), guanine (G), cytosine (C), and uracil (U). These nucleobases can be modified or wholly replaced to provide modified residues that can be incorporated into modified nucleic acids. The nucleobase of the nucleotide can be independently selected from a purine, a pyrimidine, a purine analog, or pyrimidine analog. In some embodiments, the nucleobase can include, for example, naturally-occurring and synthetic derivatives of a base.

[00321] In embodiments employing a dual guide RNA, each of the crRNA and the tracr RNA can contain modifications. Such modifications may be at one or both ends of the crRNA and/or tracr RNA. In embodiments comprising an sgRNA, one or more residues at one or both ends of the sgRNA may be chemically modified, or the entire sgRNA may be

chemically modified. Certain embodiments comprise a 5' end modification. Certain embodiments comprise a 3' end modification. In certain embodiments, one or more or all of the nucleotides in single stranded overhang of a gRNA molecule are deoxynucleotides.

[00322] In some embodiments, the gRNAs disclosed herein comprise one of the modification patterns disclosed in WO2018/107028 A1, published June 14, 2018 the contents of which are hereby incorporated by reference in their entirety.

[00323] The terms “mA,” “mC,” “mU,” or “mG” may be used to denote a nucleotide that has been modified with 2’-O-Me. The terms “fA,” “fC,” “fU,” or “fG” may be used to denote a nucleotide that has been substituted with 2’-F. A “*” may be used to depict a PS modification. The terms A*, C*, U*, or G* may be used to denote a nucleotide that is linked to the next (e.g., 3’) nucleotide with a PS bond. The terms “mA*,” “mC*,” “mU*,” or “mG*” may be used to denote a nucleotide that has been substituted with 2’-O-Me and that is linked to the next (e.g., 3’) nucleotide with a PS bond.

[00324] **Exemplary spyCas9 sgRNA-1 (SEQ ID NO: 215)**

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
G	U	U	U	U	A	G	A	G	C	U	A	G	A	A	A	U	A	G	C	A	A	G	U	U	A	A	A	A	U
LS1-LS6						B1-B2		US1-US12												B2-B6				LS7-LS12					

31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
A	A	G	G	C	U	A	G	U	C	C	G	U	U	A	U	C	A	A	C	U	U	G	A	A	A	A	A	G	U
Nexus																		H1-1 through H1-12											

61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76
G	G	C	A	C	C	G	A	G	U	C	G	G	U	G	C
N	H2-1 through H2-15														

I. Ribonucleoprotein complex

[00325] In some embodiments, the disclosure provides compositions comprising one or more gRNAs comprising one or more guide sequences from **Tables 2-5** and an RNA-guided DNA binding agent, *e.g.*, a nuclease, such as a Cas nuclease, such as Cas9. In some embodiments, the RNA-guided DNA-binding agent has cleavase activity, which can also be referred to as double-strand endonuclease activity. In some embodiments, the RNA-guided DNA-binding agent comprises a Cas nuclease. Examples of Cas9 nucleases include those of the type II CRISPR systems of *S. pyogenes, S. aureus*, and other prokaryotes (*see e.g.*, the list in the next paragraph), and modified (*e.g.*, engineered or mutant) versions thereof. *See e.g.*, US2016/0312198 A1; US 2016/0312199 A1. Other examples of Cas nucleases include a Csm or Cmr complex of a type III CRISPR system or the Cas10, Csm1, or Cmr2 subunit thereof; and a Cascade complex of a type I CRISPR system, or the Cas3 subunit thereof. In some embodiments, the Cas nuclease may be from a Type-IIA, Type-IIB, or Type-IIC system. For discussion of various CRISPR systems and Cas nucleases see, e.g., Makarova et al., NAT. REV. MICROBIOL. 9:467-477 (2011); Makarova et al., NAT. REV. MICROBIOL, 13: 722-36 (2015); Shmakov et al., MOLECULAR CELL, 60:385-397 (2015). In some embodiments, the RNA-guided DNA-binding agent comprises a Cas nickase. In some embodiments, the RNA-guided nickase is modified or derived from a Cas protein, such as a Class 2 Cas nuclease (which may be, e.g., a Cas nuclease of Type II, V, or VI). Class 2 Cas nuclease include, for example, Cas9, Cpf1, C2c1, C2c2, and C2c3 proteins and modifications thereof.

[00326] Non-limiting exemplary species that the Cas nuclease or Cas nickase can be derived from include *Streptococcus pyogenes, Streptococcus thermophilus, Streptococcus sp., Staphylococcus aureus, Listeria innocua, Lactobacillus gasseri, Francisella novicida, Wolinella succinogenes, Sutterella wadsworthensis, Gammaproteobacterium, Neisseria meningitidis, Campylobacter jejuni, Pasteurella multocida, Fibrobacter succinogene, Rhodospirillum rubrum, Nocardiopsis dassonvillei, Streptomyces pristinaespiralis, Streptomyces viridochromogenes, Streptomyces viridochromogenes, Streptosporangium roseum, Streptosporangium roseum, Alicyclobacillus acidocaldarius, Bacillus pseudomycoides, Bacillus selenitireducens, Exiguobacterium sibiricum, Lactobacillus delbrueckii, Lactobacillus salivarius, Lactobacillus buchneri, Treponema denticola, Microscilla marina, Burkholderiales bacterium, Polaromonas naphthalenivorans, Polaromonas sp., Crocosphaera watsonii, Cyanothece sp., Microcystis aeruginosa, Synechococcus sp., Acetohalobium arabaticum, Ammonifex degensii, Caldicelulosiruptor*

becscii, Candidatus Desulforudis, Clostridium botulinum, Clostridium difficile, Finegoldia magna, Natranaerobius thermophilus, Pelotomaculum thermopropionicum, Acidithiobacillus caldus, Acidithiobacillus ferrooxidans, Allochromatium vinosum, Marinobacter sp., Nitrosococcus halophilus, Nitrosococcus watsoni, Pseudoalteromonas haloplanktis, Ktedonobacter racemifer, Methanohalobium evestigatum, Anabaena variabilis, Nodularia spumigena, Nostoc sp., Arthrospira maxima, Arthrospira platensis, Arthrospira sp., Lyngbya sp., Microcoleus chthonoplastes, Oscillatoria sp., Petrotoga mobilis, Thermosipho africanus, Streptococcus pasteurianus, Neisseria cinerea, Campylobacter lari, Parvibaculum lavamentivorans, Corynebacterium diphtheria, Acidaminococcus sp., Lachnospiraceae bacterium ND2006, and *Acaryochloris marina*.

[00327] In some embodiments, the Cas nuclease is the Cas9 nuclease from *Streptococcus pyogenes*. In some embodiments, the Cas nuclease is the Cas9 nuclease from *Streptococcus thermophilus*. In some embodiments, the Cas nuclease is the Cas9 nuclease from *Neisseria meningitidis*. In some embodiments, the Cas nuclease is the Cas9 nuclease is from *Staphylococcus aureus*. In some embodiments, the Cas nuclease is the Cpf1 nuclease from *Francisella novicida*. In some embodiments, the Cas nuclease is the Cpf1 nuclease from *Acidaminococcus sp.* In some embodiments, the Cas nuclease is the Cpf1 nuclease from *Lachnospiraceae* bacterium ND2006. In further embodiments, the Cas nuclease is the Cpf1 nuclease from *Francisella tularensis, Lachnospiraceae bacterium, Butyrivibrio proteoclasticus, Peregrinibacteria bacterium, Parcubacteria bacterium, Smithella, Acidaminococcus, Candidatus Methanoplasma termitum, Eubacterium eligens, Moraxella bovoculi, Leptospira inadai, Porphyromonas crevioricanis, Prevotella disiens,* or *Porphyromonas macacae*. In certain embodiments, the Cas nuclease is a Cpf1 nuclease from an *Acidaminococcus* or *Lachnospiraceae*.

[00328] In some embodiments, the Cas nickase is derived from the Cas9 nuclease from *Streptococcus pyogenes*. In some embodiments, the Cas nickase is derived from the Cas9 nuclease from *Streptococcus thermophilus*. In some embodiments, the Cas nickase is a nickase form of the Cas9 nuclease from *Neisseria meningitidis*. See e.g., WO/2020081568, describing an Nme2Cas9 D16A nickase fusion protein. In some embodiments, the Cas nickase is derived from the Cas9 nuclease is from *Staphylococcus aureus*. In some embodiments, the Cas nickase is derived from the Cpf1 nuclease from *Francisella novicida*. In some embodiments, the Cas nickase is derived from the Cpf1 nuclease from *Acidaminococcus sp.* In some embodiments, the Cas nickase is derived from the Cpf1 nuclease from *Lachnospiraceae bacterium* ND2006. In further embodiments, the Cas nickase

is derived from the Cpf1 nuclease from *Francisella tularensis, Lachnospiraceae bacterium, Butyrivibrio proteoclasticus, Peregrinibacteria bacterium, Parcubacteria bacterium, Smithella, Acidaminococcus, Candidatus Methanoplasma termitum, Eubacterium eligens, Moraxella bovoculi, Leptospira inadai, Porphyromonas crevioricanis, Prevotella disiens, or Porphyromonas macacae*. In certain embodiments, the Cas nickase is derived from a Cpf1 nuclease from an *Acidaminococcus* or *Lachnospiraceae*. As discussed elsewhere, a nickase may be derived from a nuclease by inactivating one of the two catalytic domains, e.g., by mutating an active site residue essential for nucleolysis, such as D10, H840, of N863 in Spy Cas9. One skilled in the art will be familiar with techniques for easily identifying corresponding residues in other Cas proteins, such as sequence alignment and structural alignment, which is discussed in detail below.

[00329] In some embodiments, the gRNA together with an RNA-guided DNA binding agent is called a ribonucleoprotein complex (RNP). In some embodiments, the RNA-guided DNA binding agent is a Cas nuclease. In some embodiments, the gRNA together with a Cas nuclease is called a Cas RNP. In some embodiments, the RNP comprises Type-I, Type-II, or Type-III components. In some embodiments, the Cas nuclease is the Cas9 protein from the Type-II CRISPR/Cas system. In some embodiment, the gRNA together with Cas9 is called a Cas9 RNP.

[00330] Wild type Cas9 has two nuclease domains: RuvC and HNH. The RuvC domain cleaves the non-target DNA strand, and the HNH domain cleaves the target strand of DNA. In some embodiments, the Cas9 protein comprises more than one RuvC domain and/or more than one HNH domain. In some embodiments, the Cas9 protein is a wild type Cas9. In each of the composition, use, and method embodiments, the Cas induces a double strand break in target DNA.

[00331] In some embodiments, chimeric Cas nucleases are used, where one domain or region of the protein is replaced by a portion of a different protein. In some embodiments, a Cas nuclease domain may be replaced with a domain from a different nuclease such as Fok1. In some embodiments, a Cas nuclease may be a modified nuclease.

[00332] In other embodiments, the Cas nuclease or Cas nickase may be from a Type-I CRISPR/Cas system. In some embodiments, the Cas nuclease may be a component of the Cascade complex of a Type-I CRISPR/Cas system. In some embodiments, the Cas nuclease may be a Cas3 protein. In some embodiments, the Cas nuclease may be from a Type-III CRISPR/Cas system. In some embodiments, the Cas nuclease may have an RNA cleavage activity.

[00333] In some embodiments, the RNA-guided DNA-binding agent has single-strand nickase activity, i.e., can cut one DNA strand to produce a single-strand break, also known as a “nick.” In some embodiments, the RNA-guided DNA-binding agent comprises a Cas nickase. A nickase is an enzyme that creates a nick in dsDNA, i.e., cuts one strand but not the other of the DNA double helix. In some embodiments, a Cas nickase is a version of a Cas nuclease (e.g., a Cas nuclease discussed above) in which an endonucleolytic active site is inactivated, e.g., by one or more alterations (*e.g.*, point mutations) in a catalytic domain. *See e.g.*, US Pat. No. 8,889,356 for discussion of Cas nickases and exemplary catalytic domain alterations. In some embodiments, a Cas nickase such as a Cas9 nickase has an inactivated RuvC or HNH domain.

[00334] In some embodiments, the RNA-guided DNA-binding agent is modified to contain only one functional nuclease domain. For example, the agent protein may be modified such that one of the nuclease domains is mutated or fully or partially deleted to reduce its nucleic acid cleavage activity. In some embodiments, a nickase is used having a RuvC domain with reduced activity. In some embodiments, a nickase is used having an inactive RuvC domain. In some embodiments, a nickase is used having an HNH domain with reduced activity. In some embodiments, a nickase is used having an inactive HNH domain.

[00335] In some embodiments, a conserved amino acid within a Cas protein nuclease domain is substituted to reduce or alter nuclease activity. In some embodiments, a Cas nuclease may comprise an amino acid substitution in the RuvC or RuvC-like nuclease domain. Exemplary amino acid substitutions in the RuvC or RuvC-like nuclease domain include D10A (based on the S. *pyogenes* Cas9 protein). *See*, *e.g.*, Zetsche et al. (2015) *Cell* Oct 22:163(3): 759-771. In some embodiments, the Cas nuclease may comprise an amino acid substitution in the HNH or HNH-like nuclease domain. Exemplary amino acid substitutions in the HNH or HNH-like nuclease domain include E762A, H840A, N863A, H983A, and D986A (based on the S. *pyogenes* Cas9 protein). *See*, *e.g.*, Zetsche et al. (2015). Further exemplary amino acid substitutions include D917A, E1006A, and D1255A (based on the *Francisella novicida* U112 Cpf1 (FnCpf1) sequence (UniProtKB - A0Q7Q2 (CPF1_FRATN)).

[00336] In some embodiments, an mRNA encoding a nickase is provided in combination with a pair of guide RNAs that are complementary to the sense and antisense strands of the target sequence, respectively. In this embodiment, the guide RNAs direct the nickase to a target sequence and introduce a DSB by generating a nick on opposite strands of the target sequence (i.e., double nicking). In some embodiments, use of double nicking may improve

specificity and reduce off-target effects. In some embodiments, a nickase is used together with two separate guide RNAs targeting opposite strands of DNA to produce a double nick in the target DNA. In some embodiments, a nickase is used together with two separate guide RNAs that are selected to be in close proximity to produce a double nick in the target DNA.

[00337] In some embodiments, the RNA-guided DNA-binding agent lacks cleavase and nickase activity. In some embodiments, the RNA-guided DNA-binding agent comprises a dCas DNA-binding polypeptide. A dCas polypeptide has DNA-binding activity while essentially lacking catalytic (cleavase/nickase) activity. In some embodiments, the dCas polypeptide is a dCas9 polypeptide. In some embodiments, the RNA-guided DNA-binding agent lacking cleavase and nickase activity or the dCas DNA-binding polypeptide is a version of a Cas nuclease (*e.g.*, a Cas nuclease discussed above) in which its endonucleolytic active sites are inactivated, *e.g.*, by one or more alterations (e.g., point mutations) in its catalytic domains. See, e.g., US 2014/0186958 A1; US 2015/0166980 A1.

[00338] In some embodiments, the RNA-guided DNA binding agent comprises one or more heterologous functional domains (e.g., is or comprises a fusion polypeptide).

[00339] In some embodiments, the RNA-guided DNA binding agent comprises a APOBEC3 deaminase. In some embodiments, a APOBEC3 deaminase is a APOBEC3A (A3A). In some embodiments, the A3A is a human A3A. In some embodiments, the A3A is a wild-type A3A.

[00340] In some embodiments, the RNA-guided DNA binding agent comprises a deaminase and an RNA-guided nickase. In some embodiments, the mRNA further comprises a linker to link the sequencing encoding A3A to the sequence sequencing encoding RNA-guided nickase. In some embodiments, the linker is an organic molecule, group, polymer, or chemical moiety. In some embodiments, the linker is a peptide linker. In some embodiments, the peptide linker is any stretch of amino acids having at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, or more amino acids. In some embodiments, the peptide linker is the 16 residue "XTEN" linker, or a variant thereof (See, e.g., the Examples; and Schellenberger et al. A recombinant polypeptide extends the in vivo half-life of peptides and proteins in a tunable manner. Nat. Biotechnol. 27, 1186-1190 (2009)). In some embodiments, the XTEN linker comprises the sequence SGSETPGTSESATPES (SEQ ID NO: 900), SGSETPGTSESA (SEQ ID NO: 901), or SGSETPGTSESATPEGGSGGS (SEQ ID NO: 902).

[00341] In some embodiments, the heterologous functional domain may facilitate transport of the RNA-guided DNA-binding agent into the nucleus of a cell. For example, the heterologous functional domain may be a nuclear localization signal (NLS). In some embodiments, the RNA-guided DNA-binding agent may be fused with 1-10 NLS(s). In some embodiments, the RNA-guided DNA-binding agent may be fused with 1-5 NLS(s). In some embodiments, the RNA-guided DNA-binding agent may be fused with one NLS. Where one NLS is used, the NLS may be fused at the N-terminus or the C-terminus of the RNA-guided DNA-binding agent sequence. It may also be inserted within the RNA-guided DNA binding agent sequence. In other embodiments, the RNA-guided DNA-binding agent may be fused with more than one NLS. In some embodiments, the RNA-guided DNA-binding agent may be fused with 2, 3, 4, or 5 NLSs. In some embodiments, the RNA-guided DNA-binding agent may be fused with two NLSs. In certain circumstances, the two NLSs may be the same (*e.g.*, two SV40 NLSs) or different. In some embodiments, the RNA-guided DNA-binding agent is fused to two NLS sequences (e.g., SV40) fused at the carboxy terminus. In some embodiments, the RNA-guided DNA-binding agent may be fused with two NLSs, one linked at the N-terminus and one at the C-terminus. In some embodiments, the RNA-guided DNA-binding agent may be fused with 3 NLSs. In some embodiments, the RNA-guided DNA-binding agent may be fused with no NLS. In some embodiments, the NLS may be a monopartite sequence, such as, *e.g.*, the SV40 NLS, PKKKRKV (SEQ ID NO: 600) or PKKKRRV (SEQ ID NO: 601). In some embodiments, the NLS may be a bipartite sequence, such as the NLS of nucleoplasmin, KRPAATKKAGQAKKKK (SEQ ID NO: 602). In a specific embodiment, a single PKKKRKV (SEQ ID NO: 600) NLS may be fused at the C-terminus of the RNA-guided DNA-binding agent. One or more linkers are optionally included at the fusion site.

[00342] In some embodiments, the RNA-guided DNA binding agent comprises an editor. An exemplary editor is BC22n which includes a *H. sapiens* APOBEC3A fused to *S. pyogenes*-D10A Cas9 nickase by an XTEN linker, and mRNA encoding BC22n. An mRNA encoding BC22n is provided (SEQ ID NO:806).

[00343] In some embodiments, the heterologous functional domain may be capable of modifying the intracellular half-life of the RNA-guided DNA binding agent. In some embodiments, the half-life of the RNA-guided DNA binding agent may be increased. In some embodiments, the half-life of the RNA-guided DNA-binding agent may be reduced. In some embodiments, the heterologous functional domain may be capable of increasing the stability of the RNA-guided DNA-binding agent. In some embodiments, the heterologous

functional domain may be capable of reducing the stability of the RNA-guided DNA-binding agent. In some embodiments, the heterologous functional domain may act as a signal peptide for protein degradation. In some embodiments, the protein degradation may be mediated by proteolytic enzymes, such as, for example, proteasomes, lysosomal proteases, or calpain proteases. In some embodiments, the heterologous functional domain may comprise a PEST sequence. In some embodiments, the RNA-guided DNA-binding agent may be modified by addition of ubiquitin or a polyubiquitin chain. In some embodiments, the ubiquitin may be a ubiquitin-like protein (UBL). Non-limiting examples of ubiquitin-like proteins include small ubiquitin-like modifier (SUMO), ubiquitin cross-reactive protein (UCRP, also known as interferon-stimulated gene-15 (ISG15)), ubiquitin-related modifier-1 (URM1), neuronal-precursor-cell-expressed developmentally downregulated protein-8 (NEDD8, also called Rub1 in *S. cerevisiae*), human leukocyte antigen F-associated (FAT10), autophagy-8 (ATG8) and -12 (ATG12), Fau ubiquitin-like protein (FUB1), membrane-anchored UBL (MUB), ubiquitin fold-modifier-1 (UFM1), and ubiquitin-like protein-5 (UBL5).

[00344] In some embodiments, the heterologous functional domain may be a marker domain. Non-limiting examples of marker domains include fluorescent proteins, purification tags, epitope tags, and reporter gene sequences. In some embodiments, the marker domain may be a fluorescent protein. Non-limiting examples of suitable fluorescent proteins include green fluorescent proteins (*e.g.*, GFP, GFP-2, tagGFP, turboGFP, sfGFP, EGFP, Emerald, Azami Green, Monomeric Azami Green, CopGFP, AceGFP, ZsGreen1), yellow fluorescent proteins (*e.g.*, YFP, EYFP, Citrine, Venus, YPet, PhiYFP, ZsYellow1), blue fluorescent proteins (*e.g.*, EBFP, EBFP2, Azurite, mKalamal, GFPuv, Sapphire, T-sapphire,), cyan fluorescent proteins (*e.g.*, ECFP, Cerulean, CyPet, AmCyan1, Midoriishi-Cyan), red fluorescent proteins (*e.g.*, mKate, mKate2, mPlum, DsRed monomer, mCherry, mRFP1, DsRed-Express, DsRed2, DsRed-Monomer, HcRed-Tandem, HcRed1, AsRed2, eqFP611, mRasberry, mStrawberry, Jred), and orange fluorescent proteins (mOrange, mKO, Kusabira-Orange, Monomeric Kusabira-Orange, mTangerine, tdTomato) or any other suitable fluorescent protein. In other embodiments, the marker domain may be a purification tag and/or an epitope tag. Non-limiting exemplary tags include glutathione-S-transferase (GST), chitin binding protein (CBP), maltose binding protein (MBP), thioredoxin (TRX), poly(NANP), tandem affinity purification (TAP) tag, myc, AcV5, AU1, AU5, E, ECS, E2, FLAG, HA, nus, Softag 1, Softag 3, Strep, SBP, Glu-Glu, HSV, KT3, S, S1, T7, V5, VSV-G, 6xHis, 8xHis, biotin carboxyl carrier protein (BCCP), poly-His, and calmodulin. Non-limiting exemplary reporter genes include glutathione-S-transferase (GST), horseradish

peroxidase (HRP), chloramphenicol acetyltransferase (CAT), beta-galactosidase, beta-glucuronidase, luciferase, or fluorescent proteins.

[00345] In additional embodiments, the heterologous functional domain may target the RNA-guided DNA-binding agent to a specific organelle, cell type, tissue, or organ. In some embodiments, the heterologous functional domain may target the RNA-guided DNA-binding agent to mitochondria.

[00346] In further embodiments, the heterologous functional domain may be an effector domain such as an editor domain. When the RNA-guided DNA-binding agent is directed to its target sequence, *e.g.*, when a Cas nuclease is directed to a target sequence by a gRNA, the effector such as an editor domain may modify or affect the target sequence. In some embodiments, the effector such as an editor domain may be chosen from a nucleic acid binding domain, a nuclease domain (e.g., a non-Cas nuclease domain), an epigenetic modification domain, a transcriptional activation domain, or a transcriptional repressor domain. In some embodiments, the heterologous functional domain is a nuclease, such as a FokI nuclease. See, e.g., US Pat. No. 9,023,649. In some embodiments, the heterologous functional domain is a transcriptional activator or repressor. See, e.g., Qi et al., "Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression," *Cell* 152:1173-83 (2013); Perez-Pinera et al., "RNA-guided gene activation by CRISPR-Cas9-based transcription factors," *Nat. Methods* 10:973-6 (2013); Mali et al., "CAS9 transcriptional activators for target specificity screening and paired nickases for cooperative genome engineering," *Nat. Biotechnol.* 31:833-8 (2013); Gilbert et al., "CRISPR-mediated modular RNA-guided regulation of transcription in eukaryotes," *Cell* 154:442-51 (2013). As such, the RNA-guided DNA-binding agent essentially becomes a transcription factor that can be directed to bind a desired target sequence using a guide RNA.

J. Determination of Efficacy of Guide RNAs

[00347] In some embodiments, the efficacy of a guide RNA is determined when delivered or expressed together with other components (*e.g.*, an RNA-guided DNA binding agent) forming an RNP. In some embodiments, the guide RNA is expressed together with an RNA-guided DNA binding agent, such as a Cas protein, *e.g.*, Cas9. In some embodiments, the guide RNA is delivered to or expressed in a cell line that already stably expresses an RNA-guided DNA nuclease, such as a Cas nuclease or nickase, *e.g.*, Cas9 nuclease or nickase. In some embodiments the guide RNA is delivered to a cell as part of a RNP. In some

embodiments, the guide RNA is delivered to a cell along with a mRNA encoding an RNA-guided DNA nuclease, such as a Cas nuclease or nickase, *e.g.*, Cas9 nuclease or nickase.

[00348] As described herein, use of an RNA-guided DNA nuclease and a guide RNA disclosed herein can lead to DSBs, SSBs, and/or site-specific binding that results in nucleic acid modification in the DNA or pre-mRNA which can produce errors in the form of insertion/deletion (indel) mutations upon repair by cellular machinery. Many mutations due to indels alter the reading frame, introduce premature stop codons, or induce exon skipping and, therefore, produce a non-functional protein.

[00349] In some embodiments, the efficacy of particular guide RNAs is determined based on *in vitro* models. In some embodiments, the *in vitro* model is T cell line. In some embodiments, the *in vitro* model is HEK293 T cells. In some embodiments, the *in vitro* model is HEK293 cells stably expressing Cas9 (HEK293_Cas9). In some embodiments, the *in vitro* model is a lymphoblastoid cell line. In some embodiments, the *in vitro* model is primary human T cells. In some embodiments, the *in vitro* model is primary human B cells. In some embodiments, the *in vitro* model is primary human peripheral blood lymphocytes. In some embodiments, the *in vitro* model is primary human peripheral blood mononuclear cells.

[00350] In some embodiments, the number of off-target sites at which a deletion or insertion occurs in an *in vitro* model is determined, e.g., by analyzing genomic DNA from the cells transfected *in vitro* with Cas9 mRNA and the guide RNA. In some embodiments, such a determination comprises analyzing genomic DNA from cells transfected *in vitro* with Cas9 mRNA, the guide RNA, and a donor oligonucleotide. Exemplary procedures for such determinations are provided in the working examples below.

[00351] In some embodiments, the efficacy of particular gRNAs is determined across multiple *in vitro* cell models for a guide RNA selection process. In some embodiments, a cell line comparison of data with selected guide RNAs is performed. In some embodiments, cross screening in multiple cell models is performed.

[00352] In some embodiments, the efficacy of a guide RNA is evaluated by on target cleavage efficiency. In some embodiments, the efficacy of a guide RNA is measured by percent editing at the target location, *e.g.*, HLA-A, or CIITA. In some embodiments, deep sequencing may be utilized to identify the presence of modifications (*e.g.*, insertions, deletions) introduced by gene editing. Indel percentage can be calculated from next generation sequencing "NGS."

[00353] In some embodiments, the efficacy of a guide RNA is measured by the number and/or frequency of indels at off-target sequences within the genome of the target cell type.

In some embodiments, efficacious guide RNAs are provided which produce indels at off target sites at very low frequencies (e.g., <5%) in a cell population and/or relative to the frequency of indel creation at the target site. Thus, the disclosure provides for guide RNAs which do not exhibit off-target indel formation in the target cell type (*e.g.*, T cells or B cells), or which produce a frequency of off-target indel formation of <5% in a cell population and/or relative to the frequency of indel creation at the target site. In some embodiments, the disclosure provides guide RNAs which do not exhibit any off target indel formation in the target cell type (*e.g.*, T cells or B cells). In some embodiments, guide RNAs are provided which produce indels at less than 5 off-target sites, e.g., as evaluated by one or more methods described herein. In some embodiments, guide RNAs are provided which produce indels at less than or equal to 4, 3, 2, or 1 off-target site(s) e.g., as evaluated by one or more methods described herein. In some embodiments, the off-target site(s) does not occur in a protein coding region in the target cell (*e.g.*, T cells or B cells) genome.

[00354] In some embodiments, linear amplification is used to detect gene editing events, such as the formation of insertion/deletion ("indel") mutations, translocations, and homology directed repair (HDR) events in target DNA. For example, linear amplification with a unique sequence-tagged primer and isolating the tagged amplification products (herein after referred to as "UnIT," or "Unique Identifier Tagmentation" method) may be used.

[00355] In some embodiments, the efficacy of a guide RNA is measured by the number of chromosomal rearrangements within the target cell type. Kromatid dGH assay may used to detect chromosomal rearrangements, including e.g., translocations, reciprocal translocations, translocations to off-target chromosomes, deletions (*i.e.*, chromosomal rearrangements where fragments were lost during the cell replication cycle due to the editing event). In some embodiments, the target cell type has less than 10, less than 8, less than 5, less than 4, less than 3, less than 2, or less than 1 chromosomal rearrangement. In some embodiments, the target cell type has no chromosomal rearrangements.

K. Delivery of gRNA Compositions

[00356] Lipid nanoparticles (LNP compositions) are a well-known means for delivery of nucleotide and protein cargo and may be used for delivery of the guide RNAs, compositions, or pharmaceutical formulations disclosed herein. In some embodiments, the LNP compositions deliver nucleic acid, protein, or nucleic acid together with protein.

[00357] In some embodiments, the invention comprises a method for delivering any one of the gRNAs disclosed herein to a subject, wherein the gRNA is formulated as an LNP. In some embodiments, the LNP comprises the gRNA and a Cas9 or an mRNA encoding Cas9.

[00358] In some embodiments, the invention comprises a composition comprising any one of the gRNAs disclosed and an LNP. In some embodiments, the composition further comprises a Cas9 or an mRNA encoding Cas9.

[00359] In some embodiments, the LNP compositions comprise cationic lipids. In some embodiments, the LNP compositions comprise (9Z,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate, also called 3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,12Z)-octadeca-9,12-dienoate) or another ionizable lipid. See, e.g., lipids of WO/2017/173054 and references described therein. In some embodiments, the LNP compositions comprise molar ratios of a cationic lipid amine to RNA phosphate (N:P) of about 4.5, 5.0, 5.5, 6.0, or 6.5. In some embodiments, the term cationic and ionizable in the context of LNP lipids is interchangeable, e.g., wherein ionizable lipids are cationic depending on the pH.

[00360] In some embodiments, the gRNAs disclosed herein are formulated as LNP compositions for use in preparing a medicament for treating a disease or disorder.

[00361] Electroporation is a well-known means for delivery of cargo, and any electroporation methodology may be used for delivery of any one of the gRNAs disclosed herein. In some embodiments, electroporation may be used to deliver any one of the gRNAs disclosed herein and Cas9 or an mRNA encoding Cas9.

[00362] In some embodiments, the invention comprises a method for delivering any one of the gRNAs disclosed herein to an *ex vivo* cell, wherein the gRNA is formulated as an LNP or not formulated as an LNP. In some embodiments, the LNP comprises the gRNA and a Cas9 or an mRNA encoding Cas9.

[00363] In some embodiments, the guide RNA compositions described herein, alone or encoded on one or more vectors, are formulated in or administered via a lipid nanoparticle; see e.g., WO/2017/173054 and WO 2019/067992, the contents of which are hereby incorporated by reference in their entirety.

[00364] In certain embodiments, the invention comprises DNA or RNA vectors encoding any of the guide RNAs comprising any one or more of the guide sequences described herein. In some embodiments, in addition to guide RNA sequences, the vectors further comprise

nucleic acids that do not encode guide RNAs. Nucleic acids that do not encode guide RNA include, but are not limited to, promoters, enhancers, regulatory sequences, and nucleic acids encoding an RNA-guided DNA nuclease, which can be a nuclease such as Cas9. In some embodiments, the vector comprises one or more nucleotide sequence(s) encoding a crRNA, a trRNA, or a crRNA and trRNA. In some embodiments, the vector comprises one or more nucleotide sequence(s) encoding a sgRNA and an mRNA encoding an RNA-guided DNA nuclease, which can be a Cas nuclease, such as Cas9 or Cpf1. In some embodiments, the vector comprises one or more nucleotide sequence(s) encoding a crRNA, a trRNA, and an mRNA encoding an RNA-guided DNA nuclease, which can be a Cas protein, such as, Cas9. In one embodiment, the Cas9 is from *Streptococcus pyogenes* (i.e., Spy Cas9). In some embodiments, the nucleotide sequence encoding the crRNA, trRNA, or crRNA and trRNA (which may be a sgRNA) comprises or consists of a guide sequence flanked by all or a portion of a repeat sequence from a naturally-occurring CRISPR/Cas system. The nucleic acid comprising or consisting of the crRNA, trRNA, or crRNA and trRNA may further comprise a vector sequence wherein the vector sequence comprises or consists of nucleic acids that are not naturally found together with the crRNA, trRNA, or crRNA and trRNA.

L. Therapeutic Methods and Uses

[00365] Any of the engineered human cells and compositions described herein can be used in a method of treating a variety of diseases and disorders, as described herein. In some embodiments, the genetically modified cell (engineered cell) and/or population of genetically modified cells (engineered cells) and compositions may be used in methods of treating a variety of diseases and disorders. In some embodiments, a method of treating any one of the diseases or disorders described herein is encompassed, comprising administering any one or more composition described herein.

[00366] In some embodiments, the methods and compositions described herein may be used to treat diseases or disorders in need of delivery of a therapeutic agent. In some embodiments, the invention provides a method of providing an immunotherapy in a subject, the method including administering to the subject an effective amount of an engineered cell (or population of engineered cells) as described herein, for example, a cell of any of the aforementioned cell aspects and embodiments.

[00367] In some embodiments, the methods comprise administering to a subject a composition comprising an engineered cell described herein as an adoptive cell transfer therapy. In some embodiments, the engineered cell is an allogeneic cell.

[00368] In some embodiments, the methods comprise administering to a subject a composition comprising an engineered cell described herein, wherein the cell produces, secretes, and/or expresses a polypeptide (e.g., a targeting receptor) useful for treatment of a disease or disorder in a subject. In some embodiments, the cell acts as a cell factory to produce a soluble polypeptide. In some embodiments, the cell acts as a cell factory to produce an antibody. In some embodiments, the cell continuously secretes the polypeptide *in vivo*. In some embodiments, the cell continuously secretes the polypeptide following transplantation *in vivo* for at least 1, 2, 3, 4, 5, or 6 weeks. In some embodiments, the cell continuously secretes the polypeptide following transplantation *in vivo* for more than 6 weeks. In some embodiments, the soluble polypeptide (*e.g.*, an antibody) is produced by the cell at a concentration of at least 10^2, 10^3, 10^4, 10^5, 10^6, 10^7, or 10^8 copies per day. In some embodiments, the polypeptide is an antibody and is produced by the cell at a concentration of at least 10^8 copies per day.

[00369] In some embodiments of the methods, the method includes administering a lymphodepleting agent or immunosuppressant prior to administering to the subject an effective amount of the engineered cell (or engineered cells) as described herein, for example, a cell of any of the aforementioned cell aspects and embodiments. In another aspect, the invention provides a method of preparing engineered cells (*e.g.*, a population of engineered cells).

[00370] Immunotherapy is the treatment of disease by activating or suppressing the immune system. Immunotherapies designed to elicit or amplify an immune response are classified as activation immunotherapies. Cell-based immunotherapies have been demonstrated to be effective in the treatment of some cancers. Immune effector cells such as lymphocytes, macrophages, dendritic cells, natural killer (NK) cells, cytotoxic T lymphocytes (CTLs), T helper cells, B cells, or their progenitors such as hematopoietic stem cells (HSC) or induced pluripotent stem cells (iPSC) can be programmed to act in response to abnormal antigens expressed on the surface of tumor cells. Thus, cancer immunotherapy allows components of the immune system to destroy tumors or other cancerous cells. Cell-based immunotherapies have also been demonstrated to be effective in the treatment of autoimmune diseases or transplant rejection. Immune effector cells such as regulatory T cells (Tregs) or mesenchymal stem cells can be programmed to act in response to autoantigens or transplant antigens expressed on the surface of normal tissues.

[00371] In some embodiments, the invention provides a method of preparing engineered cells (*e.g.*, a population of engineered cells). The population of engineered cells may be used for immunotherapy.

[00372] In some embodiments, the invention provides a method of treating a subject in need thereof that includes administering engineered cells prepared by a method of preparing cells described herein, for example, a method of any of the aforementioned aspects and embodiments of methods of preparing cells.

[00373] In some embodiments, the engineered cells can be used to treat cancer, infectious diseases, inflammatory diseases, autoimmune diseases, cardiovascular diseases, neurological diseases, ophthalmologic diseases, renal diseases, liver diseases, musculoskeletal diseases, red blood cell diseases, or transplant rejections. In some embodiments, the engineered cells can be used in cell transplant, e.g., to the heart, liver, lung, kidney, pancreas, skin, or brain. (*See e.g.*, Deuse et al., Nature Biotechnology 37:252-258 (2019).)

[00374] In some embodiments, the engineered cells can be used as a cell therapy comprising an allogeneic stem cell therapy. In some embodiments, the cell therapy comprises induced pluripotent stem cells (iPSCs). iPSCs may be induced to differentiate into other cell types including *e.g.*, beta islet cells, neurons, and blood cells. In some embodiments, the cell therapy comprises hematopoietic stem cells. In some embodiments, the stem cells comprise mesenchymal stem cells that can develop into bone, cartilage, muscle, and fat cells. In some embodiments, the stem cells comprise ocular stem cells. In some embodiments, the allogeneic stem cell transplant comprises allogeneic bone marrow transplant. In some embodiments, the stem cells comprise pluripotent stem cells (PSCs). In some embodiments, the stem cells comprise induced embryonic stem cells (ESCs).

[00375] The engineered human cells disclosed herein are suitable for further engineering, *e.g.*, by introduction of further edited, or modified genes or alleles. Cells of the invention may also be suitable for further engineering by introduction of an exogenous nucleic acid encoding e.g., a targeting receptor, *e.g.*, a TCR, CAR, UniCAR. CARs are also known as chimeric immunoreceptors, chimeric T cell receptors or artificial T cell receptors. In some embodiments, the TCR is a wild-type or variant TCR.

[00376] In some embodiments, the cell therapy is a transgenic T cell therapy. In some embodiments, the cell therapy comprises a Wilms' Tumor 1 (WT1) targeting transgenic T cell. In some embodiments, the cell therapy comprises a targeting receptor or a donor nucleic acid encoding a targeting receptor of a commercially available T cell therapy, such as a CAR T cell therapy. There are number of targeting receptors currently approved for cell therapy.

The cells and methods provided herein can be used with these known constructs. Commercially approved cell products that include targeting receptor constructs for use as cell therapies include *e.g.*, Kymriah® (tisagenlecleucel); Yescarta® (axicabtagene ciloleucel); Tecartus™ (brexucabtagene autoleucel); Tabelecleucel (Tab-cel®); Viralym-M (ALVR105); and Viralym-C.

[00377] In some embodiments, the methods provide for administering the engineered cells to a subject, wherein the administration is an injection. In some embodiments, the methods provide for administering the engineered cells to a subject, wherein the administration is an intravascular injection or infusion. In some embodiments, the methods provide for administering the engineered cells to a subject, wherein the administration is a single dose.

[00378] In some embodiments, the methods provide for reducing a sign or symptom associated of a subject's disease treated with a composition disclosed herein. In some embodiments, the subject has a response to treatment with a composition disclosed herein that lasts more than one week. In some embodiments, the subject has a response to treatment with a composition disclosed herein that lasts more than two weeks. In some embodiments, the subject has a response to treatment with a composition disclosed herein that lasts more than three weeks. In some embodiments, the subject has a response to treatment with a composition disclosed herein that lasts more than one month.

[00379] In some embodiments, the methods provide for administering the engineered cells to an subject, and wherein the subject has a response to the administered cell that comprises a reduction in a sign or symptom associated with the disease treated by the cell therapy. In some embodiments, the subject has a response that lasts more than one week. In some embodiments, the subject has a response that lasts more than one month. In some embodiments, the subject has a response that lasts for at least 1-6 weeks.

[00380] **Table 6. ADDITIONAL SEQUENCES**

Description	**SEQ ID NO**	**Sequence**
Exemplary guide sequence for EMX1 gene	230	GAGUCCGAGCAGAAGAAGAA
Exemplary guide sequence for VEGFA gene	231	GACCCCCUCCACCCCGCCUC
Exemplary guide	232	GACUUGUUUUCAUUGUUCUC

sequence for RAG1B gene		
Exemplary guide sequence for TRAC gene	233	CUCUCAGCUGGUACACGGCA
Exemplary guide sequence for CIITA gene	234	UGUGCAGACUCAGAGGUGAG
Exemplary guide sequence for B2M gene	235	GGCCACGGAGCGAGACAUCU
Exemplary guide for CIITA gene	236	CCCCCGGACGGUUCAAGCAA
	237-239	Not Used
G000644 guide RNA targeting EMX1 with guide sequence SEQ ID NO: 230	240	mG*mA*mG*UCCGAGCAGAAGAAGAAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
G000645 guide RNA targeting VEGFA with guide sequence SEQ ID NO: 231	241	mG*mA*mC*CCCCUCCACCCCGCCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
G000646 guide RNA targeting RAG1B with guide sequence SEQ ID NO: 232	242	mG*mA*mC*UUGUUUUCAUUGUUCUCGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
G013006 guide RNA targeting TRAC with guide sequence SEQ ID NO: 233	243	mC*mU*mC*UCAGCUGGUACACGGCAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGmCmU*mU*mU*mU
G018091	244	mU*mG*mU*GCAGACUCAGAGGUGAGGUUUUAGAmG

RNA targeting CIITA with guide SEQ ID NO:234		mCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAG GCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmA mGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmG mCmU*mU*mU*mU
G000529 RNA targeting B2M with guide SEQ ID NO: 235	245	mG*mG*mC*CACGGAGCGAGACAUCUGUUUUAGAmG mCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAG GCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmA mGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmG mCmU*mU*mU*mU
G013675 RNA targeting CIITA with guide SEQ ID NO: 236	246	mC*mC*mC*CCGGACGGUUCAAGCAAGUUUUAGAmG mCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAG GCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmA mGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmG mCmU*mU*mU*mU
G016239	247	mG*mG*mC*CUCGGCGCUGACGAUCUGUUUUAGAmG mCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAG GCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmA mGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmG mCmU*mU*mU*mU
G013676	248	mU*mG*mG*UCAGGGCAAGAGCUAUUGUUUUAGAmG mCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAG GCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmA mGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmG mCmU*mU*mU*mU
Recombinant Cas9-NLS amino acid sequence	800	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNT DRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKN RICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHP IFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLA LAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLF EENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNG LFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDL DNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKA PLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQ SKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKL NREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFL KDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETI TPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHS LLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVD LLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNAS LGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDRE MIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLIN GIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDI QKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDEL VKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIE

		EGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMY VDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDN LTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSR MNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVRE INNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKV YDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLAN GEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVN IVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYG GFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMER SSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRK RMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSP EDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDK VLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDT TIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDG GGSPKKKRKV
ORF encoding Sp. Cas9	801	ATGGACAAGAAGTACAGCATCGGACTGGACATCGGAA CAAACAGCGTCGGATGGGCAGTCATCACAGACGAATA CAAGGTCCCGAGCAAGAAGTTCAAGGTCCTGGGAAAC ACAGACAGACACAGCATCAAGAAGAACCTGATCGGA GCACTGCTGTTCGACAGCGGAGAAACAGCAGAAGCAA CAAGACTGAAGAGAACAGCAAGAAGAAGATACACAA GAAGAAAGAACAGAATCTGCTACCTGCAGGAAATCTT CAGCAACGAAATGGCAAAGGTCGACGACAGCTTCTTC CACAGACTGGAAGAAAGCTTCCTGGTCGAAGAAGACA AGAAGCACGAAAGACACCCGATCTTCGGAAACATCGT CGACGAAGTCGCATACCACGAAAAGTACCCGACAATC TACCACCTGAGAAAGAAGCTGGTCGACAGCACAGACA AGGCAGACCTGAGACTGATCTACCTGGCACTGGCACA CATGATCAAGTTCAGAGGACACTTCCTGATCGAAGGA GACCTGAACCCGGACAACAGCGACGTCGACAAGCTGT TCATCCAGCTGGTCCAGACATACAACCAGCTGTTCGA AGAAAACCCGATCAACGCAAGCGGAGTCGACGCAAA GGCAATCCTGAGCGCAAGACTGAGCAAGAGCAGAAG ACTGGAAAACCTGATCGCACAGCTGCCGGGAGAAAAG AAGAACGGACTGTTCGGAAACCTGATCGCACTGAGCC TGGGACTGACACCGAACTTCAAGAGCAACTTCGACCT GGCAGAAGACGCAAAGCTGCAGCTGAGCAAGGACAC ATACGACGACGACCTGGACAACCTGCTGGCACAGATC GGAGACCAGTACGCAGACCTGTTCCTGGCAGCAAAGA ACCTGAGCGACGCAATCCTGCTGAGCGACATCCTGAG AGTCAACACAGAAATCACAAAGGCACCGCTGAGCGCA AGCATGATCAAGAGATACGACGAACACCACCAGGACC TGACACTGCTGAAGGCACTGGTCAGACAGCAGCTGCC GGAAAAGTACAAGGAAATCTTCTTCGACCAGAGCAAG AACGGATACGCAGGATACATCGACGGAGGAGCAAGC CAGGAAGAATTCTACAAGTTCATCAAGCCGATCCTGG AAAAGATGGACGGAACAGAAGAACTGCTGGTCAAGC TGAACAGAGAAGACCTGCTGAGAAAGCAGAGAACAT

		TCGACAACGGAAGCATCCCGCACCAGATCCACCTGGG AGAACTGCACGCAATCCTGAGAAGACAGGAAGACTTC TACCCGTTCCTGAAGGACAACAGAGAAAAGATCGAAA AGATCCTGACATTCAGAATCCCGTACTACGTCGGACC GCTGGCAAGAGGAAACAGCAGATTCGCATGGATGACA AGAAAGAGCGAAGAAACAATCACACCGTGGAACTTC GAAGAAGTCGTCGACAAGGGAGCAAGCGCACAGAGC TTCATCGAAAGAATGACAAACTTCGACAAGAACCTGC CGAACGAAAAGGTCCTGCCGAAGCACAGCCTGCTGTA CGAATACTTCACAGTCTACAACGAACTGACAAAGGTC AAGTACGTCACAGAAGGAATGAGAAAGCCGGCATTCC TGAGCGGAGAACAGAAGAAGGCAATCGTCGACCTGCT GTTCAAGACAAACAGAAAGGTCACAGTCAAGCAGCTG AAGGAAGACTACTTCAAGAAGATCGAATGCTTCGACA GCGTCGAAATCAGCGGAGTCGAAGACAGATTCAACGC AAGCCTGGGAACATACCACGACCTGCTGAAGATCATC AAGGACAAGGACTTCCTGGACAACGAAGAAAACGAA GACATCCTGGAAGACATCGTCCTGACACTGACACTGT TCGAAGACAGAGAAATGATCGAAGAAAGACTGAAGA CATACGCACACCTGTTCGACGACAAGGTCATGAAGCA GCTGAAGAGAAGAAGATACACAGGATGGGGAAGACT GAGCAGAAAGCTGATCAACGGAATCAGAGACAAGCA GAGCGGAAAGACAATCCTGGACTTCCTGAAGAGCGAC GGATTCGCAAACAGAAACTTCATGCAGCTGATCCACG ACGACAGCCTGACATTCAAGGAAGACATCCAGAAGGC ACAGGTCAGCGGACAGGGAGACAGCCTGCACGAACA CATCGCAAACCTGGCAGGAAGCCCGGCAATCAAGAAG GGAATCCTGCAGACAGTCAAGGTCGTCGACGAACTGG TCAAGGTCATGGGAAGACACAAGCCGGAAAACATCGT CATCGAAATGGCAAGAGAAAACCAGACAACACAGAA GGGACAGAAGAACAGCAGAGAAAGAATGAAGAGAAT CGAAGAAGGAATCAAGGAACTGGGAAGCCAGATCCT GAAGGAACACCCGGTCGAAAACACACAGCTGCAGAA CGAAAAGCTGTACCTGTACTACCTGCAGAACGGAAGA GACATGTACGTCGACCAGGAACTGGACATCAACAGAC TGAGCGACTACGACGTCGACCACATCGTCCCGCAGAG CTTCCTGAAGGACGACAGCATCGACAACAAGGTCCTG ACAAGAAGCGACAAGAACAGAGGAAAGAGCGACAAC GTCCCGAGCGAAGAAGTCGTCAAGAAGATGAAGAACT ACTGGAGACAGCTGCTGAACGCAAAGCTGATCACACA GAGAAAGTTCGACAACCTGACAAAGGCAGAGAGAGG AGGACTGAGCGAACTGGACAAGGCAGGATTCATCAAG AGACAGCTGGTCGAAACAAGACAGATCACAAAGCAC GTCGCACAGATCCTGGACAGCAGAATGAACACAAAGT ACGACGAAAACGACAAGCTGATCAGAGAAGTCAAGG TCATCACACTGAAGAGCAAGCTGGTCAGCGACTTCAG AAAGGACTTCCAGTTCTACAAGGTCAGAGAAATCAAC AACTACCACCACGCACACGACGCATACCTGAACGCAG TCGTCGGAACAGCACTGATCAAGAAGTACCCGAAGCT

		GGAAAGCGAATTCGTCTACGGAGACTACAAGGTCTAC GACGTCAGAAAGATGATCGCAAAGAGCGAACAGGAA ATCGGAAAGGCAACAGCAAAGTACTTCTTCTACAGCA ACATCATGAACTTCTTCAAGACAGAAATCACACTGGC AAACGGAGAAATCAGAAAGAGACCGCTGATCGAAAC AAACGGAGAAACAGGAGAAATCGTCTGGGACAAGGG AAGAGACTTCGCAACAGTCAGAAAGGTCCTGAGCATG CCGCAGGTCAACATCGTCAAGAAGACAGAAGTCCAGA CAGGAGGATTCAGCAAGGAAAGCATCCTGCCGAAGA GAAACAGCGACAAGCTGATCGCAAGAAAGAAGGACT GGGACCCGAAGAAGTACGGAGGATTCGACAGCCCGA CAGTCGCATACAGCGTCCTGGTCGTCGCAAAGGTCGA AAAGGGAAAGAGCAAGAAGCTGAAGAGCGTCAAGGA ACTGCTGGGAATCACAATCATGGAAAGAAGCAGCTTC GAAAAGAACCCGATCGACTTCCTGGAAGCAAAGGGAT ACAAGGAAGTCAAGAAGGACCTGATCATCAAGCTGCC GAAGTACAGCCTGTTCGAACTGGAAAACGGAAGAAA GAGAATGCTGGCAAGCGCAGGAGAACTGCAGAAGGG AAACGAACTGGCACTGCCGAGCAAGTACGTCAACTTC CTGTACCTGGCAAGCCACTACGAAAAGCTGAAGGGAA GCCCGGAAGACAACGAACAGAAGCAGCTGTTCGTCGA ACAGCACAAGCACTACCTGGACGAAATCATCGAACAG ATCAGCGAATTCAGCAAGAGAGTCATCCTGGCAGACG CAAACCTGGACAAGGTCCTGAGCGCATACAACAAGCA CAGAGACAAGCCGATCAGAGAACAGGCAGAAAACAT CATCCACCTGTTCACACTGACAAACCTGGGAGCACCG GCAGCATTCAAGTACTTCGACACAACAATCGACAGAA AGAGATACACAAGCACAAAGGAAGTCCTGGACGCAA CACTGATCCACCAGAGCATCACAGGACTGTACGAAAC AAGAATCGACCTGAGCCAGCTGGGAGGAGACGGAGG AGGAAGCCCGAAGAAGAAGAGAAAGGTCTAG
ORF encoding Sp. Cas9	802	ATGGACAAGAAGTACTCCATCGGCCTGGACATCGGCA CCAACTCCGTGGGCTGGGCCGTGATCACCGACGAGTA CAAGGTGCCCTCCAAGAAGTTCAAGGTGCTGGGCAAC ACCGACCGGCACTCCATCAAGAAGAACCTGATCGGCG CCCTGCTGTTCGACTCCGGCGAGACCGCCGAGGCCAC CCGGCTGAAGCGGACCGCCCGGCGGCGGTACACCCGG CGGAAGAACCGGATCTGCTACCTGCAGGAGATCTTCT CCAACGAGATGGCCAAGGTGGACGACTCCTTCTTCCA CCGGCTGGAGGAGTCCTTCCTGGTGGAGGAGGACAAG AAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGG ACGAGGTGGCCTACCACGAGAAGTACCCCACCATCTA CCACCTGCGGAAGAAGCTGGTGGACTCCACCGACAAG GCCGACCTGCGGCTGATCTACCTGGCCCTGGCCCACAT GATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGAC CTGAACCCCGACAACTCCGACGTGGACAAGCTGTTCA TCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGA GAACCCCATCAACGCCTCCGGCGTGGACGCCAAGGCC ATCCTGTCCGCCCGGCTGTCCAAGTCCCGGCGGCTGG

		AGAACCTGATCGCCCAGCTGCCCGGCGAGAAGAAGAA CGGCCTGTTCGGCAACCTGATCGCCCTGTCCCTGGGCC TGACCCCCAACTTCAAGTCCAACTTCGACCTGGCCGA GGACGCCAAGCTGCAGCTGTCCAAGGACACCTACGAC GACGACCTGGACAACCTGCTGGCCCAGATCGGCGACC AGTACGCCGACCTGTTCCTGGCCGCCAAGAACCTGTC CGACGCCATCCTGCTGTCCGACATCCTGCGGGTGAAC ACCGAGATCACCAAGGCCCCCCTGTCCGCCTCCATGA TCAAGCGGTACGACGAGCACCACCAGGACCTGACCCT GCTGAAGGCCCTGGTGCGGCAGCAGCTGCCCGAGAAG TACAAGGAGATCTTCTTCGACCAGTCCAAGAACGGCT ACGCCGGCTACATCGACGGCGGCGCCTCCCAGGAGGA GTTCTACAAGTTCATCAAGCCCATCCTGGAGAAGATG GACGGCACCGAGGAGCTGCTGGTGAAGCTGAACCGGG AGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGG CTCCATCCCCCACCAGATCCACCTGGGCGAGCTGCAC GCCATCCTGCGGCGGCAGGAGGACTTCTACCCCTTCCT GAAGGACAACCGGGAGAAGATCGAGAAGATCCTGAC CTTCCGGATCCCCTACTACGTGGGCCCCCTGGCCCGGG GCAACTCCCGGTTCGCCTGGATGACCCGGAAGTCCGA GGAGACCATCACCCCCTGGAACTTCGAGGAGGTGGTG GACAAGGGCGCCTCCGCCCAGTCCTTCATCGAGCGGA TGACCAACTTCGACAAGAACCTGCCCAACGAGAAGGT GCTGCCCAAGCACTCCCTGCTGTACGAGTACTTCACCG TGTACAACGAGCTGACCAAGGTGAAGTACGTGACCGA GGGCATGCGGAAGCCCGCCTTCCTGTCCGGCGAGCAG AAGAAGGCCATCGTGGACCTGCTGTTCAAGACCAACC GGAAGGTGACCGTGAAGCAGCTGAAGGAGGACTACTT CAAGAAGATCGAGTGCTTCGACTCCGTGGAGATCTCC GGCGTGGAGGACCGGTTCAACGCCTCCCTGGGCACCT ACCACGACCTGCTGAAGATCATCAAGGACAAGGACTT CCTGGACAACGAGGAGAACGAGGACATCCTGGAGGA CATCGTGCTGACCCTGACCCTGTTCGAGGACCGGGAG ATGATCGAGGAGCGGCTGAAGACCTACGCCCACCTGT TCGACGACAAGGTGATGAAGCAGCTGAAGCGGCGGC GGTACACCGGCTGGGGCCGGCTGTCCCGGAAGCTGAT CAACGGCATCCGGGACAAGCAGTCCGGCAAGACCATC CTGGACTTCCTGAAGTCCGACGGCTTCGCCAACCGGA ACTTCATGCAGCTGATCCACGACGACTCCCTGACCTTC AAGGAGGACATCCAGAAGGCCCAGGTGTCCGGCCAG GGCGACTCCCTGCACGAGCACATCGCCAACCTGGCCG GCTCCCCCGCCATCAAGAAGGGCATCCTGCAGACCGT GAAGGTGGTGGACGAGCTGGTGAAGGTGATGGGCCG GCACAAGCCCGAGAACATCGTGATCGAGATGGCCCGG GAGAACCAGACCACCCAGAAGGGCCAGAAGAACTCC CGGGAGCGGATGAAGCGGATCGAGGAGGGCATCAAG GAGCTGGGCTCCCAGATCCTGAAGGAGCACCCCGTGG AGAACACCCAGCTGCAGAACGAGAAGCTGTACCTGTA CTACCTGCAGAACGGCCGGGACATGTACGTGGACCAG

		GAGCTGGACATCAACCGGCTGTCCGACTACGACGTGG ACCACATCGTGCCCCAGTCCTTCCTGAAGGACGACTCC ATCGACAACAAGGTGCTGACCCGGTCCGACAAGAACC GGGGCAAGTCCGACAACGTGCCCTCCGAGGAGGTGGT GAAGAAGATGAAGAACTACTGGCGGCAGCTGCTGAAC GCCAAGCTGATCACCCAGCGGAAGTTCGACAACCTGA CCAAGGCCGAGCGGGGCGGCCTGTCCGAGCTGGACAA GGCCGGCTTCATCAAGCGGCAGCTGGTGGAGACCCGG CAGATCACCAAGCACGTGGCCCAGATCCTGGACTCCC GGATGAACACCAAGTACGACGAGAACGACAAGCTGA TCCGGGAGGTGAAGGTGATCACCCTGAAGTCCAAGCT GGTGTCCGACTTCCGGAAGGACTTCCAGTTCTACAAG GTGCGGGAGATCAACAACTACCACCACGCCCACGACG CCTACCTGAACGCCGTGGTGGGCACCGCCCTGATCAA GAAGTACCCCAAGCTGGAGTCCGAGTTCGTGTACGGC GACTACAAGGTGTACGACGTGCGGAAGATGATCGCCA AGTCCGAGCAGGAGATCGGCAAGGCCACCGCCAAGTA CTTCTTCTACTCCAACATCATGAACTTCTTCAAGACCG AGATCACCCTGGCCAACGGCGAGATCCGGAAGCGGCC CCTGATCGAGACCAACGGCGAGACCGGCGAGATCGTG TGGGACAAGGGCCGGGACTTCGCCACCGTGCGGAAGG TGCTGTCCATGCCCCAGGTGAACATCGTGAAGAAGAC CGAGGTGCAGACCGGCGGCTTCTCCAAGGAGTCCATC CTGCCCAAGCGGAACTCCGACAAGCTGATCGCCCGGA AGAAGGACTGGGACCCCAAGAAGTACGGCGGCTTCGA CTCCCCCACCGTGGCCTACTCCGTGCTGGTGGTGGCCA AGGTGGAGAAGGGCAAGTCCAAGAAGCTGAAGTCCG TGAAGGAGCTGCTGGGCATCACCATCATGGAGCGGTC CTCCTTCGAGAAGAACCCCATCGACTTCCTGGAGGCC AAGGGCTACAAGGAGGTGAAGAAGGACCTGATCATC AAGCTGCCCAAGTACTCCCTGTTCGAGCTGGAGAACG GCCGGAAGCGGATGCTGGCCTCCGCCGGCGAGCTGCA GAAGGGCAACGAGCTGGCCCTGCCCTCCAAGTACGTG AACTTCCTGTACCTGGCCTCCCACTACGAGAAGCTGA AGGGCTCCCCCGAGGACAACGAGCAGAAGCAGCTGTT CGTGGAGCAGCACAAGCACTACCTGGACGAGATCATC GAGCAGATCTCCGAGTTCTCCAAGCGGGTGATCCTGG CCGACGCCAACCTGGACAAGGTGCTGTCCGCCTACAA CAAGCACCGGGACAAGCCCATCCGGGAGCAGGCCGA GAACATCATCCACCTGTTCACCCTGACCAACCTGGGC GCCCCCGCCGCCTTCAAGTACTTCGACACCACCATCGA CCGGAAGCGGTACACCTCCACCAAGGAGGTGCTGGAC GCCACCCTGATCCACCAGTCCATCACCGGCCTGTACG AGACCCGGATCGACCTGTCCCAGCTGGGCGGCGACGG CGGCGGCTCCCCCAAGAAGAAGCGGAAGGTGTGA
Open reading frame for Cas9 with Hibit tag	803	AUGGACAAGAAGUACUCCAUCGGCCUGGACAUCGGC ACCAACUCCGUGGGCUGGGCCGUGAUCACCGACGAG UACAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGC AACACCGACCGGCACUCCAUCAAGAAGAACCUGAUC

		GGCGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAG GCCACCCGGCUGAAGCGGACCGCCCGGCGGCGGUAC ACCCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAG AUCUUCUCCAACGAGAUGGCCAAGGUGGACGACUCC UUCUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAG GAGGACAAGAAGCACGAGCGGCACCCCAUCUUCGGC AACAUCGUGGACGAGGUGGCCUACCACGAGAAGUAC CCCACCAUCUACCACCUGCGGAAGAAGCUGGUGGAC UCCACCGACAAGGCCGACCUGCGGCUGAUCUACCUG GCCCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUC CUGAUCGAGGGCGACCUGAACCCCGACAACUCCGAC GUGGACAAGCUGUUCAUCCAGCUGGUGCAGACCUAC AACCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCC GGCGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUG UCCAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAG CUGCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAAC CUGAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCA AGUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGC AGCUGUCCAAGGACACCUACGACGACGACCUGGACA ACCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACC UGUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCC UGCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCA CCAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGU ACGACGAGCACCACCAGGACCUGACCCUGCUGAAGG CCCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGG AGAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCG GCUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCU ACAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACG GCACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGG ACCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCU CCAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGC CAUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCU GAAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGAC CUUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGG GGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCC GAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUG GUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAG CGGAUGACCAACUUCGACAAGAACCUGCCCAACGAG AAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUAC UUCACCGUGUACAACGAGCUGACCAAGGUGAAGUAC GUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCC GGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUC AAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAG GAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCC GUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCC UCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUC AAGGACAAGGACUUCCUGGACAACGAGGAGAACGAG GACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUG UUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAG

		ACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAG CAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGG CUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAG CAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCC GACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUC CACGACGACUCCCUGACCUUCAAGGAGGACAUCCAG AAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCAC GAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCA AGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACG AGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGA ACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCA CCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGA AGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCC AGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGC UGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGA ACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACA UCAACCGGCUGUCCGACUACGACGUGGACCACAUCG UGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACA ACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCA AGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGA AGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCA AGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCA AGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGG CCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGC AGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCC GGAUGAACACCAAGUACGACGAGAACGACAAGCUGA UCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGC UGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACA AGGUGCGGGAGAUCAACAACUACCACCACGCCCACG ACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGA UCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGU ACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGA UCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCG CCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCU UCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCC GGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCG GCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCA CCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACA UCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCU CCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACA AGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGA AGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACU CCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGU CCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCA UCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACC CCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGG UGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACU CCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGC UGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGC

		UGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACC UGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCG AGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGC ACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCU CCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCA ACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACC GGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCA UCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGC CGCCUUCAAGUACUUCGACACCACCAUCGACCGGAA GCGGUACACCUCCACCAAGGAGGUGCUGGACGCCAC CCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGAC CCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGG CGGCUCCCCCAAGAAGAAGCGGAAGGUGUCCGAGUC CGCCACCCCCGAGUCCGUGUCCGGCUGGCGGCUGUU CAAGAAGAUCUCCUGA
Open Reading frame for BC22n	804	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGA UGGACCCCCACAUCUUCACCUCCAACUUCAACAACG GCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGG UGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGG ACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGA ACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGC UGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGG ACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCU CCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCG AGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGC GGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACG ACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGG ACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACG AGUUCAAGCACUGCUGGGACACCUUCGUGGACCACC AGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACG AGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCA UCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCC CCGGCACCUCCGAGUCCGCCACCCCCGAGUCCGACAA GAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUC CGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGU GCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGA CCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCU GCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCG GCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCG GAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUC CAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCA CCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAA GAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGU GGACGAGGUGGCCUACCACGAGAAGUACCCCACCAU CUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGA CAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGC CCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGA GGGCGACCUGAACCCCGACAACUCCGACGUGGACAA GCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCU

		GUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGA CGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCC CGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGC GAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCC CUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAAC UUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCC AAGGACACCUACGACGACGACCUGGACAACCUGCUG GCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUG GCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCC GACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCC CCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAG CACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUG CGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUC UUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUC GACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUC AUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAG GAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUG CGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCC CACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUG CGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGAC AACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGG AUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAAC UCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAG ACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGAC AAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUG ACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUG CUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACC GUGUACAACGAGCUGACCAAGGUGAAGUACGUGACC GAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAG CAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACC AACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGAC UACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAG AUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUG GGCACCUACCACGACCUGCUGAAGAUCAUCAAGGAC AAGGACUUCCUGGACAACGAGGAGAACGAGGACAUC CUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAG GACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUAC GCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUG AAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCC CGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCC GGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGC UUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGAC GACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCC CAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCAC AUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAG GGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUG GUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUC GUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAG AAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGG

		AUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUC CUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAG AACGAGAAGCUGUACCUGUACUACCUGCAGAACGGC CGGGACAUGUACGUGGACCAGGAGCUGGACAUCAAC CGGCUGUCCGACUACGACGUGGACCACAUCGUGCCC CAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAG GUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCC GACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUG AAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUG AUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCC GAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGC UUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUC ACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUG AACACCAAGUACGACGAGAACGACAAGCUGAUCCGG GAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUG UCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUG CGGGAGAUCAACAACUACCACCACGCCCACGACGCC UACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAG AAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGC GACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCC AAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAG UACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAG ACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAG CGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAG AUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUG CGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUG AAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAG GAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUG AUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUAC GGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGC UGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGA AGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCA UCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCG ACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGA AGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGU UCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCU CCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCC UGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCU CCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACA ACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGC ACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGU UCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGG ACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACA AGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACC UGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUU CAAGUACUUCGACACCACCAUCGACCGGAAGCGGUA CACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAU CCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAU CGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUC

		CCCCAAGAAGAAGCGGAAGGUGUGA
Open reading frame for BC22n with Hibit tag	805	AUGGAGGCCUCCCCCGCCUCCGGCCCCCGGCACCUGA UGGACCCCCACAUCUUCACCUCCAACUUCAACAACG GCAUCGGCCGGCACAAGACCUACCUGUGCUACGAGG UGGAGCGGCUGGACAACGGCACCUCCGUGAAGAUGG ACCAGCACCGGGGCUUCCUGCACAACCAGGCCAAGA ACCUGCUGUGCGGCUUCUACGGCCGGCACGCCGAGC UGCGGUUCCUGGACCUGGUGCCCUCCCUGCAGCUGG ACCCCGCCCAGAUCUACCGGGUGACCUGGUUCAUCU CCUGGUCCCCCUGCUUCUCCUGGGGCUGCGCCGGCG AGGUGCGGGCCUUCCUGCAGGAGAACACCCACGUGC GGCUGCGGAUCUUCGCCGCCCGGAUCUACGACUACG ACCCCCUGUACAAGGAGGCCCUGCAGAUGCUGCGGG ACGCCGGCGCCCAGGUGUCCAUCAUGACCUACGACG AGUUCAAGCACUGCUGGGACACCUUCGUGGACCACC AGGGCUGCCCCUUCCAGCCCUGGGACGGCCUGGACG AGCACUCCCAGGCCCUGUCCGGCCGGCUGCGGGCCA UCCUGCAGAACCAGGGCAACUCCGGCUCCGAGACCC CCGGCACCUCCGAGUCCGCCACCCCCGAGUCCGACAA GAAGUACUCCAUCGGCCUGGCCAUCGGCACCAACUC CGUGGGCUGGGCCGUGAUCACCGACGAGUACAAGGU GCCCUCCAAGAAGUUCAAGGUGCUGGGCAACACCGA CCGGCACUCCAUCAAGAAGAACCUGAUCGGCGCCCU GCUGUUCGACUCCGGCGAGACCGCCGAGGCCACCCG GCUGAAGCGGACCGCCCGGCGGCGGUACACCCGGCG GAAGAACCGGAUCUGCUACCUGCAGGAGAUCUUCUC CAACGAGAUGGCCAAGGUGGACGACUCCUUCUUCCA CCGGCUGGAGGAGUCCUUCCUGGUGGAGGAGGACAA GAAGCACGAGCGGCACCCCAUCUUCGGCAACAUCGU GGACGAGGUGGCCUACCACGAGAAGUACCCCACCAU CUACCACCUGCGGAAGAAGCUGGUGGACUCCACCGA CAAGGCCGACCUGCGGCUGAUCUACCUGGCCCUGGC CCACAUGAUCAAGUUCCGGGGCCACUUCCUGAUCGA GGGCGACCUGAACCCCGACAACUCCGACGUGGACAA GCUGUUCAUCCAGCUGGUGCAGACCUACAACCAGCU GUUCGAGGAGAACCCCAUCAACGCCUCCGGCGUGGA CGCCAAGGCCAUCCUGUCCGCCCGGCUGUCCAAGUCC CGGCGGCUGGAGAACCUGAUCGCCCAGCUGCCCGGC GAGAAGAAGAACGGCCUGUUCGGCAACCUGAUCGCC CUGUCCCUGGGCCUGACCCCCAACUUCAAGUCCAAC UUCGACCUGGCCGAGGACGCCAAGCUGCAGCUGUCC AAGGACACCUACGACGACGACCUGGACAACCUGCUG GCCCAGAUCGGCGACCAGUACGCCGACCUGUUCCUG GCCGCCAAGAACCUGUCCGACGCCAUCCUGCUGUCC GACAUCCUGCGGGUGAACACCGAGAUCACCAAGGCC CCCCUGUCCGCCUCCAUGAUCAAGCGGUACGACGAG CACCACCAGGACCUGACCCUGCUGAAGGCCCUGGUG CGGCAGCAGCUGCCCGAGAAGUACAAGGAGAUCUUC UUCGACCAGUCCAAGAACGGCUACGCCGGCUACAUC

		GACGGCGGCGCCUCCCAGGAGGAGUUCUACAAGUUC AUCAAGCCCAUCCUGGAGAAGAUGGACGGCACCGAG GAGCUGCUGGUGAAGCUGAACCGGGAGGACCUGCUG CGGAAGCAGCGGACCUUCGACAACGGCUCCAUCCCC CACCAGAUCCACCUGGGCGAGCUGCACGCCAUCCUG CGGCGGCAGGAGGACUUCUACCCCUUCCUGAAGGAC AACCGGGAGAAGAUCGAGAAGAUCCUGACCUUCCGG AUCCCCUACUACGUGGGCCCCCUGGCCCGGGGCAAC UCCCGGUUCGCCUGGAUGACCCGGAAGUCCGAGGAG ACCAUCACCCCCUGGAACUUCGAGGAGGUGGUGGAC AAGGGCGCCUCCGCCCAGUCCUUCAUCGAGCGGAUG ACCAACUUCGACAAGAACCUGCCCAACGAGAAGGUG CUGCCCAAGCACUCCCUGCUGUACGAGUACUUCACC GUGUACAACGAGCUGACCAAGGUGAAGUACGUGACC GAGGGCAUGCGGAAGCCCGCCUUCCUGUCCGGCGAG CAGAAGAAGGCCAUCGUGGACCUGCUGUUCAAGACC AACCGGAAGGUGACCGUGAAGCAGCUGAAGGAGGAC UACUUCAAGAAGAUCGAGUGCUUCGACUCCGUGGAG AUCUCCGGCGUGGAGGACCGGUUCAACGCCUCCCUG GGCACCUACCACGACCUGCUGAAGAUCAUCAAGGAC AAGGACUUCCUGGACAACGAGGAGAACGAGGACAUC CUGGAGGACAUCGUGCUGACCCUGACCCUGUUCGAG GACCGGGAGAUGAUCGAGGAGCGGCUGAAGACCUAC GCCCACCUGUUCGACGACAAGGUGAUGAAGCAGCUG AAGCGGCGGCGGUACACCGGCUGGGGCCGGCUGUCC CGGAAGCUGAUCAACGGCAUCCGGGACAAGCAGUCC GGCAAGACCAUCCUGGACUUCCUGAAGUCCGACGGC UUCGCCAACCGGAACUUCAUGCAGCUGAUCCACGAC GACUCCCUGACCUUCAAGGAGGACAUCCAGAAGGCC CAGGUGUCCGGCCAGGGCGACUCCCUGCACGAGCAC AUCGCCAACCUGGCCGGCUCCCCCGCCAUCAAGAAG GGCAUCCUGCAGACCGUGAAGGUGGUGGACGAGCUG GUGAAGGUGAUGGGCCGGCACAAGCCCGAGAACAUC GUGAUCGAGAUGGCCCGGGAGAACCAGACCACCCAG AAGGGCCAGAAGAACUCCCGGGAGCGGAUGAAGCGG AUCGAGGAGGGCAUCAAGGAGCUGGGCUCCCAGAUC CUGAAGGAGCACCCCGUGGAGAACACCCAGCUGCAG AACGAGAAGCUGUACCUGUACUACCUGCAGAACGGC CGGGACAUGUACGUGGACCAGGAGCUGGACAUCAAC CGGCUGUCCGACUACGACGUGGACCACAUCGUGCCC CAGUCCUUCCUGAAGGACGACUCCAUCGACAACAAG GUGCUGACCCGGUCCGACAAGAACCGGGGCAAGUCC GACAACGUGCCCUCCGAGGAGGUGGUGAAGAAGAUG AAGAACUACUGGCGGCAGCUGCUGAACGCCAAGCUG AUCACCCAGCGGAAGUUCGACAACCUGACCAAGGCC GAGCGGGGCGGCCUGUCCGAGCUGGACAAGGCCGGC UUCAUCAAGCGGCAGCUGGUGGAGACCCGGCAGAUC ACCAAGCACGUGGCCCAGAUCCUGGACUCCCGGAUG AACACCAAGUACGACGAGAACGACAAGCUGAUCCGG

		GAGGUGAAGGUGAUCACCCUGAAGUCCAAGCUGGUG UCCGACUUCCGGAAGGACUUCCAGUUCUACAAGGUG CGGGAGAUCAACAACUACCACCACGCCCACGACGCC UACCUGAACGCCGUGGUGGGCACCGCCCUGAUCAAG AAGUACCCCAAGCUGGAGUCCGAGUUCGUGUACGGC GACUACAAGGUGUACGACGUGCGGAAGAUGAUCGCC AAGUCCGAGCAGGAGAUCGGCAAGGCCACCGCCAAG UACUUCUUCUACUCCAACAUCAUGAACUUCUUCAAG ACCGAGAUCACCCUGGCCAACGGCGAGAUCCGGAAG CGGCCCCUGAUCGAGACCAACGGCGAGACCGGCGAG AUCGUGUGGGACAAGGGCCGGGACUUCGCCACCGUG CGGAAGGUGCUGUCCAUGCCCCAGGUGAACAUCGUG AAGAAGACCGAGGUGCAGACCGGCGGCUUCUCCAAG GAGUCCAUCCUGCCCAAGCGGAACUCCGACAAGCUG AUCGCCCGGAAGAAGGACUGGGACCCCAAGAAGUAC GGCGGCUUCGACUCCCCCACCGUGGCCUACUCCGUGC UGGUGGUGGCCAAGGUGGAGAAGGGCAAGUCCAAGA AGCUGAAGUCCGUGAAGGAGCUGCUGGGCAUCACCA UCAUGGAGCGGUCCUCCUUCGAGAAGAACCCCAUCG ACUUCCUGGAGGCCAAGGGCUACAAGGAGGUGAAGA AGGACCUGAUCAUCAAGCUGCCCAAGUACUCCCUGU UCGAGCUGGAGAACGGCCGGAAGCGGAUGCUGGCCU CCGCCGGCGAGCUGCAGAAGGGCAACGAGCUGGCCC UGCCCUCCAAGUACGUGAACUUCCUGUACCUGGCCU CCCACUACGAGAAGCUGAAGGGCUCCCCCGAGGACA ACGAGCAGAAGCAGCUGUUCGUGGAGCAGCACAAGC ACUACCUGGACGAGAUCAUCGAGCAGAUCUCCGAGU UCUCCAAGCGGGUGAUCCUGGCCGACGCCAACCUGG ACAAGGUGCUGUCCGCCUACAACAAGCACCGGGACA AGCCCAUCCGGGAGCAGGCCGAGAACAUCAUCCACC UGUUCACCCUGACCAACCUGGGCGCCCCCGCCGCCUU CAAGUACUUCGACACCACCAUCGACCGGAAGCGGUA CACCUCCACCAAGGAGGUGCUGGACGCCACCCUGAU CCACCAGUCCAUCACCGGCCUGUACGAGACCCGGAU CGACCUGUCCCAGCUGGGCGGCGACGGCGGCGGCUC CCCCAAGAAGAAGCGGAAGGUGUCCGAGUCCGCCAC CCCCGAGUCCGUGUCCGGCUGGCGGCUGUUCAAGAA GAUCUCCUGA
	806	Not used
Open reading frame for UGI	807	AUGGGACCGAAGAAGAAGAGAAAGGUCGGAGGAGG AAGCACAAACCUGUCGGACAUCAUCGAAAAGGAAAC AGGAAAGCAGCUGGUCAUCCAGGAAUCGAUCCUGAU GCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAA GCCGGAAUCGGACAUCCUGGUCCACACAGCAUACGA CGAAUCGACAGACGAAAACGUCAUGCUGCUGACAUC GGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAU CCAGGACUCGAACGGAGAAAACAAGAUCAAGAUGCU

		GUGA
Open reading frame for UGI	808	AUGACCAACCUGUCCGACAUCAUCGAGAAGGAGACC GGCAAGCAGCUGGUGAUCCAGGAGUCCAUCCUGAUG CUGCCCGAGGAGGUGGAGGAGGUGAUCGGCAACAAG CCCGAGUCCGACAUCCUGGUGCACACCGCCUACGAC GAGUCCACCGACGAGAACGUGAUGCUGCUGACCUCC GACGCCCCCGAGUACAAGCCCUGGGCCCUGGUGAUC CAGGACUCCAACGGCGAGAACAAGAUCAAGAUGCUG UCCGGCGGCUCCAAGCGGACCGCCGACGGCUCCGAG UUCGAGUCCCCCAAGAAGAAGCGGAAGGUGGAGUGA
Amino acid sequence for Cas9 encoded by SEQ ID Nos. 801-802	809	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNT DRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKN RICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHP IFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLA LAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLF EENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNG LFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDL DNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKA PLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQ SKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKL NREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFL KDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETI TPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHS LLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVD LLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNAS LGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDRE MIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLIN GIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDI QKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDEL VKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIE EGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMY VDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDN LTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSR MNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVRE INNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKV YDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLAN GEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVN IVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYG GFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMER SSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRK RMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSP EDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDK VLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDT TIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDG GGSPKKKRKV
Amino acid sequence for	810	MDKKYSIGLDIGTNSVGWAVITDEYKVPSKKFKVLGNT DRHSIKKNLIGALLFDSGETAEATRLKRTARRRYTRRKN

Cas9 with Hibit tag		RICYLQEIFSNEMAKVDDSFFHRLEESFLVEEDKKHERHP IFGNIVDEVAYHEKYPTIYHLRKKLVDSTDKADLRLIYLA LAHMIKFRGHFLIEGDLNPDNSDVDKLFIQLVQTYNQLF EENPINASGVDAKAILSARLSKSRRLENLIAQLPGEKKNG LFGNLIALSLGLTPNFKSNFDLAEDAKLQLSKDTYDDDL DNLLAQIGDQYADLFLAAKNLSDAILLSDILRVNTEITKA PLSASMIKRYDEHHQDLTLLKALVRQQLPEKYKEIFFDQ SKNGYAGYIDGGASQEEFYKFIKPILEKMDGTEELLVKL NREDLLRKQRTFDNGSIPHQIHLGELHAILRRQEDFYPFL KDNREKIEKILTFRIPYYVGPLARGNSRFAWMTRKSEETI TPWNFEEVVDKGASAQSFIERMTNFDKNLPNEKVLPKHS LLYEYFTVYNELTKVKYVTEGMRKPAFLSGEQKKAIVD LLFKTNRKVTVKQLKEDYFKKIECFDSVEISGVEDRFNAS LGTYHDLLKIIKDKDFLDNEENEDILEDIVLTLTLFEDRE MIEERLKTYAHLFDDKVMKQLKRRRYTGWGRLSRKLIN GIRDKQSGKTILDFLKSDGFANRNFMQLIHDDSLTFKEDI QKAQVSGQGDSLHEHIANLAGSPAIKKGILQTVKVVDEL VKVMGRHKPENIVIEMARENQTTQKGQKNSRERMKRIE EGIKELGSQILKEHPVENTQLQNEKLYLYYLQNGRDMY VDQELDINRLSDYDVDHIVPQSFLKDDSIDNKVLTRSDK NRGKSDNVPSEEVVKKMKNYWRQLLNAKLITQRKFDN LTKAERGGLSELDKAGFIKRQLVETRQITKHVAQILDSR MNTKYDENDKLIREVKVITLKSKLVSDFRKDFQFYKVRE INNYHHAHDAYLNAVVGTALIKKYPKLESEFVYGDYKV YDVRKMIAKSEQEIGKATAKYFFYSNIMNFFKTEITLAN GEIRKRPLIETNGETGEIVWDKGRDFATVRKVLSMPQVN IVKKTEVQTGGFSKESILPKRNSDKLIARKKDWDPKKYG GFDSPTVAYSVLVVAKVEKGKSKKLKSVKELLGITIMER SSFEKNPIDFLEAKGYKEVKKDLIIKLPKYSLFELENGRK RMLASAGELQKGNELALPSKYVNFLYLASHYEKLKGSP EDNEQKQLFVEQHKHYLDEIIEQISEFSKRVILADANLDK VLSAYNKHRDKPIREQAENIIHLFTLTNLGAPAAFKYFDT TIDRKRYTSTKEVLDATLIHQSITGLYETRIDLSQLGGDG GGSPKKKRKVSESATPESVSGWRLFKKIS
Amino acid sequence for BC22n	811	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVER LDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFL DLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQ ENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMT YDEFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLR AILQNQGNSGSETPGTSESATPESDKKYSIGLAIGTNSVG WAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSG ETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDD SFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTI YHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDL NPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSA RLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKS NFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLA AKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDL TLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEE

		FYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIP HQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYV GPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKY VTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKED YFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFL DNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKV MKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSD GFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIA NLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMA RENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVEN TQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHI VPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKM KNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFI KRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVI TLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVG TALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKAT AKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVW DKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPK RNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEK GKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVK KDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPS KYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDE IIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENI IHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIH QSITGLYETRIDLSQLGGDGGGSPKKKRKV*
Amino acid sequence for BC22n with Hibit tag	812	MEASPASGPRHLMDPHIFTSNFNNGIGRHKTYLCYEVER LDNGTSVKMDQHRGFLHNQAKNLLCGFYGRHAELRFL DLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQ ENTHVRLRIFAARIYDYDPLYKEALQMLRDAGAQVSIMT YDEFKHCWDTFVDHQGCPFQPWDGLDEHSQALSGRLR AILQNQGNSGSETPGTSESATPESDKKYSIGLAIGTNSVG WAVITDEYKVPSKKFKVLGNTDRHSIKKNLIGALLFDSG ETAEATRLKRTARRRYTRRKNRICYLQEIFSNEMAKVDD SFFHRLEESFLVEEDKKHERHPIFGNIVDEVAYHEKYPTI YHLRKKLVDSTDKADLRLIYLALAHMIKFRGHFLIEGDL NPDNSDVDKLFIQLVQTYNQLFEENPINASGVDAKAILSA RLSKSRRLENLIAQLPGEKKNGLFGNLIALSLGLTPNFKS NFDLAEDAKLQLSKDTYDDDLDNLLAQIGDQYADLFLA AKNLSDAILLSDILRVNTEITKAPLSASMIKRYDEHHQDL TLLKALVRQQLPEKYKEIFFDQSKNGYAGYIDGGASQEE FYKFIKPILEKMDGTEELLVKLNREDLLRKQRTFDNGSIP HQIHLGELHAILRRQEDFYPFLKDNREKIEKILTFRIPYYV GPLARGNSRFAWMTRKSEETITPWNFEEVVDKGASAQS FIERMTNFDKNLPNEKVLPKHSLLYEYFTVYNELTKVKY VTEGMRKPAFLSGEQKKAIVDLLFKTNRKVTVKQLKED YFKKIECFDSVEISGVEDRFNASLGTYHDLLKIIKDKDFL DNEENEDILEDIVLTLTLFEDREMIEERLKTYAHLFDDKV MKQLKRRRYTGWGRLSRKLINGIRDKQSGKTILDFLKSD

		GFANRNFMQLIHDDSLTFKEDIQKAQVSGQGDSLHEHIA NLAGSPAIKKGILQTVKVVDELVKVMGRHKPENIVIEMA RENQTTQKGQKNSRERMKRIEEGIKELGSQILKEHPVEN TQLQNEKLYLYYLQNGRDMYVDQELDINRLSDYDVDHI VPQSFLKDDSIDNKVLTRSDKNRGKSDNVPSEEVVKKM KNYWRQLLNAKLITQRKFDNLTKAERGGLSELDKAGFI KRQLVETRQITKHVAQILDSRMNTKYDENDKLIREVKVI TLKSKLVSDFRKDFQFYKVREINNYHHAHDAYLNAVVG TALIKKYPKLESEFVYGDYKVYDVRKMIAKSEQEIGKAT AKYFFYSNIMNFFKTEITLANGEIRKRPLIETNGETGEIVW DKGRDFATVRKVLSMPQVNIVKKTEVQTGGFSKESILPK RNSDKLIARKKDWDPKKYGGFDSPTVAYSVLVVAKVEK GKSKKLKSVKELLGITIMERSSFEKNPIDFLEAKGYKEVK KDLIIKLPKYSLFELENGRKRMLASAGELQKGNELALPS KYVNFLYLASHYEKLKGSPEDNEQKQLFVEQHKHYLDE IIEQISEFSKRVILADANLDKVLSAYNKHRDKPIREQAENI IHLFTLTNLGAPAAFKYFDTTIDRKRYTSTKEVLDATLIH QSITGLYETRIDLSQLGGDGGGSPKKKRKVSESATPESVS GWRLFKKIS
	813	Not used
Amino acid sequence for UGI	814	MTNLSDIIEKETGKQLVIQESILMLPEEVEEVIGNKPESDI LVHTAYDESTDENVMLLTSDAPEYKPWALVIQDSNGEN KIKMLSGGSKRTADGSEFESPKKKRKVE
	815	Not used
G023519 Guide RNA Targeting B2M	816	mA*mC*mU*CACGCUGGAUAGCCUCCGUUUUAGAmG mCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAG GCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmU mGmC*mU
Open reading frame for Cas9	817	AUGGACAAGAAGUACAGCAUCGGACUGGACAUCGGA ACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAA UACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGA AACACAGACAGACACAGCAUCAAGAAGAACCUGAUC GGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAA GCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUAC ACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAA AUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGC UUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAA GAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGA AACAUCGUCGACGAAGUCGCAUACCACGAAAAGUAC CCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGAC AGCACAGACAAGGCAGACCUGAGACUGAUCUACCUG GCACUGGCACACAUGAUCAAGUUCAGAGGACACUUC CUGAUCGAAGGAGACCUGAACCCGGACAACAGCGAC GUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUAC AACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGC GGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUG AGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAG CUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAAC

		CUGAUCGCACUGAGCCUGGGACUGACACCGAACUUC AAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUG CAGCUGAGCAAGGACACAUACGACGACGACCUGGAC AACCUGCUGGCACAGAUCGGAGACCAGUACGCAGAC CUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUC CUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUC ACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGA UACGACGAACACCACCAGGACCUGACACUGCUGAAG GCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAG GAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCA GGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUC UACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGAC GGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAA GACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGA AGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCAC GCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUC CUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUG ACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCA AGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAG AGCGAAGAAACAAUCACACCGUGGAACUUCGAAGAA GUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUC GAAAGAAUGACAAACUUCGACAAGAACCUGCCGAAC GAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAA UACUUCACAGUCUACAACGAACUGACAAAGGUCAAG UACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUG AGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUG UUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUG AAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGAC AGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAAC GCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUC AUCAAGGACAAGGACUUCCUGGACAACGAAGAAAAC GAAGACAUCCUGGAAGACAUCGUCCUGACACUGACA CUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUG AAGACAUACGCACACCUGUUCGACGACAAGGUCAUG AAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGA AGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGAC AAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAG AGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUG AUCCACGACGACAGCCUGACAUUCAAGGAAGACAUC CAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUG CACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCA AUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUC GACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCG GAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAG ACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGA AUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGG AAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACAC ACAGCUGCAGAACGAAAAGCUGUACCUGUACUACCU GCAGAACGGAAGAGACAUGUACGUCGACCAGGAACU

		GGACAUCAACAGACUGAGCGACUACGACGUCGACCA CAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAU CGACAACAAGGUCCUGACAAGAAGCGACAAGAACAG AGGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGU CAAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAA CGCAAAGCUGAUCACACAGAGAAAGUUCGACAACCU GACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGA CAAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAAC AAGACAGAUCACAAAGCACGUCGCACAGAUCCUGGA CAGCAGAAUGAACACAAAGUACGACGAAAACGACAA GCUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAG CAAGCUG GUCAGCGACUUCAGAAAGGACUUCCAGUUCUACAAG GUCAGAGAAAUCAACAACUACCACCACGCACACGAC GCAUACCUGAACGCAGUCGUCGGAACAGCACUGAUC AAGAAGUACCCGAAGCUGGAAAGCGAAUUCGUCUAC GGAGACUACAAGGUCUACGACGUCAGAAAGAUGAUC GCAAAGAGCGAACAGGAAAUCGGAAAGGCAACAGCA AAGUACUUCUUCUACAGCAACAUCAUGAACUUCUUC AAGACAGAAAUCACACUGGCAAACGGAGAAAUCAGA AAGAGACCGCUGAUCGAAACAAACGGAGAAACAGGA GAAAUCGUCUGGGACAAGGGAAGAGACUUCGCAACA GUCAGAAAGGUCCUGAGCAUGCCGCAGGUCAACAUC GUCAAGAAGACAGAAGUCCAGACAGGAGGAUUCAGC AAGGAAAGCAUCCUGCCGAAGAGAAACAGCGACAAG CUGAUCGCAAGAAAGAAGGACUGGGACCCGAAGAAG UACGGAGGAUUCGACAGCCCGACAGUCGCAUACAGC GUCCUGGUCGUCGCAAAGGUCGAAAAGGGAAAGAGC AAGAAGCUGAAGAGCGUCAAGGAACUGCUGGGAAUC ACAAUCAUGGAAAGAAGCAGCUUCGAAAAGAACCCG AUCGACUUCCUGGAAGCAAAGGGAUACAAGGAAGUC AAGAAGGACCUGAUCAUCAAGCUGCCGAAGUACAGC CUGUUCGAACUGGAAAACGGAAGAAAGAGAAUGCUG GCAAGCGCAGGAGAACUGCAGAAGGGAAACGAACUG GCACUGCCGAGCAAGUACGUCAACUUCCUGUACCUG GCAAGCCACUACGAAAAGCUGAAGGGAAGCCCGGAA GACAACGAACAGAAGCAGCUGUUCGUCGAACAGCAC AAGCACUACCUGGACGAAAUCAUCGAACAGAUCAGC GAAUUCAGCAAGAGAGUCAUCCUGGCAGACGCAAAC CUGGACAAGGUCCUGAGCGCAUACAACAAGCACAGA GACAAGCCGAUCAGAGAACAGGCAGAAAACAUCAUC CACCUGUUCACACUGACAAACCUGGGAGCACCGGCA GCAUUCAAGUACUUCGACACAACAAUCGACAGAAAG AGAUACACAAGCACAAAGGAAGUCCUGGACGCAACA CUGAUCCACCAGAGCAUCACAGGACUGUACGAAACA AGAAUCGACCUGAGCCAGCUGGGAGGAGACGGAGGA GGAAGCCCGAAGAAGAAGAGAAAGGUCUAG
Open reading frame for	818	AUGGAAGCAAGCCCGGCAAGCGGACCGAGACACCUG AUGGACCCGCACAUCUUCACAAGCAACUUCAACAAC

BC22		GGAAUCGGAAGACACAAGACAUACCUGUGCUACGAA GUCGAAAGACUGGACAACGGAACAAGCGUCAAGAUG GACCAGCACAGAGGAUUCCUGCACAACCAGGCAAAG AACCUGCUGUGCGGAUUCUACGGAAGACACGCAGAA CUGAGAUUCCUGGACCUGGUCCCGAGCCUGCAGCUG GACCCGGCACAGAUCUACAGAGUCACAUGGUUCAUC AGCUGGAGCCCGUGCUUCAGCUGGGGAUGCGCAGGA GAAGUCAGAGCAUUUCUGCAGGAAAACACACACGUC AGACUGAGAAUCUUCGCAGCAAGAAUCUAC GACUACGACCCGCUGUACAAGGAAGCACUGCAGAUG CUGAGAGACGCAGGAGCACAGGUCAGCAUCAUGACA UACGACGAAUUCAAGCACUGCUGGGACACAUUCGUC GACCACCAGGGAUGCCCGUUCCAGCCGUGGGACGGA CUGGACGAACACAGCCAGGCACUGAGCGGAAGACUG AGAGCAAUCCUGCAGAACCAGGGAAACAGCGGAAGC GAAACACCGGGAACAAGCGAAAGCGCAACACCGGAA AGCGACAAGAAGUACAGCAUCGGACUGGCCAUCGGA ACAAACAGCGUCGGAUGGGCAGUCAUCACAGACGAA UACAAGGUCCCGAGCAAGAAGUUCAAGGUCCUGGGA AACACAGACAGACACAGCAUCAAGAAGAACCUGAUC GGAGCACUGCUGUUCGACAGCGGAGAAACAGCAGAA GCAACAAGACUGAAGAGAACAGCAAGAAGAAGAUAC ACAAGAAGAAAGAACAGAAUCUGCUACCUGCAGGAA AUCUUCAGCAACGAAAUGGCAAAGGUCGACGACAGC UUCUUCCACAGACUGGAAGAAAGCUUCCUGGUCGAA GAAGACAAGAAGCACGAAAGACACCCGAUCUUCGGA AACAUCGUCGACGAAGUCGCAUACCACGAAAAGUAC CCGACAAUCUACCACCUGAGAAAGAAGCUGGUCGAC AGCACAGACAAGGCAGACCUGAGACUGAUCUACCUG GCACUGGCACACAUGAUCAAGUUCAGAGGACACUUC CUGAUCGAAGGAGACCUGAACCCGGACAACAGCGAC GUCGACAAGCUGUUCAUCCAGCUGGUCCAGACAUAC AACCAGCUGUUCGAAGAAAACCCGAUCAACGCAAGC GGAGUCGACGCAAAGGCAAUCCUGAGCGCAAGACUG AGCAAGAGCAGAAGACUGGAAAACCUGAUCGCACAG CUGCCGGGAGAAAAGAAGAACGGACUGUUCGGAAAC CUGAUCGCACUGAGCCUGGGACUGACACCGAACUUC AAGAGCAACUUCGACCUGGCAGAAGACGCAAAGCUG CAGCUGAGCAAGGACACAUACGACGACGACCUGGAC AACCUGCUGGCACAGAUCGGAGACCAGUACGCAGAC CUGUUCCUGGCAGCAAAGAACCUGAGCGACGCAAUC CUGCUGAGCGACAUCCUGAGAGUCAACACAGAAAUC ACAAAGGCACCGCUGAGCGCAAGCAUGAUCAAGAGA UACGACGAACACCACCAGGACCUGACACUGCUGAAG GCACUGGUCAGACAGCAGCUGCCGGAAAAGUACAAG GAAAUCUUCUUCGACCAGAGCAAGAACGGAUACGCA GGAUACAUCGACGGAGGAGCAAGCCAGGAAGAAUUC UACAAGUUCAUCAAGCCGAUCCUGGAAAAGAUGGAC GGAACAGAAGAACUGCUGGUCAAGCUGAACAGAGAA

		GACCUGCUGAGAAAGCAGAGAACAUUCGACAACGGA AGCAUCCCGCACCAGAUCCACCUGGGAGAACUGCAC GCAAUCCUGAGAAGACAGGAAGACUUCUACCCGUUC CUGAAGGACAACAGAGAAAAGAUCGAAAAGAUCCUG ACAUUCAGAAUCCCGUACUACGUCGGACCGCUGGCA AGAGGAAACAGCAGAUUCGCAUGGAUGACAAGAAAG AGCGAAGAAACAAUCACACCGUGGAACUUCGAAGAA GUCGUCGACAAGGGAGCAAGCGCACAGAGCUUCAUC GAAAGAAUGACAAACUUCGACAAGAACCUGCCGAAC GAAAAGGUCCUGCCGAAGCACAGCCUGCUGUACGAA UACUUCACAGUCUACAACGAACUGACAAAGGUCAAG UACGUCACAGAAGGAAUGAGAAAGCCGGCAUUCCUG AGCGGAGAACAGAAGAAGGCAAUCGUCGACCUGCUG UUCAAGACAAACAGAAAGGUCACAGUCAAGCAGCUG AAGGAAGACUACUUCAAGAAGAUCGAAUGCUUCGAC AGCGUCGAAAUCAGCGGAGUCGAAGACAGAUUCAAC GCAAGCCUGGGAACAUACCACGACCUGCUGAAGAUC AUCAAGGACAAGGACUUCCUGGACAACGAAGAAAAC GAAGACAUCCUGGAAGACAUCGUCCUGACACUGACA CUGUUCGAAGACAGAGAAAUGAUCGAAGAAAGACUG AAGACAUACGCACACCUGUUCGACGACAAGGUCAUG AAGCAGCUGAAGAGAAGAAGAUACACAGGAUGGGGA AGACUGAGCAGAAAGCUGAUCAACGGAAUCAGAGAC AAGCAGAGCGGAAAGACAAUCCUGGACUUCCUGAAG AGCGACGGAUUCGCAAACAGAAACUUCAUGCAGCUG AUCCACGACGACAGCCUGACAUUCAAGGAAGACAUC CAGAAGGCACAGGUCAGCGGACAGGGAGACAGCCUG CACGAACACAUCGCAAACCUGGCAGGAAGCCCGGCA AUCAAGAAGGGAAUCCUGCAGACAGUCAAGGUCGUC GACGAACUGGUCAAGGUCAUGGGAAGACACAAGCCG GAAAACAUCGUCAUCGAAAUGGCAAGAGAAAACCAG ACAACACAGAAGGGACAGAAGAACAGCAGAGAAAGA AUGAAGAGAAUCGAAGAAGGAAUCAAGGAACUGGG AAGCCAGAUCCUGAAGGAACACCCGGUCGAAAACAC ACAGCUGCAGAACGAAAAGCUGUACCUGUACUACCU GCAGAACGGAAGAGACAUGUACGUCGACCAGGAACU GGACAUCAACAGACUGAGCGACUACGACGUCGACCA CAUCGUCCCGCAGAGCUUCCUGAAGGACGACAGCAU C GACAACAAGGUCCUGACAAGAAGCGACAAGAACAGA GGAAAGAGCGACAACGUCCCGAGCGAAGAAGUCGUC AAGAAGAUGAAGAACUACUGGAGACAGCUGCUGAAC GCAAAGCUGAUCACACAGAGAAAGUUCGACAACCUG ACAAAGGCAGAGAGAGGAGGACUGAGCGAACUGGAC AAGGCAGGAUUCAUCAAGAGACAGCUGGUCGAAACA AGACAGAUCACAAAGCACGUCGCACAGAUCCUGGAC AGCAGAAUGAACACAAAGUACGACGAAAACGACAAG CUGAUCAGAGAAGUCAAGGUCAUCACACUGAAGAGC AAGCUGGUCAGCGACUUCAGAAAGGACUUCCAGUUC

		UACAAGGUCAGAGAAAUCAACAACUACCACCACGCA CACGACGCAUACCUGAACGCAGUCGUCGGAACAGCA CUGAUCAAGAAGUACCCGAAGCUGGAAAGCGAAUUC GUCUACGGAGACUACAAGGUCUACGACGUCAGAAAG AUGAUCGCAAAGAGCGAACAGGAAAUCGGAAAGGCA ACAGCAAAGUACUUCUUCUACAGCAACAUCAUGAAC UUCUUCAAGACAGAAAUCACACUGGCAAACGGAGAA AUCAGAAAGAGACCGCUGAUCGAAACAAACGGAGAA ACAGGAGAAAUCGUCUGGGACAAGGGAAGAGACUUC GCAACAGUCAGAAAGGUCCUGAGCAUGCCGCAGGUC AACAUCGUCAAGAAGACAGAAGUCCAGACAGGAGGA UUCAGCAAGGAAAGCAUCCUGCCGAAGAGAAACAGC GACAAGCUGAUCGCAAGAAAGAAGGACUGGGACCCG AAGAAGUACGGAGGAUUCGACAGCCCGACAGUCGCA UACAGCGUCCUGGUCGUCGCAAAGGUCGAAAAGGGA AAGAGCAAGAAGCUGAAGAGCGUCAAGGAACUGCUG GGAAUCACAAUCAUGGAAAGAAGCAGCUUCGAAAAG AACCCGAUCGACUUCCUGGAAGCAAAGGGAUACAAG GAAGUCAAGAAGGACCUGAUCAUCAAGCUGCCGAAG UACAGCCUGUUCGAACUGGAAAACGGAAGAAAGAGA AUGCUGGCAAGCGCAGGAGAACUGCAGAAGGGAAAC GAACUGGCACUGCCGAGCAAGUACGUCAACUUCCUG UACCUGGCAAGCCACUACGAAAAGCUGAAGGGAAGC CCGGAAGACAACGAACAGAAGCAGCUGUUCGUCGAA CAGCACAAGCACUACCUGGACGAAAUCAUCGAACAG AUCAGCGAAUUCAGCAAGAGAGUCAUCCUGGCAGAC GCAAACCUGGACAAGGUCCUGAGCGCAUACAACAAG CACAGAGACAAGCCGAUCAGAGAACAGGCAGAAAAC AUCAUCCACCUGUUCACACUGACAAACCUGGGAGCA CCGGCAGCAUUCAAGUACUUCGACACAACAAUCGAC AGAAAGAGAUACACAAGCACAAAGGAAGUCCUGGAC GCAACACUGAUCCACCAGAGCAUCACAGGACUGUAC GAAACAAGAAUCGAUCUGAGCCAGCUGGGAGGAGAC AGCGGAGGAAGCACAAACCUGAGCGACAUCAUCGAA AAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAAGC AUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUC GGAAACAAGCCGGAAAGCGACAUCCUGGUCCACACA GCAUACGACGAAAGCACAGACGAAAACGUCAUGCUG CUGACAAGCGACGCACCGGAAUACAAGCCGUGGGCA CUGGUCAUCCAGGACAGCAACGGAGAAAACAAGAUC AAGAUGCUGAGCGGAGGAAGCCCGAAGAAGAAGAGA AAGGUCUAA
Open reading frame for UGI	819	AUGGGACCGAAGAAGAAGAGAAAGGUCGGAGGAGG AAGCACAAACCUGUCGGACAUCAUCGAAAAGGAAAC AGGAAAGCAGCUGGUCAUCCAGGAAUCGAUCCUGAU GCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAA GCCGGAAUCGGACAUCCUGGUCCACACAGCAUACGA CGAAUCGACAGACGAAAACGUCAUGCUGCUGACAUC GGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAU

		CCAGGACUCGAACGGAGAAAACAAGAUCAAGAUGCU GUGA
	820-899, 903-971	Not used
mRNA encoding BC22n	972	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAU CUGCCACCAUGGAGGCCUCCCCCGCCUCCGGCCCCCG GCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUC AACAACGGCAUCGGCCGGCACAAGACCUACCUGUGC UACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUG AAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAG GCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCAC GCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUG CAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGG UUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGC GCCGGCGAGGUGCGGGCCUUCCUGCAGGAGAACACC CACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUAC GACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUG CUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACC UACGACGAGUUCAAGCACUGCUGGGACACCUUCGUG GACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCC UGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGC GGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCG AGACCCCCGGCACCUCCGAGUCCGCCACCCCCGAGUC CGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCAC CAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUA CAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAA CACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGG CGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGC CACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACAC CCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAU CUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUU CUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGA GGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAA CAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCC CACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUC CACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGC CCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCU GAUCGAGGGCGACCUGAACCCCGACAACUCCGACGU GGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAA CCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGG CGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUC CAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCU GCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCU GAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAA GUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCA GCUGUCCAAGGACACCUACGACGACGACCUGGACAA CCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCU GUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCU

		GCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCAC CAAGGCCCCCCUGUCCGCCUCCAUGAUCAAGCGGUA CGACGAGCACCACCAGGACCUGACCCUGCUGAAGGC CCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGA GAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGG CUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUA CAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGG CACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGA CCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUC CAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCC AUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUG AAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACC UUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGG GGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCC GAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUG GUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAG CGGAUGACCAACUUCGACAAGAACCUGCCCAACGAG AAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUAC UUCACCGUGUACAACGAGCUGACCAAGGUGAAGUAC GUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCC GGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUC AAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAG GAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCC GUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCC UCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUC AAGGACAAGGACUUCCUGGACAACGAGGAGAACGAG GACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUG UUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAG ACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAG CAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGG CUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAG CAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCC GACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUC CACGACGACUCCCUGACCUUCAAGGAGGACAUCCAG AAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCAC GAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCA AGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACG AGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGA ACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCA CCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGA AGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCC AGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGC UGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGA ACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACA UCAACCGGCUGUCCGACUACGACGUGGACCACAUCG UGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACA ACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCA AGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGA AGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCA AGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCA

		AGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGG CCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGC AGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCC GGAUGAACACCAAGUACGACGAGAACGACAAGCUGA UCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGC UGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACA AGGUGCGGGAGAUCAACAACUACCACCACGCCCACG ACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGA UCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGU ACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGA UCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCG CCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCU UCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCC GGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCG GCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCA CCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACA UCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCU CCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACA AGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGA AGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACU CCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGU CCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCA UCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACC CCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGG UGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACU CCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGC UGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGC UGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACC UGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCG AGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGC ACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCU CCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCA ACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACC GGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCA UCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGC CGCCUUCAAGUACUUCGACACCACCAUCGACCGGAA GCGGUACACCUCCACCAAGGAGGUGCUGGACGCCAC CCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGAC CCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGG CGGCUCCCCCAAGAAGAAGCGGAAGGUGUGACUAGC ACCAGCCUCAAGAACACCCGAAUGGAGUCUCUAAGC UACAUAAUACCAACUUACACUUUACAAAAUGUUGUC CCCCAAAAUGUAGCCAUUCGUAUCUGCUCCUAAUAA AAAGAAAGUUUCUUCACAUUCUCUCGAGAAAAAAAA AAAAUGGAAAAAAAAAAAACGGAAAAAAAAAAAAG GUAAAAAAAAAAAAUAUAAAAAAAAAAAACAUAAA AAAAAAAAACGAAAAAAAAAAAACGUAAAAAAAAA AAACUCAAAAAAAAAAAAGAUAAAAAAAAAAAACCU AAAAAAAAAAAAUGUAAAAAAAAAAAAGGGAAAAA AAAAAAACGCAAAAAAAAAAAACACAAAAAAAAAAA

		AUGCAAAAAAAAAAAAUCGAAAAAAAAAAAAUCUA AAAAAAAAAAAACGAAAAAAAAAAAACCCAAAAAAAA AAAAGACAAAAAAAAAAAAUAGAAAAAAAAAAAAG UUAAAAAAAAAAAACUGAAAAAAAAAAAAUUUAAA AAAAAAAAAUCUAG
mRNA encoding BC22n with HiBit tag	973	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAU CUGCCACCAUGGAGGCCUCCCCGCCUCCGGCCCCCG GCACCUGAUGGACCCCCACAUCUUCACCUCCAACUUC AACAACGGCAUCGGCCGGCACAAGACCUACCUGUGC UACGAGGUGGAGCGGCUGGACAACGGCACCUCCGUG AAGAUGGACCAGCACCGGGGCUUCCUGCACAACCAG GCCAAGAACCUGCUGUGCGGCUUCUACGGCCGGCAC GCCGAGCUGCGGUUCCUGGACCUGGUGCCCUCCCUG CAGCUGGACCCCGCCCAGAUCUACCGGGUGACCUGG UUCAUCUCCUGGUCCCCCUGCUUCUCCUGGGGCUGC GCCGGCGAGGUGCGGCCUUCCUGCAGGAGAACACC CACGUGCGGCUGCGGAUCUUCGCCGCCCGGAUCUAC GACUACGACCCCCUGUACAAGGAGGCCCUGCAGAUG CUGCGGGACGCCGGCGCCCAGGUGUCCAUCAUGACC UACGACGAGUUCAAGCACUGCUGGGACACCUUCGUG GACCACCAGGGCUGCCCCUUCCAGCCCUGGGACGGCC UGGACGAGCACUCCCAGGCCCUGUCCGGCCGGCUGC GGGCCAUCCUGCAGAACCAGGGCAACUCCGGCUCCG AGACCCCCGGCACCUCCGAGUCCGCCACCCCCGAGUC CGACAAGAAGUACUCCAUCGGCCUGGCCAUCGGCAC CAACUCCGUGGGCUGGGCCGUGAUCACCGACGAGUA CAAGGUGCCCUCCAAGAAGUUCAAGGUGCUGGGCAA CACCGACCGGCACUCCAUCAAGAAGAACCUGAUCGG CGCCCUGCUGUUCGACUCCGGCGAGACCGCCGAGGC CACCCGGCUGAAGCGGACCGCCCGGCGGCGGUACAC CCGGCGGAAGAACCGGAUCUGCUACCUGCAGGAGAU CUUCUCCAACGAGAUGGCCAAGGUGGACGACUCCUU CUUCCACCGGCUGGAGGAGUCCUUCCUGGUGGAGGA GGACAAGAAGCACGAGCGGCACCCCAUCUUCGGCAA CAUCGUGGACGAGGUGGCCUACCACGAGAAGUACCC CACCAUCUACCACCUGCGGAAGAAGCUGGUGGACUC CACCGACAAGGCCGACCUGCGGCUGAUCUACCUGGC CCUGGCCCACAUGAUCAAGUUCCGGGGCCACUUCCU GAUCGAGGGCGACCUGAACCCCGACAACUCCGACGU GGACAAGCUGUUCAUCCAGCUGGUGCAGACCUACAA CCAGCUGUUCGAGGAGAACCCCAUCAACGCCUCCGG CGUGGACGCCAAGGCCAUCCUGUCCGCCCGGCUGUC CAAGUCCCGGCGGCUGGAGAACCUGAUCGCCCAGCU GCCCGGCGAGAAGAAGAACGGCCUGUUCGGCAACCU GAUCGCCCUGUCCCUGGGCCUGACCCCCAACUUCAA GUCCAACUUCGACCUGGCCGAGGACGCCAAGCUGCA GCUGUCCAAGGACACCUACGACGACGACCUGGACAA CCUGCUGGCCCAGAUCGGCGACCAGUACGCCGACCU GUUCCUGGCCGCCAAGAACCUGUCCGACGCCAUCCU GCUGUCCGACAUCCUGCGGGUGAACACCGAGAUCAC

		CAAGGCCCCCUGUCCGCCUCCAUGAUCAAGCGGUA CGACGAGCACCACCAGGACCUGACCCUGCUGAAGGC CCUGGUGCGGCAGCAGCUGCCCGAGAAGUACAAGGA GAUCUUCUUCGACCAGUCCAAGAACGGCUACGCCGG CUACAUCGACGGCGGCGCCUCCCAGGAGGAGUUCUA CAAGUUCAUCAAGCCCAUCCUGGAGAAGAUGGACGG CACCGAGGAGCUGCUGGUGAAGCUGAACCGGGAGGA CCUGCUGCGGAAGCAGCGGACCUUCGACAACGGCUC CAUCCCCCACCAGAUCCACCUGGGCGAGCUGCACGCC AUCCUGCGGCGGCAGGAGGACUUCUACCCCUUCCUG AAGGACAACCGGGAGAAGAUCGAGAAGAUCCUGACC UUCCGGAUCCCCUACUACGUGGGCCCCCUGGCCCGG GGCAACUCCCGGUUCGCCUGGAUGACCCGGAAGUCC GAGGAGACCAUCACCCCCUGGAACUUCGAGGAGGUG GUGGACAAGGGCGCCUCCGCCCAGUCCUUCAUCGAG CGGAUGACCAACUUCGACAAGAACCUGCCCAACGAG AAGGUGCUGCCCAAGCACUCCCUGCUGUACGAGUAC UUCACCGUGUACAACGAGCUGACCAAGGUGAAGUAC GUGACCGAGGGCAUGCGGAAGCCCGCCUUCCUGUCC GGCGAGCAGAAGAAGGCCAUCGUGGACCUGCUGUUC AAGACCAACCGGAAGGUGACCGUGAAGCAGCUGAAG GAGGACUACUUCAAGAAGAUCGAGUGCUUCGACUCC GUGGAGAUCUCCGGCGUGGAGGACCGGUUCAACGCC UCCCUGGGCACCUACCACGACCUGCUGAAGAUCAUC AAGGACAAGGACUUCCUGGACAACGAGGAGAACGAG GACAUCCUGGAGGACAUCGUGCUGACCCUGACCCUG UUCGAGGACCGGGAGAUGAUCGAGGAGCGGCUGAAG ACCUACGCCCACCUGUUCGACGACAAGGUGAUGAAG CAGCUGAAGCGGCGGCGGUACACCGGCUGGGGCCGG CUGUCCCGGAAGCUGAUCAACGGCAUCCGGGACAAG CAGUCCGGCAAGACCAUCCUGGACUUCCUGAAGUCC GACGGCUUCGCCAACCGGAACUUCAUGCAGCUGAUC CACGACGACUCCCUGACCUUCAAGGAGGACAUCCAG AAGGCCCAGGUGUCCGGCCAGGGCGACUCCCUGCAC GAGCACAUCGCCAACCUGGCCGGCUCCCCCGCCAUCA AGAAGGGCAUCCUGCAGACCGUGAAGGUGGUGGACG AGCUGGUGAAGGUGAUGGGCCGGCACAAGCCCGAGA ACAUCGUGAUCGAGAUGGCCCGGGAGAACCAGACCA CCCAGAAGGGCCAGAAGAACUCCCGGGAGCGGAUGA AGCGGAUCGAGGAGGGCAUCAAGGAGCUGGGCUCCC AGAUCCUGAAGGAGCACCCCGUGGAGAACACCCAGC UGCAGAACGAGAAGCUGUACCUGUACUACCUGCAGA ACGGCCGGGACAUGUACGUGGACCAGGAGCUGGACA UCAACCGGCUGUCCGACUACGACGUGGACCACAUCG UGCCCCAGUCCUUCCUGAAGGACGACUCCAUCGACA ACAAGGUGCUGACCCGGUCCGACAAGAACCGGGGCA AGUCCGACAACGUGCCCUCCGAGGAGGUGGUGAAGA AGAUGAAGAACUACUGGCGGCAGCUGCUGAACGCCA AGCUGAUCACCCAGCGGAAGUUCGACAACCUGACCA AGGCCGAGCGGGGCGGCCUGUCCGAGCUGGACAAGG

		CCGGCUUCAUCAAGCGGCAGCUGGUGGAGACCCGGC AGAUCACCAAGCACGUGGCCCAGAUCCUGGACUCCC GGAUGAACACCAAGUACGACGAGAACGACAAGCUGA UCCGGGAGGUGAAGGUGAUCACCCUGAAGUCCAAGC UGGUGUCCGACUUCCGGAAGGACUUCCAGUUCUACA AGGUGCGGGAGAUCAACAACUACCACCACGCCCACG ACGCCUACCUGAACGCCGUGGUGGGCACCGCCCUGA UCAAGAAGUACCCCAAGCUGGAGUCCGAGUUCGUGU ACGGCGACUACAAGGUGUACGACGUGCGGAAGAUGA UCGCCAAGUCCGAGCAGGAGAUCGGCAAGGCCACCG CCAAGUACUUCUUCUACUCCAACAUCAUGAACUUCU UCAAGACCGAGAUCACCCUGGCCAACGGCGAGAUCC GGAAGCGGCCCCUGAUCGAGACCAACGGCGAGACCG GCGAGAUCGUGUGGGACAAGGGCCGGGACUUCGCCA CCGUGCGGAAGGUGCUGUCCAUGCCCCAGGUGAACA UCGUGAAGAAGACCGAGGUGCAGACCGGCGGCUUCU CCAAGGAGUCCAUCCUGCCCAAGCGGAACUCCGACA AGCUGAUCGCCCGGAAGAAGGACUGGGACCCCAAGA AGUACGGCGGCUUCGACUCCCCCACCGUGGCCUACU CCGUGCUGGUGGUGGCCAAGGUGGAGAAGGGCAAGU CCAAGAAGCUGAAGUCCGUGAAGGAGCUGCUGGGCA UCACCAUCAUGGAGCGGUCCUCCUUCGAGAAGAACC CCAUCGACUUCCUGGAGGCCAAGGGCUACAAGGAGG UGAAGAAGGACCUGAUCAUCAAGCUGCCCAAGUACU CCCUGUUCGAGCUGGAGAACGGCCGGAAGCGGAUGC UGGCCUCCGCCGGCGAGCUGCAGAAGGGCAACGAGC UGGCCCUGCCCUCCAAGUACGUGAACUUCCUGUACC UGGCCUCCCACUACGAGAAGCUGAAGGGCUCCCCCG AGGACAACGAGCAGAAGCAGCUGUUCGUGGAGCAGC ACAAGCACUACCUGGACGAGAUCAUCGAGCAGAUCU CCGAGUUCUCCAAGCGGGUGAUCCUGGCCGACGCCA ACCUGGACAAGGUGCUGUCCGCCUACAACAAGCACC GGGACAAGCCCAUCCGGGAGCAGGCCGAGAACAUCA UCCACCUGUUCACCCUGACCAACCUGGGCGCCCCCGC CGCCUUCAAGUACUUCGACACCACCAUCGACCGGAA GCGGUACACCUCCACCAAGGAGGUGCUGGACGCCAC CCUGAUCCACCAGUCCAUCACCGGCCUGUACGAGAC CCGGAUCGACCUGUCCCAGCUGGGCGGCGACGGCGG CGGCUCCCCCAAGAAGAAGCGGAAGGUGUCCGAGUC CGCCACCCCCGAGUCCGUGUCCGGCUGGCGGCUGUU CAAGAAGAUCUCCUGACUAGCACCAGCCUCAAGAAC ACCCGAAUGGAGUCUCUAAGCUACAUAAUACCAACU UACACUUUACAAAAUGUUGUCCCCCAAAAUGUAGCC AUUCGUAUCUGCUCCUAAUAAAAAGAAAGUUUCUUC ACAUUCUCUCGAGAAAAAAAAAAAAAUGGAAAAAAA AAAACGGAAAAAAAAAAAAAGGUAAAAAAAAAAAAU AUAAAAAAAAAAAAACAUAAAAAAAAAAAAACGAAAA AAAAAAAACGUAAAAAAAAAAAAACUCAAAAAAAAA AAAGAUAAAAAAAAAAAAACCUAAAAAAAAAAAAAUG UAAAAAAAAAAAAGGGAAAAAAAAAAAACGCAAAA

		AAAAAAAACACAAAAAAAAAAAAUGCAAAAAAAAAAAAUCGAAAAAAAAAAAAAUCUAAAAAAAAAAAAACGAAAAAAAAAAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAAUAGAAAAAAAAAAAAGUUAAAAAAAAAAACUGAAAAAAAAAAAAUUUAAAAAAAAAAAAUCUAG
	974	Not used
mRNA encoding UGI	975	GGGAGACCCAAGCUGGCUAGCUCCCGCAGUCGGCGUCCAGCGGCUCUGCUUGUUCGUGUGUGUGUCGUUGCAGGCCUUAUUCGGAUCCGCCACCAUGGGACCGAAGAAGAAGAGAAAGGUCGGAGGAGGAAGCACAAACCUGUCGGACAUCAUCGAAAAGGAAACAGGAAAGCAGCUGGUCAUCCAGGAAUCGAUCCUGAUGCUGCCGGAAGAAGUCGAAGAAGUCAUCGGAAACAAGCCGGAAUCGGACAUCCUGGUCCACACAGCAUACGACGAAUCGACAGACGAAAACGUCAUGCUGCUGACAUCGGACGCACCGGAAUACAAGCCGUGGGCACUGGUCAUCCAGGACUCGAACGGAGAAAACAAGAUCAAGAUGCUGUGAUAGUCUAGACAUCACAUUUAAAAGCAUCUCAGCCUACCAUGAGAAUAAGAGAAAGAAAAUGAAGAUCAAUAGCUUAUUCAUCUCUUUUUCUUUUUCGUUGGUGUAAAGCCAACACCCUGUCUAAAAAACAUAAAUUUCUUUAAUCAUUUUGCCUCUUUUCUCUGUGCUUCAAUUAAUAAAAAAUGGAAAGAACCUCGAGUCUAG
	976-999	Not used
Lentiviral genome encoding HLA-E expressed by an EF1a promoter	1000	gcgatcgcagtaatcaattacggggtcattagttcatagcccatatatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtcatcgctattaccatgGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTcgtttagtgaaccggggtctctctggttagaccagatctgagcctgggagctctctggctaactagggaacccactgcttaagcctcaataaagcttgccttgagtgcttcaagtagtgtgtgcccgtctgttgtgtgactctggtaactagagatccctcagaccctttagtcagtgtggaaaatctctagcagtggcgcccgaacagggacctgaaagcgaaagggaaaccagagctctctcgacgcaggactcggcttgctgaagcgcgcacggcaagaggcgaggggcggcgactggtgagtacgccaaaaattttgactagcggaggctagaaggagagagatgggtgcgagagcgtcagtattaagcgggggagaattagatcgcgatgggaaaaaattcggttaaggccagggggaaagaaaaaatataaattaaaacatatagtatgggcaagcagggagctagaacgattcgcagttaatcctggcctgttagaaacatcagaaggctgtagacaaatactgggacagctacaaccatcccttcagacaggatcagaagaacttagatcattatataatacagtagcaaccctctattgtgtgcatcaaaggatagagataaaagacaccaaggaagctttagacaagatagaggaagagcaaaacaaaagtaagaccaccgcacagcaagcggccgctgatcttcagacctggaggaggagatatgagggacaattggagaagtgaattatata

		aatataaagtagtaaaaattgaaccattaggagtagcacccaccaaggcaaagagaaga gtggtgcagagagaaaaaagagcagtgggaataggagctttgttccttgggttcttggga gcagcaggaagcactatgggcgcagcctcaatgacgctgacggtacaggccagacaat tattgtctggtatagtgcagcagcagaacaatttgctgagggctattgaggcgcaacagca tctgttgcaactcacagtctggggcatcaagcagctccaggcaagaatcctggctgtgga aagatacctaaaggatcaacagctcctggggatttggggttgctctggaaaactcatttgca ccactgctgtgccttggaatgctagttggagtaataaatctctggaacagatttggaatcaca cgacctggatggagtgggacagagaaattaacaattacacaagcttaatacactccttaatt gaagaatcgcaaaaccagcaagaaaagaatgaacaagaattattggaattagataaatgg gcaagtttgtggaattggtttaacataacaaattggctgtggtatataaaattattcataatgat agtaggaggcttggtaggtttaagaatagtttttgctgtactttctatagtgaatagagttagg cagggatattcaccattatcgtttcagacccacctcccaaccccgaggggacccgacagg cccgaaggaatagaagaagaaggtggagagagagacagagacagatccattcgattag tgaacggatctcgacggtatcggttaacttttaaaagaaaaggggggattggggggtaca gtgcaggggaaagaatagtagacataatagcaacagacatacaaactaaagaattacaaa aacaaattacaaaaattcaaaattttggctcccgatcgttgcgttacacacacaattactgct gatcgagtgtagccttcccacagtccccgagaagttggggggaggggtcggcaattgaa ccggtgcctagagaaggtggcgcggggtaaactgggaaagtgatgtcgtgtactggctc cgcctttttcccgagggtgggggagaaccgtatataagtgcagtagtcgccgtgaacgttc tttttcgcaacgggtttgccgccagaacacaggtaagtgccgtgtgtggttcccgcgggcc tggcctctttacgggttatggcccttgcgtgccttgaattacttccacgcccctggctgcagt acgtgattcttgatcccgagcttcgggttggaagtgggtgggagagttcgaggccttgcgc ttaaggagccccttcgcctcgtgcttgagttgaggcctggcttgggcgctggggccgccg cgtgcgaatctggtggcaccttcgcgcctgtctcgctgctttcgataagtctctagccattta aaatttttgatgacctgctgcgacgctttttttctggcaagatagtcttgtaaatgcgggccaa gatgtgcacactggtatttcggtttttggggccgcgggcggcgacggggcccgtgcgtcc cagcgcacatgttcggcgaggcggggcctgcgagcgcggccaccgagaatcggacgg gggtagtctcaagctggccggcctgctctggtgcctggcctcgcgccgccgtgtatcgcc ccgccctgggcggcaaggctggcccggtcggcaccagttgcgtgagcggaaagatgg ccgcttcccggccctgctgcagggagctcaaaatggaggacgcggcgctcgggagagc gggcgggtgagtcacccacacaaaggaaaagggcctttccgtcctcagccgtcgcttcat gtgactccacggagtaccgggcgccgtccaggcacctcgattagttctcgagcttttggag tacgtcgtctttaggttggggggaggggttttatgcgatggagtttccccacactgagtggg tggagactgaagttaggccagcttggcacttgatgtaattctccttggaatttgcccttttga gtttggatcttggttcattctcaagcctcagacagtggttcaaagtttttttCTTCCATT TCAGGTGTCGTGAtctagacgccaccATGTCTCGCTCCGTGGC CTTAGCTGTGCTCGCGCTACTCTCTCTTTCTGGCCTAG AGGCTGTTATGGCTCCGCGGACTTTAATTTTAGGTGGT GGCGGATCCGGTGGAGGCGGTTCTGGTGGAGGCGGCT CCATCCAGCGTACGCCAAAGATTCAGGTTTACTCACGT CATCCAGCAGAGAATGGAAAGTCAAATTTCCTGAATT GCTATGTGTCTGGGTTTCATCCATCCGACATTGAAGTT GACTTACTGAAGAATGGAGAGAGAATTGAAAAAGTG GAGCATTCAGACTTGTCTTTCAGCAAGGACTGGTCTTT CTATCTCTTGTACTACACTGAATTCACCCCCACTGAAA AAGATGAGTATGCCTGCCGTGTGAACCATGTGACTTT GTCACAGCCCAAGATAGTTAAGTGGGATCGCGACATG GGTGGTGGCGGTTCTGGTGGTGGCGGTAGTGGCGGCG GAGGAAGCGGTGGTGGCGGTTCCGGATCTCACTCCTT GAAGTATTTCCACACTTCCGTGTCCCGGCCCGGCCGCG

		GGGAGCCCCGCTTCATCTCTGTGGGCTACGTGGACGA CACCCAGTTCGTGCGCTTCGACAACGACGCCGCGAGT CCGAGGATGGTGCCGCGGGCGCCGTGGATGGAGCAGG AGGGGTCAGAGTATTGGGACCGGGAGACACGGAGCG CCAGGGACACCGCACAGATTTTCCGAGTGAACCTGCG GACGCTGCGCGGCTACTACAATCAGAGCGAGGCCGGG TCTCACACCCTGCAGTGGATGCATGGCTGCGAGCTGG GGCCCGACAGGCGCTTCCTCCGCGGGTATGAACAGTT CGCCTACGACGGCAAGGATTATCTCACCCTGAATGAG GACCTGCGCTCCTGGACCGCGGTGGACACGGCGGCTC AGATCTCCGAGCAAAAGTCAAATGATGCCTCTGAGGC GGAGCACCAGAGAGCCTACCTGGAAGACACATGCGTG GAGTGGCTCCACAAATACCTGGAGAAGGGGAAGGAG ACGCTGCTTCACCTGGAGCCCCCAAAGACACACGTGA CTCACCACCCCATCTCTGACCATGAGGCCACCCTGAG GTGCTGGGCTCTGGGCTTCTACCCTGCGGAGATCACAC TGACCTGGCAGCAGGATGGGGAGGGCCATACCCAGGA CACGGAGCTCGTGGAGACCAGGCCTGCTGGGGATGGA ACCTTCCAGAAGTGGGCAGCTGTGGTGGTGCCTTCTG GAGAGGAGCAGAGATACACGTGCCATGTGCAGCATGA GGGGCTACCCGAGCCCGTCACCCTGAGATGGAAGCCG GCTTCCCAGCCCACCATCCCCATCGTGGGCATCATTGC TGGCCTGGTTCTCCTTGGATCTGTGGTCTCTGGAGCTG TGGTTGCTGCTGTGATATGGAGGAAGAAGAGCTCAGG TGGAAAAGGAGGGAGCTACTATAAGGCTGAGTGGAG CGACAGTGCCCAGGGGTCTGAGTCTCACAGCTTGTAAa agtagaagttgtctcctcctgcactgactgactgatacaatcgatttctggatccgcaggcct ctgctagaagttgtctcctcctgcactgactgactgatacaatcgatttctggatccgcaggc ctctgctagcttgactgactgagtcgacAATCAACCTCTGGATTACAA AATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTG CTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCT TTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTC TCCTCCTTGTATAAATCCTGGTTGCTGTCTCTTTATGAG GAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGT GCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGC ATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGC TTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCG CCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTG GGCACTGACAATTCCGTGGTGTTGTCGGGGAAGCTGA CGTCCTTTCCATGGCTGCTCGCCTGTGTTGCCACCTGG ATTCTGCGCGGGACGTCCTTCTGCTACGTCCCTTCGGC CCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGC CGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCT CAGACGAGTCGGATCTCCCTTTGGGCcgcctccccgcctggaatt cgagctcggtacctttaagaccaatgacttacaaggcagctgtagatcttagccactttttaa aagaaaagggggggactggaagggctaattcactcccaacgaagacaagatctgcttttttg cttgtactgggtctctctggttagaccagatctgagcctgggagctctctggctaactaggg aacccactgcttaagcctcaataaagcttgccttgagtgcttcaagtagtgtgtgcccgtctg ttgtgtgactctggtaactagagatccctcagacccttttagtcagtgtggaaaatctctagc agtcctggccaacgtgagcaccgtgctgacctccaaatatcgttaagctggagcctggga

		gccggcctggccctccgcccccccccacccccgcagcccacccctggtctttgaataaagt ctgagtgagtggccgacagtgcccgtggagttctcgtgacctgaggtgcagggccggcg ctagggacacgtccgtgcacgtgccgaggcccctgtgcagctgcaagggacaggcct agccctgcaggcctaactccgcccatcccgcccctaactccgcccagttccgcccattctc cgcctcatggctgactaattttttttatttatgcagaggccgaggccgcctcggcctctgagc tattccagaagtagtgaggacgcttttttggaggccgaggcttttgcaaagatcgaacaag agacaggacctgcaggttaattaaatttaaatcatgtgagcaaaaggccagcaaaaggcc aggaaccgtaaaaaggccgcgttgctggcgtttttccataggctccgcccccctgacgag catcacaaaaatcgacgctcaagtcagaggtggcgaaacccgacaggactataaagata ccaggcgtttccccctggaagctccctcgtgcgctctcctgttccgaccctgccgcttaccg gatacctgtccgcctttctcccttcgggaagcgtggcgctttctcatagctcacgctgtaggt atctcagttcggtgtaggtcgttcgctccaagctgggctgtgtgcacgaaccccccgttca gcccgaccgctgcgccttatccggtaactatcgtcttgagtccaacccggtaagacacga cttatcgccactggcagcagccactggtaacaggattagcagagcgaggtatgtaggcg gtgctacagagttcttgaagtggtggcctaactacggctacactagaagaacagtatttggt atctgcgctctgctgaagccagttaccttcggaaaaagagttggtagctcttgatccggcaa acaaaccaccgctggtagcggtggtttttttgtttgcaagcagcagattacgcgcagaaaa aaaggatctcaagaagatcctttgatcttttctacggggtctgacgctcagtggaacgaaaa ctcacgttaagggattttggtcatgagattatcaaaaaggatcttcacctagatccttttaaatt aaaaatgaagttttaaatcaatctaaagtatatatgagtaaacttggtctgacagttaccaatg cttaatcagtgaggcacctatctcagcgatctgtctatttcgttcatccatagttgcatttaaat ggccggcctggcgcgccgtttaaacctagatattgatagtctgatcggtcaacgtataatcg agtcctagcttttgcaaacatctatcaagagacaggatcagcaggaggctttcgcatgagt attcaacatttccgtgtcgcccttattcccttttttgcggcattttgccttcctgtttttgctcaccc agaaacgctggtgaaagtaaaagatgctgaagatcagttgggtgcgcgagtgggttacat cgaactggatctcaacagcggtaagatccttgagagttttcgccccgaagaacgctttcca atgatgagcacttttaaagttctgctatgtggcgcggtattatcccgtattgacgccgggcaa gagcaactcggtcgccgcatacactattctcagaatgacttggttgagtattcaccagtcac agaaaagcatcttacggatggcatgacagtaagagaattatgcagtgctgccataaccatg agtgataacactgcggccaacttacttctgacaacgattggaggaccgaaggagctaacc gcttttttgcacaacatgggggatcatgtaactcgccttgatcgttgggaaccggagctgaa tgaagccataccaaacgacgagcgtgacaccacgatgcctgtagcaatggcaacaacct tgcgtaaactattaactggcgaactacttactctagcttcccggcaacagttgatagactgg atggaggcggataaagttgcaggaccacttctgcgctcggcccttccggctggctggttta ttgctgataaatctggagccggtgagcgtgggtctcgcggtatcattgcagcactggggcc agatggtaagccctcccgtatcgtagttatctacacgacggggagtcaggcaactatggat gaacgaaatagacagatcgctgagataggtgcctcactgattaagcattggtaaccgattc taggtgcattggcgcagaaaaaaatgcctgatgcgacgctgcgcgtcttatactcccacat atgccagattcagcaacggatacggcttccccaacttgcccacttccatacgtgtcctcctt accagaaatttatccttaagatcccgaatcgtttaaac
HD1 TCR insertion including ITRs	1001	ttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcc cgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagagaggg agtggccaactccatcactaggggttcctagatcttgccaacataccataaacctcccattct gctaatgcccagcctaagttggggagaccactccagattccaagatgtacagtttgctttgc tgggcctttttcccatgcctgcctttactctgccagagttatattgctggggttttgaagaagat cctattaaataaaagaataagcagtattattaagtagccctgcatttcaggtttccttgagtgg caggccaggcctggccgtgaacgttcactgaaatcatggcctcttggccaagattgatag cttgtgcctgtccctgagtcccagtccatcacgagcagctggtttctaagatgctatttcccg tataaagcatgagaccgtgacttgccagccccacagagccccgcccttgtccatcactgg catctggactccagcctgggttggggcaaagagggaaatgagatcatgtcctaaccctga

		tcctcttgtcccacagatatccagaaccctgaccctgcggctccggtgcccgtcagtgggc agagcgcacatcgcccacagtccccgagaagttggggggaggggtcggcaattgaacc ggtgcctagagaaggtggcgcggggtaaactgggaaagtgatgtcgtgtactggctccg cctttttcccgagggtgggggagaaccgtatataagtgcagtagtcgccgtgaacgttcttt ttcgcaacgggtttgccgccagaacacaggtaagtgccgtgtgtggttcccgcgggcctg gcctctttacgggttatggcccttgcgtgccttgaattacttccacgcccctggctgcagtac gtgattcttgatcccgagcttcgggttggaagtgggtgggagagttcgaggccttgcgctt aaggagccccttcgcctcgtgcttgagttgaggcctggcttgggcgctggggccgccgc gtgcgaatctggtggcaccttcgcgcctgtctcgctgctttcgataagtctctagccatttaa aatttttgatgacctgctgcgacgctttttttctggcaagatagtcttgtaaatgcgggccaag atgtgcacactggtatttcggtttttggggccgcgggcggcgacggggcccgtgcgtccc agcgcacatgttcggcgaggcggggcctgcgagcgcggccaccgagaatcggacgg gggtagtctcaagctggccggcctgctctggtgcctggcctcgcgccgccgtgtatcgcc ccgccctgggcggcaaggctggcccggtcggcaccagttgcgtgagcggaaagatgg ccgcttcccggccctgctgcagggagctcaaaatggaggacgcggcgctcgggagagc gggcgggtgagtcacccacacaaaggaaaagggcctttccgtcctcagccgtcgcttcat gtgactccacggagtaccgggcgccgtccaggcacctcgattagttctcgagcttttggag tacgtcgtctttaggttggggggaggggttttatgcgatggagtttccccacactgagtggg tggagactgaagttaggccagcttggcacttgatgtaattctccttggaatttgcccttttga gtttggatcttggttcattctcaagcctcagacagtggttcaaagtttttttcttccatttcaggt gtcgtgatgcggccgccaccatgggatcttggacactgtgttgcgtgtccctgtgcatcctg gtggccaagcacacagatgccggcgtgatccagtctcctagacacgaagtgaccgagat gggccaagaagtgaccctgcgctgcaagcctatcagcggccacgattacctgttctggta cagacagaccatgatgagaggcctggaactgctgatctacttcaacaacaacgtgcccat cgacgacagcggcatgcccgaggatagattcagcgccaagatgcccaacgccagcttc agcaccctgaagatccagcctagcgagcccagagatagcgccgtgtacttctgcgccag cagaaagacaggcggctacagcaatcagccccagcactttggagatggcacccggctg agcatcctggaagatctgaagaacgtgttcccacctgaggtggccgtgttcgagccttctg aggccgagatcagccacacacagaaagccacactcgtgtgtctggccaccggcttctatc ccgatcacgtggaactgtcttggtgggtcaacggcaaagaggtgcacagcggcgtcagc accgatcctcagcctctgaaagagcagcccgctctgaacgacagcagatactgcctgag cagcagactgagagtgtccgccaccttctggcagaaccccagaaaccacttcagatgcc aggtgcagttctacggcctgagcgagaacgatgagtggacccaggatagagccaagcct gtgacacagatcgtgtctgccgaagcctggggcagagccgattgtggctttaccagcgag agctaccagcagggcgtgctgtctgccacaatcctgtacgagatcctgctgggcaaagcc actctgtacgccgtgctggtgtctgccctggtgctgatggccatggtcaagcggaaggata gcaggggcggctccggtgccacaaacttctccctgctcaagcaggccggagatgtggaa gagaaccctggccctatggaaaccctgctgaaggtgctgagcggcacactgctgtggca gctgacatgggtccgatctcagcagcctgtgcagtctcctcaggccgtgattctgagagaa ggcgaggacgccgtgatcaactgcagcagctctaaggccctgtacagcgtgcactggta cagacagaagcacggcgaggcccctgtgttcctgatgatcctgctgaaaggcggcgagc agaagggccacgagaagatcagcgccagcttcaacgagaagaagcagcagtccagcc tgtacctgacagccagccagctgagctacagcggcacctacttttgtggcaccgcctggat caacgactacaagctgtctttcggagccggcaccacagtgacagtgcgggccaatattca gaaccccgatcctgccgtgtaccagctgagagacagcaagagcagcgacaagagcgtg tgcctgttcaccgacttcgacagccagaccaacgtgtcccagagcaaggacagcgacgt gtacatcaccgataagactgtgctggacatgcggagcatggacttcaagagcaacagcg ccgtggcctggtccaacaagagcgatttcgcctgcgccaacgccttcaacaacagcattat ccccgaggacacattcttcccaagtcctgagagcagctgcgacgtgaagctggtggaaa agagcttcgagacagacaccaacctgaacttccagaacctgagcgtgatcggcttcagaa

		tcctgctgctcaaggtggccggcttcaacctgctgatgaccctgagactgtggtccagcta acctCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTT GCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCC ACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGC ATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGG GTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGG AAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCTC TATGGcttctgaggcggaaagaaccagctggggctctagggggtatccccactagtc gtgtaccagctgagagactctaaatccagtgacaagtctgtctgcctattcaccgattttgatt ctcaaacaaatgtgtcacaaagtaaggattctgatgtgtatatcacagacaaaactgtgcta gacatgaggtctatggacttcaagagcaacagtgctgtggcctggagcaacaaatctgac tttgcatgtgcaaacgccttcaacaacagcattattccagaagacaccttcttccccagccc aggtaagggcagctttggtgccttcgcaggctgtttccttgcttcaggaatggccaggttct gcccagagctctggtcaatgatgtctaaaactcctctgattggtggtctcggccttatccatt gccaccaaaaccctctttttactaagaaacagtgagccttgttctggcagtccagagaatga cacgggaaaaaagcagatgaagagaaggtggcaggagagggcacgtggcccagcct cagtctctagatctaggaacccctagtgatggagttggccactccctctctgcgcgctcgct cgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggc ctcagtgagcgagcgagcgcgcagagagggagtggccaa
Guide Scaffold	1002	NNNNNNNNNNNNNNNNNNNNGUUUUAGAGCUAGAA AUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGA AAGGGCACCGAGUCGGUGCU
Guide scaffold	1003	mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAmG mCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAG GCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmU mGmC*mU
	1004	Not Used
mRNA sequence encoding UGI	1005	GGGAAGCUCAGAAUAAACGCUCAACUUUGGCCGGAU CUGCCACCAUGACCAACCUGUCCGACAUCAUCGAGA AGGAGACCGGCAAGCAGCUGGUGAUCCAGGAGUCCA UCCUGAUGCUGCCCGAGGAGGUGGAGGAGGUGAUCG GCAACAAGCCCGAGUCCGACAUCCUGGUGCACACCG CCUACGACGAGUCCACCGACGAGAACGUGAUGCUGC UGACCUCCGACGCCCCCGAGUACAAGCCCUGGGCCCU GGUGAUCCAGGACUCCAACGGCGAGAACAAGAUCAA GAUGCUGUCCGGCGGCUCCAAGCGGACCGCCGACGG CUCCGAGUUCGAGUCCCCCAAGAAGAAGCGGAAGGU GGAGUGAUAGCUAGCACCAGCCUCAAGAACACCCGA AUGGAGUCUCUAAGCUACAUAAUACCAACUUACACU UUACAAAAUGUUGUCCCCCAAAAUGUAGCCAUUCGU AUCUGCUCCUAAUAAAAAGAAAGUUUCUUCACAUUC UCUCGAGAAAAAAAAAAAAUGGAAAAAAAAAAAAC GGAAAAAAAAAAAAGGUAAAAAAAAAAAAUAUAAA AAAAAAAAACAUAAAAAAAAAAAACGAAAAAAAAA AAACGUAAAAAAAAAAAACUCAAAAAAAAAAAAGA UAAAAAAAAAAAACCUAAAAAAAAAAAAUGUAAAA AAAAAAAAGGGAAAAAAAAAAAACGCAAAAAAAAA AAACACAAAAAAAAAAAAUGCAAAAAAAAAAAAUCG AAAAAAAAAAAAUCUAAAAAAAAAAAACGAAAAAA AAAAAACCCAAAAAAAAAAAAGACAAAAAAAAAAAA

		UAGAAAAAAAAAAAAGUUAAAAAAAAAAAACUGAA AAAAAAAAAAUUUAAAAAAAAAAAAAUCUAG
Guide scaffold 90-mer	1006	GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGC UAGUCCGUUAUCACGAAAGGGCACCGAGUCGGUGC
Guide scaffold 90-mer with modification	1007	GUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAA GUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCA CCGAGUCGG*mU*mG*mC
Guide scaffold 90-mer with modification	1008	GUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAA GUUAAAAUAAGGCUAGUCCGUUAUCAmCmGmAmAm AmGmGmGmCmAmCmCmGmAmGmUmCmGmG*mU*mG *mC
Guide scaffold 88-mer with modification	1009	GUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAA GUUAAAAUAAGGCUAGUCCGUUAUCAACUUGGCACC GAGUCGG*mU*mG*mC
Guide scaffold 88-mer	1010	GUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGC UAGUCCGUUAUCAAAAUGGCACCGAGUCGGUGC
Guide scaffold 88-mer with modification	1011	GUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAA GUUAAAAUAAGGCUAGUCCGUUAUCAAAAUGGCACC GAGUCGG*mU*mG*mC
Guide scaffold 88-mer with modification	1012	GUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAA GUUAAAAUAAGGCUAGUCCGUUAUCAmAmAmAmUm GmGmCmAmCmCmGmAmGmUmCmGmG*mU*mG*mC
Guide scaffold	1013	GUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAA GUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUm GmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGm UmCmGmGmUmGmCmU*mU*mU*mU
Guide scaffold	1014	mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAmG mCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAG GCUAGUCCGUUAUCAmAmCmUmUmGmAmAmAmAmA mGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmG mCmU*mU*mU*mU
G023523 Exemplary 91-mer full sequence	1015	GCUGCAGCGCACGGUACCAGUUUUAGAGCUAGAAA UAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAA AGGGCACCGAGUCGGUGCU
G023523 Exemplary 91-mer modified sequence	1016	mG*mC*mU*GCAGCGCACGGUACCAGUUUUAGAmG mCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAG GCUAGUCCGUUAUCACGAAAGGGCACCGAGUCGGmU mGmC*mU

* The guide sequence disclosed in this Table may be unmodified, modified with the exemplary modification pattern shown in the Table, or modified with a different modification pattern disclosed herein or available in the art.

IV. EXAMPLES

[00381] The following examples are provided to illustrate certain disclosed embodiments and are not to be construed as limiting the scope of this disclosure in any way.

Example 1: General Methods

1.1. Next-generation sequencing ("NGS") and analysis for on-target cleavage efficiency.

[00382] Genomic DNA was extracted using QuickExtract™ DNA Extraction Solution (Lucigen, Cat. No. QE09050) according to manufacturer's protocol.

[00383] To quantitatively determine the efficiency of editing at the target location in the genome, deep sequencing was utilized to identify the presence of insertions, deletions, and substitution introduced by gene editing. PCR primers were designed around the target site within the gene of interest (*e.g.*, HLA-A) and the genomic area of interest was amplified. Primer sequence design was done as is standard in the field.

[00384] Additional PCR was performed according to the manufacturer's protocols (Illumina) to add chemistry for sequencing. The amplicons were sequenced on an Illumina MiSeq instrument. The reads were aligned to the human reference genome (e.g., hg38) after eliminating those having low quality scores. Reads that overlapped the target region of interest were re-aligned to the local genome sequence to improve the alignment. Then the number of wild type reads versus the number of reads which contain C-to-T mutations, C-to-A/G mutations or indels was calculated. Insertions and deletions were scored in a 20 bp region centered on the predicted Cas9 cleavage site. Indel percentage is defined as the total number of sequencing reads with one or more base inserted or deleted within the 20 bp scoring region divided by the total number of sequencing reads, including wild type. C-to-T mutations or C-to-A/G mutations were scored in a 40 bp region including 10 bp upstream and 10 bp downstream of the 20 bp sgRNA target sequence. The C-to-T editing percentage is defined as the total number of sequencing reads with either one or more C-to-T mutations within the 40 bp region divided by the total number of sequencing reads, including wild type. The percentage of C-to-A/G mutations are calculated similarly.

1.2. T cell culture media preparation.

[00385] T cell culture media compositions used below are described here. “X-VIVO Base Media” consists of X-VIVO™ 15 Media, 1% Penstrep, 50 μM Beta-Mercaptoethanol, 10 mM NAC. In addition to above mentioned components, other variable media components used were: 1. Serum (Fetal Bovine Serum (FBS)); and 2. Cytokines (IL-2, IL-7, IL-15).

1.3. Preparation of lipid nanoparticles.

[00386] The lipid components were dissolved in 100% ethanol at various molar ratios. The RNA cargos (e.g., Cas9 mRNA and sgRNA) were dissolved in 25 mM citrate buffer, 100 mM NaCl, pH 5.0, resulting in a concentration of RNA cargo of approximately 0.45 mg/mL.

[00387] The lipid nucleic acid assemblies contained ionizable Lipid A ((9Z,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3- (diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate, also called 3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,12Z)-octadeca-9,12-dienoate), cholesterol, DSPC, and PEG2k-DMG in a 50:38:9:3 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:1 or 1:2 by weight.

[00388] Lipid nanoparticles (LNP compositions) were prepared using a cross-flow technique utilizing impinging jet mixing of the lipid in ethanol with two volumes of RNA solutions and one volume of water. The lipids in ethanol were mixed through a mixing cross with the two volumes of RNA solution. A fourth stream of water was mixed with the outlet stream of the cross through an inline tee (*See* WO2016010840 Figure 2.). The LNP compositions were held for 1 hour at room temperature (RT), and further diluted with water (approximately 1:1 v/v). LNP compositions were concentrated using tangential flow filtration on a flat sheet cartridge (Sartorius, 100kD MWCO) and buffer exchanged using PD-10 desalting columns (GE) into 50 mM Tris, 45 mM NaCl, 5% (w/v) sucrose, pH 7.5 (TSS). Alternatively, the LNP’s were optionally concentrated using 100 kDa Amicon spin filter and buffer exchanged using PD-10 desalting columns (GE) into TSS. The resulting mixture was then filtered using a 0.2 μm sterile filter. The final LNP was stored at 4°C or -80°C until further use.

1.4. In vitro transcription (“IVT”) of mRNA

[00389] Capped and polyadenylated mRNA containing N1-methyl pseudo-U was generated by in vitro transcription using a linearized plasmid DNA template and T7 RNA polymerase. Plasmid DNA containing a T7 promoter, a sequence for transcription, and a

polyadenylation sequence was linearized by incubating at 37°C for 2 hours with XbaI with the following conditions: 200 ng/μL plasmid, 2 U/μL XbaI (NEB), and 1x reaction buffer. The XbaI was inactivated by heating the reaction at 65°C for 20 min. The linearized plasmid was purified from enzyme and buffer salts. The IVT reaction to generate modified mRNA was performed by incubating at 37°C for 1.5-4 hours in the following conditions: 50 ng/μL linearized plasmid; 2-5 mM each of GTP, ATP, CTP, and N1-methyl pseudo-UTP (Trilink); 10-25 mM ARCA (Trilink); 5 U/μL T7 RNA polymerase (NEB); 1 U/μL Murine RNase inhibitor (NEB); 0.004 U/μL Inorganic E. coli pyrophosphatase (NEB); and 1x reaction buffer. TURBO DNase (ThermoFisher) was added to a final concentration of 0.01 U/μL, and the reaction was incubated for an additional 30 minutes to remove the DNA template. The mRNA was purified using a MegaClear Transcription Clean-up kit (ThermoFisher) or a RNeasy Maxi kit (Qiagen) per the manufacturers' protocols. Alternatively, the mRNA was purified through a precipitation protocol, which in some cases was followed by HPLC-based purification. Briefly, after the DNase digestion, mRNA is purified using LiCl precipitation, ammonium acetate precipitation and sodium acetate precipitation. For HPLC purified mRNA, after the LiCl precipitation and reconstitution, the mRNA was purified by RP-IP HPLC (see, *e.g.*, Kariko, et al. Nucleic Acids Research, 2011, Vol. 39, No. 21 e142). The fractions chosen for pooling were combined and desalted by sodium acetate/ethanol precipitation as described above. In a further alternative method, mRNA was purified with a LiCl precipitation method followed by further purification by tangential flow filtration. RNA concentrations were determined by measuring the light absorbance at 260 nm (Nanodrop), and transcripts were analyzed by capillary electrophoresis by Bioanlayzer (Agilent).

[00390] *Streptococcus pyogenes* ("Spy") Cas9 mRNA was generated from plasmid DNA encoding an open reading frame according to SEQ ID NOs: 801-803 (see sequences in **Table 6)**. BC22n mRNA was generated from plasmid DNA encoding an open reading frame according to SEQ ID NOs: 804-805. UGI mRNA was generated from plasmid DNA encoding an open reading frame according to SEQ ID NOs: 807-808. When SEQ ID NOs: 801-808 are referred to below with respect to RNAs, it is understood that Ts should be replaced with Us (which were N1-methyl pseudouridines as described above). Messenger RNAs used in the Examples include a 5' cap and a 3' polyadenylation region, *e.g.*, up to 100 nts, and are identified by the SEQ ID NOs: 801-808 in **Table 6**.

Example 2: Screening of HLA-A Guide RNAs with Cas9

[00391] Eighty-eight sgRNAs designed for the disruption of the HLA-A gene were screened for efficacy in T cells by assessing loss of two allelic versions of the MHC I surface protein, HLA-A2 and HLA-A3. The donor had an HLA-A phenotype of A*02:01:01G and 03:01:01G. The percentage of T cells double negative for HLA-A2 and A3 ("% A2-/A3-") was determined by flow cytometry following editing at the *HLA-A* locus by electroporation with Cas9 ribonucleoprotein (RNP) and each test guide. Generally, unless otherwise indicated, guide RNAs used throughout the Examples identified as "GXXXXXX" refer to 100-nt modified sgRNA format, unless indicated otherwise, such as those shown in the Tables provided herein.

2.1. RNP electroporation of T cells

[00392] Cas9 editing activity was assessed using electroporation of Cas9 ribonucleoprotein (RNP). Upon thaw, Pan CD3+ T cells (StemCell, HLA-A*02.01/ A*03.01) were plated at a density of 0.5 x 10^6 cells/mL in T cell RPMI media composed of RPMI 1640 (Invitrogen, Cat. 22400-089) containing 5% (v/v) of fetal bovine serum, 1x Glutamax (Gibco, Cat. 35050-061), 50 μM of 2-Mercaptoethanol, 100 μM non-essential amino acids (Invitrogen, Cat. 11140-050), 1 mM sodium pyruvate, 10 mM HEPES buffer, 1% of Penicillin-Streptomycin, and 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02). T cells were activated with TransAct™ (1:100 dilution, Miltenyi Biotec). Cells were expanded in T cell RPMI media for 72 hours prior to RNP transfection.

[00393] HLA-A targeting sgRNAs were removed from their storage plates and denatured for 2 minutes at 95°C before cooling at room temperature for 10 minutes. RNP mixture of 20 μM sgRNA and 10 μM Cas9-NLS protein (SEQ ID NO: 800) was prepared and incubated at 25°C for 10 minutes. Five μL of RNP mixture was combined with 100,000 cells in 20 μL P3 electroporation Buffer (Lonza). 22 μL of RNP/cell mix was transferred to the corresponding wells of a Lonza shuttle 96-well electroporation plate. Cells were electroporated in duplicate with the manufacturer's pulse code. T cell RPMI media was added to the cells immediately post electroporation. Electroporated T cells were subsequently cultured and collected for NGS sequencing as described in Example 1 at 2 days post edit.

2.2. Flow cytometry

[00394] On day 7 post-edit, T cells were phenotyped by flow cytometry to determine HLA-A protein expression following editing at the HLA-A locus. Briefly, T cells were

incubated in a cocktail of antibodies targeting two allelic versions of the MHC I surface protein corresponding the cells donor's genotype HLA-A2, (eBioscience Cat. No. 17-9876-42) and HLA-A3 (eBioscience Cat. No. 12-5754-42). Cells were subsequently washed, processed on a Cytoflex flow cytometer (Beckman Coulter) and analyzed using the FlowJo software package. T cells were gated based on size, shape, viability, and HLA-A2 and HLA-A3 expression. **Table 7** shows the mean percentage of cells double negative for HLA-A2 and HLA-A3 following editing at the HLA-A locus.

[00395] **Table 7 - Mean percentage of T cells HLA-A negative (double negative for HLA-A2 and HLA-A3) following editing at the HLA-A locus**

Guide ID	Mean % A2-/A3-	SD % A2-/A3-
G018932	39.30	1.56
G018933	68.45	4.03
G018934	34.40	0.57
G018935	62.25	0.92
G018936	7.62	0.28
G018937	18.85	1.34
G018938	0.05	0.04
G018939	24.30	0.14
G018940	3.99	0.06
G018941	0.02	0.02
G018942	1.97	0.19
G018943	10.80	0.57
G018944	1.78	0.16
G018945	8.85	0.03
G018946	8.08	0.44
G018947	8.53	0.50
G018948	8.57	0.59
G018949	51.95	0.92
G018950	1.80	0.08
G018951	40.25	0.21
G018952	3.40	0.30
G018953	23.35	0.64

Guide ID	Mean % A2-/A3-	SD % A2-/A3-
G018954	57.50	1.41
G018955	5.65	0.59
G018956	40.45	0.21
G018957	33.65	2.47
G018958	1.52	0.00
G018959	4.69	0.16
G018960	0.13	0.00
G018961	0.88	0.05
G018962	0.78	0.01
G018963	37.50	1.56
G018964	12.75	0.64
G018965	1.26	0.09
G018966	0.28	0.06
G018967	0.31	0.17
G018968	0.34	0.07
G018969	0.52	0.28
G018970	0.55	0.13
G018971	0.36	0.13
G018972	17.15	0.78
G018973	2.04	0.28
G018974	1.26	0.03
G018975	7.52	1.15
G018976	3.75	0.22
G018977	22.45	0.64
G018978	7.79	0.64
G018979	45.80	0.71
G018980	35.70	1.98
G018981	1.74	0.16
G018982	3.31	0.22
G018983	0.03	0.02
G018984	0.78	0.04

Guide ID	Mean % A2-/A3-	SD % A2- /A3-
G018985	0.01	0.00
G018986	0.01	0.00
G018987	1.55	0.21
G018988	1.72	0.08
G018989	6.92	0.06
G018990	13.70	0.99
G018991	19.35	0.49
G018992	21.70	2.26
G018993	14.40	0.28
G018994	25.35	0.64
G018995	89.70	0.28
G018996	92.35	0.07
G018997	94.90	1.84
G018998	90.50	0.42
G018999	96.40	0.28
G019000	94.95	0.21
G019001	3.36	0.28
G019002	0.02	0.00
G019003	7.32	0.08
G019004	52.70	2.40
G019005	1.33	0.06
G019006	8.18	0.98
G019007	15.05	1.77
G019008	58.65	2.19
G019009	26.95	5.87
G019010	4.69	0.04
G019011	3.88	0.07
G019012	23.75	1.91
G019013	40.40	0.85
G019014	26.55	0.07
G019015	27.40	2.40

Guide ID	Mean % A2-/A3-	SD % A2- /A3-
G019016	20.20	0.00
G019017	3.53	0.15
G019018	18.60	0.28
G019019	0.91	0.06

Example 3: Screening of HLA-A Guides with BC22n and Cas9

[00396] HLA-A guide RNAs were screened for efficacy in T cells by assessing loss of HLA-A cell surface expression. The percentage of T cells negative for HLA-A protein in an HLA-A2 background ("% HLA-A2-") was assayed by flow cytometry following HLA-A editing by mRNA delivery.

3.1. mRNA electroporation of T cells

[00397] Cas9 and BC22n editing activity was assessed using electroporation of mRNA encoding Cas9 (SEQ ID NO:802), mRNA encoding BC22n (SEQ ID NO:806), or mRNA encoding UGI (SEQ ID NO:807), as provided below. Upon thaw, Pan CD3+ T cells (StemCell, HLA-A*02.01/ A*02.01) were plated at a density of 1x $10^{\wedge 6}$ cells/mL in TCGM composed of CTS OpTmizer T Cell Expansion SFM (Thermofisher, Cat. A3705001) supplemented with 5% human AB serum (Gemini, Cat. 100-512), 1X GlutaMAX (Thermofisher, Cat.35050061), 10 mM HEPES (Thermofisher, Cat. 15630080), 1x of Penicillin-Streptomycin, further supplemented with 200 U/mL IL-2 (Peprotech, Cat. 200-02), 10 ng/ml IL-7 (Peprotech, Cat. 200-07), 10 ng/ml IL-15 (Peprotech, Cat. 200-15). T cells were activated with TransAct™ (1:100 dilution, Miltenyi Biotec). Cells were expanded in T cell RPMI media for 72 hours at 37°C prior to mRNA electroporation.

[00398] HLA-A sgRNAs were removed from their storage plates and denatured for 2 minutes at 95°C before incubating at room temperature for 5 minutes. BC22n electroporation mix was prepared with 100,000 T cells in P3 buffer (Lonza), 200 ng of mRNA encoding UGI, 200 ng of mRNA encoding BC22n and 20 pmoles of sgRNA. Cas9 electroporation mix was prepared with 100,000 T cells in P3 buffer (Lonza), 200 ng of mRNA encoding UGI, 200 ng ofmRNA encoding Cas9 and 20 pmoles of sgRNA. Each mix was transferred to the corresponding wells of a Lonza shuttle 96-well electroporation plate. Cells were electroporated in duplicate using Lonza shuttle 96w using manufacturer's pulse code.

Immediately post electroporation, cells were recovered in pre-warmed TCGM without cytokines and incubated at 37°C for 15 minutes. Electroporated T cells were subsequently cultured in TCGM with further supplemented with 200 U/mL IL-2 (Peprotech, Cat. 200-02), 10 ng/ml IL-7 (Peprotech, Cat. 200-07), 10 ng/ml IL-15 (Peprotech, Cat. 200-15) and collected for flow cytometry 8 days post edit.

3.2. Flow cytometry

[00399] On day 8 post-edit, T cells were phenotyped by flow cytometry to determine HLA-A protein expression. Briefly, T cells were incubated with antibodies targeting HLA-A2, (eBioscience Cat. No. 17-9876-42). Cells were subsequently washed, processed on a Cytoflex flow cytometer (Beckman Coulter) and analyzed using the FlowJo software package. T cells were gated based on size, shape, viability, and HLA-A2 expression. **Table 8** shows the percentage of cells negative for HLA-A surface proteins following genomic editing of *HLA-A* with BC22n or Cas9.

[00400] **Table 8 – Percentage of cells negative for HLA-A surface protein following genomic editing of *HLA-A* with BC22n or Cas9.**

	BC22n		Cas9	
Intellia ID	Mean %A2-	SD % A2-	Mean %A2-	SD % A2-
G018932	20.15	2.76	43.30	1.70
G018933	10.35	1.20	74.00	0.57
G018934	0.50	0.14	15.30	1.56
G018935	0.00	0.00	69.30	0.28
G018936	0.10	0.00	29.65	2.62
G018937	0.15	0.07	50.50	0.71
G018938	0.00	0.00	0.00	0.00
G018939	0.00	0.00	44.90	1.27
G018940	0.00	0.00	12.00	0.42
G018941	0.00	0.00	2.65	0.35
G018942	0.10	0.00	2.15	0.07
G018943	0.00	0.00	16.20	0.42
G018944	0.00	0.00	3.00	0.28
G018945	0.05	0.07	3.20	0.42
G018946	0.00	0.00	2.30	0.14

	BC22n		Cas9	
Intellia ID	Mean %A2-	SD % A2-	Mean %A2-	SD % A2-
G018947	0.00	0.00	1.55	0.49
G018949	0.00	0.00	47.10	0.57
G018950	0.00	0.00	0.30	0.00
G018951	0.00	0.00	13.30	0.28
G018952	0.00	0.00	0.50	0.00
G018953	0.00	0.00	3.65	0.64
G018955	0.20	0.14	5.20	0.28
G018958	0.00	0.00	1.30	0.28
G018959	0.00	0.00	3.70	0.14
G018960	0.00	0.00	0.35	0.07
G018961	0.00	0.00	0.40	0.00
G018962	0.00	0.00	2.90	0.42
G018963	0.00	0.00	12.50	0.14
G018964	0.00	0.00	6.45	0.64
G018965	0.00	0.00	0.90	0.00
G018966	0.00	0.00	1.30	0.14
G018968	0.10	0.00	0.10	0.00
G018969	0.00	0.00	0.80	0.14
G018970	0.00	0.00	0.95	0.07
G018971	0.00	0.00	0.10	0.00
G018972	0.05	0.07	3.40	0.28
G018973	0.00	0.00	1.35	0.07
G018974	0.00	0.00	0.45	0.07
G018976	0.05	0.07	2.45	0.07
G018977	0.00	0.00	12.45	1.06
G018978	0.00	0.00	1.75	0.07
G018979	0.05	0.07	37.40	0.71
G018980	0.05	0.07	32.40	2.40
G018981	0.00	0.00	17.45	0.35
G018982	0.00	0.00	26.35	0.92
G018983	0.00	0.00	0.25	0.07

	BC22n		Cas9	
Intellia ID	**Mean %A2-**	**SD % A2-**	**Mean %A2-**	**SD % A2-**
G018984	0.00	0.00	0.65	0.07
G018986	0.00	0.00	1.85	0.21
G018987	0.00	0.00	2.25	0.07
G018988	0.00	0.00	0.15	0.07
G018989	0.00	0.00	1.85	0.07
G018990	0.25	0.07	17.45	1.06
G018991	0.20	0.00	23.15	0.92
G018992	0.20	0.14	38.15	0.07
G018993	0.15	0.07	12.15	1.34
G018994	4.35	0.35	23.75	0.49
G018995	0.55	0.07	94.27	0.30
G018996	0.85	0.07	92.39	0.83
G018997	97.80	0.08	95.03	1.87
G018998	74.75	7.71	93.33	0.18
G018999	98.26	0.30	96.05	2.27
G019000	9.05	0.35	94.67	0.74
G019001	0.05	0.07	4.05	0.64
G019002	0.00	0.00	0.05	0.07
G019003	0.00	0.00	11.10	0.00
G019004	0.00	0.00	30.70	0.00
G019005	0.00	0.00	1.65	0.35
G019006	0.00	0.00	4.75	0.49
G019007	0.00	0.00	5.35	0.78
G019008	0.00	0.00	55.20	3.54
G019009	0.00	0.00	19.55	2.19
G019010	0.05	0.07	5.40	0.14
G019011	0.00	0.00	4.40	0.85
G019012	0.05	0.07	22.90	2.55
G019013	0.00	0.00	30.60	2.40
G019014	0.05	0.07	14.65	0.49
G019015	0.00	0.00	44.70	1.70

	BC22n		Cas9	
Intellia ID	Mean %A2-	SD % A2-	Mean %A2-	SD % A2-
G019016	0.00	0.00	13.95	0.35
G019017	0.00	0.00	2.35	0.35
G019018	0.00	0.00	19.90	0.00
G019019	0.00	0.00	3.20	0.14
G021205	0.00	0.00	0.00	0.00
G021206	0.00	0.00	4.10	0.28
G021207	0.00	0.00	2.80	0.28
G021208	84.75	2.05	58.50	0.28
G021209	97.96	0.16	83.35	1.77
G021210	71.45	2.90	75.20	1.70
G021211	0.10	0.00	67.80	1.70

Example 4: NK cell functional killing assays

[00401] T cells edited in various combinations to disrupt CIITA, HLA-A, or B2M or to overexpress HLA-E were tested for their ability to resist natural killer (NK) cell mediated killing.

4.1. Engineering T cells and purification

[00402] Upon thaw, Pan CD3+ T cells (StemCell, HLA-A*02.01/ A*03.01) were plated at a density of 0.5 x 10^6 cells/mL in T cell RPMI media composed of RPMI 1640 (Invitrogen, Cat. 22400-089) containing 5% (v/v) of fetal bovine serum, 1x Glutamax (Gibco, Cat. 35050-061), 50 μM of 2-Mercaptoethanol, 100 μM non-essential amino acids (Invitrogen, Cat. 11140-050), 1 mM sodium pyruvate, 10 mM HEPES buffer, 1% of Penicillin-Streptomycin, and 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02). T cells were activated with TransAct™ (1:100 dilution, Miltenyi Biotec).

[00403] As described in **Table 9**, one day following activation, T cells were edited with to disrupt the B2M gene. Briefly, LNP compositions containing Cas9 mRNA and sgRNA G000529 (SEQ ID NO: 245) targeting B2M were formulated as described in **Example 1**. LNP compositions were incubated in RPMI-based media with cytokines as described above supplemented with 1 ug/ml recombinant human ApoE3 (Peprotech, Cat. 350-02) for 15 minutes at 37°C. LNP mix was added to two million activated T cells to yield a final concentration of 2.5 ug total LNP/mL.

[00404] **Table 9 – Order of sequential editing and viral transduction**

Condition	Day 1	Day2	Day 3
Unedited			
B2M⁻	B2M LNP		
B2M⁻ + HLA-E	B2M LNP		HLA-E lentivirus
HLA-A⁻ MHC II⁻		CIITA LNP	HLA-A LNP
HLA-A⁻			HLA-A LNP

[00405] Two days post activation, additional T cells were edited with LNP compositions to disrupt the CIITA gene. This was performed as described for B2M editing using LNP compositions containing Cas9 mRNA and sgRNA G013675 (SEQ ID NO: 246) targeting CIITA. LNP compositions used in this step were formulated with lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:38.5:10:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight.

[00406] Three days post activation, all edited and unedited cells were resuspended in fresh media without TransAct. A B2M-edited T cell sample was transduced by centrifugation at 1000g at 37C for 1 hour with lentivirus expressing HLA-E from an EF1a promoter (SEQ ID NO. 1000) at an MOI of 10. A CIITA-edited T cell sample was further edited with LNP compositions to disrupt the HLA-A gene. Editing was performed as described for B2M editing above using LNP compositions containing Cas9 mRNA and sgRNA G019000 targeting HLA-A formulated with lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:38.5:10:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. Four days post activation, all cells were transferred to GREX plate (Wilson Wolf, Cat. 80240M) for expansion.

[00407] Seven days post activation, HLA-E infected T cells were selected for HLA-E expression using Biotinylated Anti-HLA-E Antibody (Biolegend). and Anti-Biotin microbeads (Miltenyi Biotec, Cat#130-090-485) and a magnetic LS Column (Miltenyi Biotec, Cat# 130-042-401) according to manufacturer's protocols.

[00408] Similarly, nine days post activation CIITA edited T cells were negatively selected for lack of MHC II expression. using Biotinylated Anti-HLA-Class II Antibody (Miltenyi, Cat. 130-104-823), Anti-Biotin microbeads (Miltenyi Biotec, Cat. 130-090-485) and a magnetic LS Column (Miltenyi Biotec, Cat. 130-042-401) according to manufacturer's protocols.

4.2 Flow cytometry

[00409] NK cell mediated cytotoxicity towards engineered T cells was assayed. For this the T cells were co-cultured with the HLA-B/C matched CTV labelled NK cells at effector to target ratios (E:T) of 10:1, 5:1, 2.5:1, 1.25:1 and 0.625:1 for 21 hours. The cells were stained with 7AAD (BD Pharmingen, Cat. 559925), processed on a Cytoflex flow cytometer (Beckman Coulter) and analyzed using the FlowJo software package. T cells were gated based on CTV negativity, size, and shape and viability. **Table 10** and **Fig. 2** show the percentage of T cell lysis following NK cell challenge.

[00410] **Table 10 – Percentage T cell lysis following NK cell challenge to engineered T cells**

Log(E:T)	Unedited		$HLA-A^-$		$HLA-A^-$ $MHC\ II^-$		$B2M^-$		$B2M^-$ + HLA-E		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	n
Basal	12.0	1.9	15.5	0.2	8.2	0.4	11.1	0.1	18.1	2.5	2
-0.20	15.1	0.0	16.0	0.5	11.2	0.8	32.6	1.6	25.0	0.9	2
0.10	14.5	0.2	15.6	0.4	10.6	0.1	44.7	2.3	29.4	0.1	2
0.40	12.8	0.6	13.6	0.4	9.3	0.1	66.0	1.8	39.3	0.1	2
0.70	10.4	0.4	11.9	0.2	9.2	0.4	71.2	1.3	51.9	1.6	2
1.00	8.4	0.1	9.4	0.6	7.6	0.1	62.8	0.6	51.7	2.8	2

Example 5: LNP Dose Response Curves for Top HLA-A Guides

5.1 T cell preparation

[00411] Cryopreserved CD8/CD4+ selected T-cells isolated from a leukopak (Hemacare) were thawed and rested overnight at 1.5 x $10^{\wedge 6}$ cells/ml in T cell growth media (TCGM) composed of CTS OpTmizer T Cell Expansion SFM (Thermofisher, Cat. A3705001) supplemented with 5% human AB serum (Gemini, Cat. 100-512), 1X GlutaMAX (Thermofisher, Cat.35050061), 10 mM HEPES (Thermofisher, Cat. 15630080), 200 U/mL IL-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), 5 ng/ml IL-15 (Peprotech, Cat. 200-15).

[00412] T cells were activated using T cell TransAct™ (Miltenyi, Cat. 130-111-160) at 1:50 dilution and incubated in 37°C incubator for 48 hours. After the incubation, the cells were counted on Vi-cell and resuspended in TCGM as described above but with 2.5% serum to a final concentration of 0.5 x $10^{\wedge 6}$ cells/ml. After 24 hours, the cells were counted on Vi-cell, resuspended in 5% serum TCGM and transferred to a 96-well plate. Meanwhile, APOE (Peprotech, Cat. 350-02) was added into serum-free TCGM at a final concentration of 10 μg/ml and incubated with different HLA-A LNP compositions (see **Table 11)** at titrated LNP

total RNA concentrations (10 µg/mL, 5 µg/ml, 2.5 µg/ml, 1.25 µg/ml, 0.625 µg/ml, 0.3125 µg/ml, 0.15625 µg/ml, and 0.078125 µg/ml) for 15 minutes. LNP compositions were contain mRNA encoding a Cas9 (SEQ ID NO:802) and guides as specified in **Table 11** and were formulated with lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:39.5:9:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. After the incubation with APOE, LNP suspension was added to T cells at 1:1 ratio and incubated at 37°C for 24 hours. After 24 hours, the cells were counted on Vi-cell and split at 1:5 ratio and cultured for 96 hours. After incubation, an aliquot of 0.1-0.5 x $10^{\wedge 6}$ cells was taken for flow cytometry analysis.

5.2 Flow cytometry

[00413] For flow cytometric analysis, cells were washed in FACS buffer (PBS + 2% FBS + 2 mM EDTA) and incubated with APC-conjugated anti-human HLA-A2 antibody (Biolegend®, 343308) and PC5.5-conjugated CD3 antibody (Biolegend®, Cat. 317336) at 1:200 dilution for 30 mins at 4°C. After the incubation, the cells were washed, resuspended in FACS buffer and processed by flow cytometry, for example using a Beckman Coulter CytoflexS, and analyzed using the FlowJo software package. **Table 12** and **FIGS. 1A-1B** show the percent editing at each LNP dose.

[00414] **Table 11 Maximum indel% and EC50 for HLA-A targeting guides**

sgRNA	Max	EC50
G018933	90.71	0.3043
G018935	89.04	0.3906
G018954	87.68	0.5089
G018995	98.99	0.1665
G018996	98.61	0.2085
G018997	99.12	0.2196
G018998	98.64	0.2914
G018999	98.74	0.1724
G019000	98.61	0.1945
G019008	75.53	0.3322
G013006 TRAC		
G018091 CIITA	1.017	0.8941

[00415] **Table 12 Percentage of HLA-A- cells after editing with various guides.**

sgRNA	LNP Concentration (ug total RNA /ml)	Mean % HLA-A-	SD	n

sgRNA	LNP Concentration (ug total RNA /ml)	Mean % HLA-A-	SD	n
G018933	5	91.45	0.35	2
G018933	2.5	88.8	1.27	2
G018933	1.25	86.55	0.35	2
G018933	0.63	75	0.14	2
G018933	0.31	47	0.00	2
G018933	0.16	17.55	0.35	2
G018933	0.08	5.115	0.28	2
G018935	5	89.75	1.34	2
G018935	2.5	86.8	0.28	2
G018935	1.25	81.8	0.99	2
G018935	0.63	66.8	4.81	2
G018935	0.31	33.55	4.17	2
G018935	0.16	11.91	2.96	2
G018935	0.08	3.01	1.09	2
G018954	5	86.5	86.4	2
G018954	2.5	86	84	2
G018954	1.25	82	75	2
G018954	0.63	50.5	54.5	2
G018954	0.31	24.8	23	2
G018954	0.16	7.31	6.2	2
G018954	0.08	2.09	1.78	2
G018995	5	98.5	0.3	2
G018995	2.5	98.8	0.1	2
G018995	1.25	98.55	0.35	2
G018995	0.63	96	0	2
G018995	0.31	82.25	1.25	2
G018995	0.16	49.25	0.55	2
G018995	0.08	19	0.3	2
G018996	5	98.25	0.21	2
G018996	2.5	97.75	0.64	2
G018996	1.25	98.2	0.71	2
G018996	0.63	92.75	0.49	2
G018996	0.31	72.7	1.41	2
G018996	0.16	36.8	3.82	2
G018996	0.08	13.5	1.13	2
G018997	5	98.8	0.1	2
G018997	2.5	98.75	0.05	2
G018997	1.25	97.8	0.3	2
G018997	0.63	95.8	1.6	2
G018997	0.31	73.45	0.15	2
G018997	0.16	35.65	0.25	2
G018997	0.08	14.65	0.15	2
G018998	5	98.35	0.15	2
G018998	2.5	97.65	0.15	2

sgRNA	LNP Concentration (ug total RNA /ml)	Mean % HLA-A-	SD	n
G018998	1.25	97.05	0.45	2
G018998	0.63	89.6	1.4	2
G018998	0.31	55.8	0.4	2
G018998	0.16	22.6	0.8	2
G018998	0.08	8.55	0.09	2
G018999	5	98.45	0.35	2
G018999	2.5	98.5	0.3	2
G018999	1.25	98.05	0.55	2
G018999	0.63	97.1	0.1	2
G018999	0.31	84	0.4	2
G018999	0.16	51.95	0.25	2
G018999	0.08	24.7	0.4	2
G019000	5	97.9	0	2
G019000	2.5	98.5	0.1	2
G019000	1.25	97.2	0.6	2
G019000	0.63	96.05	0.35	2
G019000	0.31	77	0.6	2
G019000	0.16	43.7	1.1	2
G019000	0.08	19.1	0.2	2
G019008	5	73.35	1.20	2
G019008	2.5	77.35	0.78	2
G019008	1.25	71.25	2.19	2
G019008	0.63	60.3	1.84	2
G019008	0.31	35.65	2.19	2
G019008	0.16	11.6	0.71	2
G019008	0.08	3.17	0.41	2
G018091	5	0.99	0.29	2
G018091	2.5	1.00	0.52	2
G018091	1.25	1.12	1.10	2
G018091	0.63	0.64	0.02	2
G018091	0.31	0.44	0.02	2
G018091	0.16	1.22	0.52	2
G018091	0.08	0.35	0.16	2
G013006	5	0.51	0.28	2
G013006	2.5	0.71	0.1	2
G013006	1.25	1.13	0.315	2
G013006	0.63	0.69	0.02	2
G013006	0.31	0.36	0.015	2
G013006	0.16	0.82	0.19	2
G013006	0.08	0.7	0.02	2

Example 6: Multi-editing WT1 T cells with sequential LNP delivery

[00416] T cells were engineered with a series of gene disruptions and insertions. Healthy donor cells were treated sequentially with four LNP compositions, each LNP co-formulated with mRNA encoding Cas9 and a sgRNA targeting either TRAC (G013006) (SEQ ID NO: 243), TRBC (G016239) (SEQ ID NO: 247), CIITA (G013676) (SEQ ID NO: 248), or HLA-A (G018995) (sgRNA comprising SEQ ID NO: 13, as shown in Table 2). LNP compositions were formulated with lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:38.5:10:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. A transgenic T cell receptor targeting Wilm's tumor antigen (WT1 TCR) (SEQ ID NO: 1001) was integrated into the TRAC cut site by delivering a homology directed repair template using AAV.

6.1. T cell Preparation

[00417] T cells were isolated from the leukapheresis products of three healthy HLA-A2+ donors (STEMCELL Technologies). T cells were isolated using EasySep Human T cell Isolation kit (STEMCELL Technologies, Cat. 17951) following manufacturers protocol and cryopreserved using Cryostor CS10 (STEMCELL Technologies, Cat. 07930). The day before initiating T cell editing, cells were thawed and rested overnight in T cell activation media (TCAM): CTS OpTmizer (Thermofisher, Cat. A3705001) supplemented with 2.5% human AB serum (Gemini, Cat. 100-512), 1X GlutaMAX (Thermofisher, Cat.35050061), 10 mM HEPES (Thermofisher, Cat. 15630080), 200 U/mL IL-2 (Peprotech, Cat. 200-02), IL-7 (Peprotech, Cat. 200-07), IL-15 (Peprotech, Cat. 200-15).

6.2. LNP Treatment and Expansion of T cells

[00418] LNP compositions were prepared each day in ApoE containing media and delivered to T cells as described in **Table 13** and below.

[00419] **Table 13 – Order of editing for T cell engineering**

Group	Day 1	Day 2	Day 3	Day 4
1	Unedited	Unedited	Unedited	Unedited
2	TRBC	CIITA	TRAC	HLA-A
3	TRBC	HLA-A	TRAC	CIITA
4	TRBC		TRAC	

[00420] On day 1, LNP compositions as indicated in **Table 13** were incubated at a concentration of 5 ug/mL in TCAM containing 5 ug/mL rhApoE3 (Peprotech, Cat. 350-02).

Meanwhile, T cells were harvested, washed, and resuspended at a density of 2x10^6 cells/mL in TCAM with a 1:50 dilution of T Cell TransAct, human reagent (Miltenyi, Cat. 130-111-160). T cells and LNP-ApoE media were mixed at a 1:1 ratio and T cells plated in culture flasks overnight.

[00421] On day 1, LNP compositions as indicated in **Table 13** were incubated at a concentration of 25 ug/mL in TCAM containing 20 ug/mL rhApoE3 (Peprotech, Cat. 350-02). LNP-ApoE solution was then added to the appropriate culture at a 1:10 ratio.

[00422] On day 3, TRAC-LNP compositions was incubated at a concentration of 5 ug/mL in TCAM containing 10 ug/mL rhApoE3 (Peprotech, Cat. 350-02). T cells were harvested, washed, and resuspended at a density of 1x10^6 cells/mL in TCAM. T cells and LNP-ApoE media were mixed at a 1:1 ratio and T cells plated in culture flasks. WT1 AAV was then added to each group at a MOI of 3x10^5 genome copies/cell.

[00423] On day 4, LNP compositions as indicated in **Table 13** were incubated at a concentration of 5 ug/mL in TCAM containing 5 ug/mL rhApoE3 (Peprotech, Cat. 350-02). LNP-ApoE solution was then added to the appropriate culture at a 1:1 ratio.

[00424] On days 5-11, T cells were transferred to a 24-well GREX plate (Wilson Wolf, Cat. 80192) in T cell expansion media (TCEM): CTS OpTmizer (Thermofisher, Cat. A3705001) supplemented with 5% CTS Immune Cell Serum Replacement (Thermofisher, Cat. A2596101), 1X GlutaMAX (Thermofisher, Cat. 35050061), 10 mM HEPES (Thermofisher, Cat. 15630080), 200 U/mL IL-2 (Peprotech, Cat. 200-02), IL-7 (Peprotech, Cat. 200-07), and IL-15 (Peprotech, Cat. 200-15)). Cells were expanded per manufacturers protocols. T-cells were expanded for 6-days, with media exchanges every other day. Cells were counted using a Vi-CELL cell counter (Beckman Coulter) and fold expansion was calculated by dividing cell yield by the starting material as shown in **Table 14**.

[00425] **Table 14 – Fold expansion following multi-edit T cell engineering**

Group	Donor A	Donor B	Donor C	Mean	SD
1	331.40	362.24	533.18	408.94	108.69
2	61.82	72.15	116.13	83.37	28.84
3	64.08	76.29	157.75	99.37	50.92
4	No data	146.78	331.67	239.22	130.74

6.3. Quantification of T cell editing by flow cytometry and NGS

[00426] Post expansion, edited T cells were assayed by flow cytometry to determine HLA-A2 expression (HLA-A+), HLA-DR-DP-DQ expression (MHC II+) following knockdown CIITA, WT1-TCR expression (CD3+ Vb8+), and the expression of residual endogenous TCRs (CD3+ Vb8-) or mispaired TCRs (CD3+ Vb8low). T cells were incubated with an antibody cocktail targeting the following molecules: CD4 (Biolegend, Cat. 300524), CD8 (Biolegend, Cat. 301045), Vb8 (Biolegend, Cat. 348106), CD3 (Biolegend, Cat. 300327), HLA-A2 (Biolegend, Cat. 343306), HLA-DRDPDQ (Biolegend, Cat 361706), CD62L (Biolegend, Cat. 304844), CD45RO (Biolegend, Cat. 304230). Cells were subsequently washed, analyzed on a Cytoflex LX instrument (Beckman Coulter) using the FlowJo software package. T cells were gated on size and CD4/CD8 status, before expression of editing and insertion markers was determined. The percentage of cells expressing relevant cell surface proteins following sequential T cell engineering are shown in **Table 15** and **Figures 3A-F** for CD8+ T cells and **Table 16** and **Figures 4A-F** for CD4+ T cells. The percent of fully edited CD4+ or CD8+ T cells was gated as % CD3+ Vb8+ HLA-A- MHC II-. High levels of HLA-A and MHC II knockdown, as well as WT1-TCR insertion and endogenous TCR KO are observed in edited samples. In addition to flow cytometry analysis, genomic DNA was prepared and NGS analysis performed as described in Example 1 to determine editing rates at each target site. **Table 17** and **Figures 5A-D** show results for percent editing at the CIITA, HLA-A, and TRBC1/2 loci, with patterns across the groups consistent with what was identified by flow cytometry. TRBC1/2 loci were edited to >90-95% in all groups.

[00427] **Table 15: Percentage of $CD8^+$ cell with cell surface phenotype following sequential T cell engineering**

Donor	Group	% HLA-A I^+	% MHC II^+	% WT1 TCR	% Mispaired TCR	% Residual endogenous TCR	% Fully edited
		$HLA\text{-}A2^+$	$HLA\text{-}DR\text{-}DP\text{-}DQ^+$	$CD3^+$ $Vb8^+$	$CD3^+$ $Vb8^{low}$	$CD3^+$ $Vb8^-$	$CD3^+$ $Vb8^+$ $HLA\text{-}A2^-$ $HLA\text{-}DR\text{-}DP\text{-}DQ^-$
A	1 Unedited	100.0	60.9	6.7	0.8	93.2	0.0
B		99.7	71.0	3.4	0.6	96.1	0.2
C		99.7	52.2	5.7	0.8	94.0	0.0
A	2	2.7	1.2	68.9	1.3	0.4	66.7
B		1.3	21.0	50.4	3.1	4.5	43.3
C		1.8	2.9	62.2	2.6	2.7	60.3
A	3	1.3	0.8	66.0	1.4	0.3	64.4
B		1.4	2.2	56.8	2.2	2.0	55.1
C		1.2	5.7	63.3	1.0	0.9	60.6
B	4	99.8	64.8	62.3	2.0	2.5	0.1
C		99.0	51.5	71.0	1.0	0.5	0.4

[00428] **Table 16: Percentage of CD4+ cells with cell surface phenotype following sequential T cell engineering**

		% HLA-A I$^+$	**% MHC II$^+$**	**% WT1 TCR**	**% Mispaired TCR**	**% Residual endogenous TCR**	**% Fully edited**
Donor	**Group**	HLA-A2$^+$	HLA-DR-DP-DQ$^+$	CD3$^+$ Vb8$^+$	CD3$^+$ Vb8^{low}	CD3$^+$ Vb8$^-$	CD3$^+$ Vb8$^+$ HLA-A2$^-$ HLA-DR-DP-DQ$^-$
A	**1 Unedited**	100.0	36.3	5.4	0.4	94.5	0.0
B		98.7	27.6	5.6	0.4	94.3	0.0
C		99.3	32.3	6.2	0.3	93.6	0.1
A	**2**	2.6	0.7	62.4	2.4	1.1	60.9
B		1.8	0.5	59.7	2.2	1.0	58.5
C		1.7	3.2	58.6	1.6	1.8	55.8
A	**3**	1.3	0.8	63.0	3.4	0.8	61.7
B		1.1	1.1	61.8	2.6	0.9	60.6
C		1.1	0.4	60.9	1.7	1.0	59.9
B	**4**	99.5	25.1	61.9	1.9	5.2	0.1
C		97.9	40.1	69.5	4.7	1.9	0.8

[00429] **Table 17: Percent indels at CIITA, HLA-A, TRBC1 and TRBC2 following sequential T cell editing**

	CIITA (G013676)			**HLA-A (G018995)**			**TRBC1** (G016239)			**TRBC2** (G016239)		
Group	**Donor A**	**Donor B**	**Donor C**	**Donor A**	**Donor B**	**Donor C**	**Donor A**	**Donor B**	**Donor C**	**Donor A**	**Donor B**	**Donor C**
1	0.2	0.2	0.2	6.9	3.3	2.3	0.1	0.3	0.2	0.3	0.3	0.3
2	98.2	81.8	93.8	94.1	90.2	90.6	97.6	89.9	91.4	98.7	86.8	94.9
3	98.9	98.1	98.9	97.2	86.4	93.1	98.6	94.4	94.7	98.6	94.2	96.6
4	0.1	0.2	0.6	7.6	2.7	3.2	98.9	94	95	98.6	93.2	97.4

Example 7: Off-target analysis of HLA-A Human Guides

[00430] Screening for potential off-target genomic sites cleaved by Cas9 targeting HLA-A was performed. (*See, e.g.*, Cameron et al., *Nature Methods*. 6, 600-606; 2017). In this experiment, 10 sgRNA targeting human HLA-A and three control guides targeting EMX1, VEGFA, and RAG1B with known off-target profiles were screened using purified genomic DNA from lymphoblast cell line NA24385 (Coriell Institute). The number of potential off-target sites were detected using a sgRNA as shown in **Table 18** at a concentration of 192 nM sgRNA and 64 nM RNP in the biochemical assay. The assay identified potential off-target sites for the sgRNAs tested.

[00431] **Table 18. Off-Target Analysis**

gRNA ID	Target	Guide Sequence (SEQ ID NO:)	Off-Target Site Count
G018995	HLA-A	ACAGCGACGCCGCGAGCCAG (SEQ ID NO: 13)	17
G018996	HLA-A	CGACGCCGCGAGCCAGAGGA (SEQ ID NO: 14)	48
G018997	HLA-A	CGAGCCAGAGGAUGGAGCCG (SEQ ID NO: 15)	1299
G018998	HLA-A	CGGCUCCAUCCUCUGGCUCG (SEQ ID NO: 16)	250
G018999	HLA-A	GAGCCAGAGGAUGGAGCCGC (SEQ ID NO: 17)	733
G019000	HLA-A	GCGCCCGCGGCUCCAUCCUC (SEQ ID NO: 18)	386
G018933	HLA-A	GCACGGGUACCAGGGGCCAC (SEQ ID NO: 41)	865
G018935	HLA-A	GGGAGGCGCCCCGUGGCCCC (SEQ ID NO: 43)	258
G019008	HLA-A	GCAAGGGUCUCGGGGUCCCG (SEQ ID NO: 26)	324
G018954	HLA-A	UUGAGAAUGGACAGGACACC (SEQ ID NO: 62)	227
G000644	EMX1	GAGUCCGAGCAGAAGAAGAA (SEQ ID NO: 230)	253
G000645	VEGFA	GACCCCCUCCACCCCGCCUC (SEQ ID NO: 231)	3856
G000646	RAG1B	GACUUGUUUUCAUUGUUCUC (SEQ ID NO: 232)	62

[00432] In known off-target detection assays such as the biochemical method used above, a large number of potential off-target sites are typically recovered, by design, so as to “cast a wide net” for potential sites that can be validated in other contexts, *e.g.*, in a primary cell of interest. For example, the biochemical method typically overrepresents the number of

potential off-target sites as the assay utilizes purified high molecular weight genomic DNA free of the cell environment and is dependent on the dose of Cas9 RNP used. Accordingly, potential off-target sites identified by these methods may be validated using targeted sequencing of the identified potential off-target sites.

Example 8: HLA-A and CIITA Partial-Matching in an NK Cell *In Vivo* Killing Mouse Model

[00433] Female NOG-hIL-15 mice were engrafted with 1.5x10^6 primary NK cells followed by the injection of engineered T cells containing luciferase +/- HLA-A, CIITA, or HLA-A/CIITA KO 4 weeks later in order to determine 1) whether engrafted NK cells can readily lyse control T cells ($B2M^{-/-}$), and 2) whether the addition of a partial-matching edit (HLA-A or CIITA) provides a protective effect for T cells from NK cell lysis in vivo.

8.1. Preparation of T cells containing luciferase +/- HLA-A, CIITA, or HLA-A/CIITA KO

[00434] T cells were isolated from peripheral blood of a healthy human donor with the following MHC I phenotype: HLA-A*02:01:01G, 03:01:01G, HLA-B*07:02:01G, HLA-C*07:02:01G. Briefly, a leukapheresis pack (Stemcell Technologies) was treated in ammonium chloride RBC lysis buffer (Stemcell Technologies; Cat. 07800) for 15 minutes to lyse red blood cells. Peripheral blood mononuclear cell (PBMC) count was determined post lysis and T cell isolation was performed using EasySep Human T cell isolation kit (Stemcell Technologies, Cat. 17951) according to manufacturer's protocol. Isolated CD3+ T cells were re-suspended in Cryostor CS10 media (Stemcell Technologies, Cat. 07930) and frozen down in liquid nitrogen until further use.

[00435] Frozen T cells were thawed at a cell concentration of 1x10^6 cells/ml into T cell growth media (TCGM) composed of OpTmizer TCGM as described in Example 3 further supplemented with with 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), 5ng/ml IL-15 (Peprotech, Cat. 200-15). Cells were activated using T cell TransAct™ (Miltenyi Biotec, Cat. 130-111-160) at 1:100 dilution at 37°C for 24 hours.

[00436] Twenty-four hours post activation, 1x10^6 T cells in 500 µl fresh TCGM without cytokines were transduced by centrifugation 1000xG for 60 minutes at 37°C with 150 µl of luciferase lentivirus (Imanis Life Sciences, Cat# LV050L). Transduced cells were expanded in 24-well G-Rex plate (Wilson Wolf, Cat. 80192M) in TCGM with cytokines at 37°C for 24 hours.

[00437] Forty-eight hours post activation, luciferase LV infected T cells were edited to disrupt the B2M or HLA-A genes. Briefly, LNP compositions containing mRNA encoding cas9 (SEQ ID NO:802) and sgRNA G019000 (SEQ ID NO: 18) targeting HLA-A were formulated with lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:38.5:10:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. LNP compositions containing the Cas9 mRNA and sgRNA G000529 (SEQ ID NO: 245) targeting B2M were formulated as described in Example 1. LNP compositions were incubated in Optmizer TCGM without serum or cytokines further supplemented with 1 ug/ml recombinant human ApoE3 (Peprotech, Cat. 350-02) for 15 minutes at 37°C. T cells were washed and suspended in TCGM with cytokines. Pre-incubated LNP and T cells were mixed to yield final concentrations of $0.5x10^{\wedge 6}$ T cells/ml and 2.5 μg total RNA/mL of LNP in TCGM with 5% human AB serum, 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), 5ng/ml IL-15 (Peprotech, Cat. 200-15). An additional group of cells were mock edited with media containing ApoE3 but no LNP compositions. All cells were incubated at 37°C for 24 hours.

[00438] Seventy-two hours post activation, the cells were edited to disrupt CIITA, and LNP were administered either on luciferase and HLA-A edited cells or luciferase cells alone. Briefly, cells were transduced with LNP compositions containing the Cas9 mRNA and sgRNA G013675 (SEQ ID NO: 246) as described for HLA-A editing. LNP compositions targeting CIITA were formulated with lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:38.5:10:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. Ninety-six hours post activation, cells were washed and transferred to a 24-well G-Rex. Media with fresh cytokines was replaced every 2 days. On day 15 post activation, edited T cells were sorted on GFP^+ cells using BD FACS Aria Flow Sorter to enrich for luciferase-expressing cells. For B2M KO luciferase group, cells were sorted on GFP^+ and $MHC\text{-}I^-$. Sorted cells were rested overnight in TCGM media with cytokines in a 37°C incubator. The next day, T cells were re-stimulated with T-cell TrasnAct™ at 1:100 dilution for 24 hours. Twenty-four hours after restimulation, TransAct was washed out and T cells were cultured and maintained in G-Rex plate for 15 days with regular changes in media and cytokines.

[00439] Fifteen days after restimulation, NK cell mediated cytotoxicity towards engineered T cells was assayed *in vitro* as in **Example 4** with the following exceptions.

Assays were performed using OpTmizer TCGM with 100 µl/ml IL-2. T cells were co-cultured overnight with the HLA-B/C matched CTV labelled NK cells at effector to target ratios (E:T) of 10:1, 5:1, 2.5:1, 1.25:1 and 0.625:1. The cells were incubated with BrightGlo Luciferase reagents (Promega, Cat. E2620) and processed on the CellTiter Glo Program in ClarioStar to determine lysis of T cells by NK cells based on luciferase signal. **Table 19** and **FIG. 6A** show the percentage of T cell lysis following NK cell challenge. In vitro, B2M edited cells showed sensitivity to NK killing, while HLA-A edited, CIITA edited and HLA-A, CIITA double edited cells showed protection from NK mediated lysis.

[00440] **Table 19 – Percentage of lysis of luciferase transduced T cell following NK cell challenge**

	No edit		HLA-A KO		CIITA KO		HLA-A KO, CIITA KO		B2M KO		
E:T	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**n**
10	19.22	3.16	28.55	1.02	22.96	3.59	22.22	3.15	68.09	0.11	2
5	13.04	1.71	27.18	4.35	22.85	6.93	13.78	4.55	53.87	3.30	2
2.5	1.56	1.35	26.56	3.75	26.59	2.44	21.32	0.72	39.46	7.05	2
1.25	-0.26	1.94	19.78	3.24	19.91	5.38	12.86	0.54	25.79	7.96	2
0.625	8.67	6.81	25.44	0.23	18.32	4.28	19.80	7.20	29.31	2.67	2
0.3125	2.96	7.66	22.40	0.83	19.13	1.34	13.34	2.48	9.32	0.84	2

8.2. HLA-A and CIITA double knockout T cells are protected from NK killing

[00441] For the *in vivo* study, NK cells isolated from a leukopak by methods known in the art were washed with HBSS (Gibco, Cat. No. 14025-092) and resuspended at $10x10^{\wedge 6}$ cells/mL for injection in 150 µL HBSS. Twenty-two female NOG-hIL-15 mice (Taconic) were dosed by tail vein injection with $1.5x10^{\wedge 6}$ isolated NK cells. An addition 27 female NOG-hIL-15 served NK-non-injected controls.

[00442] Twenty-eight days after NK cell injection, mice were injected with unedited or engineered T cells as described in **Table 19**. Briefly, engineered T cells were injected 16 days post second activation after washing in PBS and resuspending in HBSS solution at a concentration of $6x10^{\wedge 6}$ cells/150 µL.

[00443] IVIS imaging of live mice was performed to identify luciferase-positive T cells by IVIS spectrum. IVIS imaging was done at 6 hours, 24 hours, 48 hours, 8 days, 13 days, 18 days, and 27 days after T cell injection. Mice were prepared for imaging with an injection of D-luciferin i.p. at 10 µL/g body weight per the manufacturer's recommendation, about 150 µL per animal. Animals were anesthetized and then placed in the IVIS imaging unit. The visualization was performed with the exposure time set to auto, field of view D, medium

binning, and F/stop set to 1. **Table 20** and **FIG. 6A** shows radiance (photons/s/cm2/sr) from luciferase expressing T cells present at the various time points after injection. **FIG. 6B** shows radiance (photons/s/cm2/sr) from luciferase expressing T cells present in the various mice groups after 27 days. In vivo, B2M edited cells showed sensitivity to NK killing, while HLA-A edited, CIITA edited and HLA-A, CIITA double edited cells showed protection from NK mediated lysis. Unexpectedly, even after a reduction in one of the three highly polymorphic MHC class I proteins (HLA-A) the cells are protected against NK-mediated rejection.

[00444] **Table 20 – Radiance (photons/s/cm2/sr) from luciferase expressing T cells in treated mice at intervals after T cell injection.**

T cell injection	Timepoint (days)	No NK cell injection			NK cell injection		
		Mean	SD	n	Mean	SD	n
No T cells	0.25	5,065	474	2	6,010	651	2
	1	5,225	431	2	5,150	467	2
	4	4,715	403	2	4,860	57	2
	6	5,145	884	2	5,110	226	2
	11	5,230	382	2	4,700	99	2
	13	6,920	948	2	6,735	35	2
	18	5,055	148	2	5,570	28	2
	27	4,740	311	2	5,185	290	2
No edit	0.25	477,200	51,237	5	464,000	112,493	4
	1	547,600	59,315	5	517,500	95,710	4
	4	285,600	43,328	5	219,750	77,298	4
	6	249,400	58,748	5	137,000	69,190	4
	11	131,500	28,671	5	111,150	36,287	4
	13	147,000	15,732	5	43,168	52,128	4
	18	112,100	20,768	5	55,825	47,391	4
	27	53,960	13,546	5	59,700	31,479	4
B2M KO	0.25	662,600	193,865	5	261,850	135,636	4
	1	555,200	122,508	5	89,400	41,151	4
	4	266,200	68,845	5	25,175	11,072	4
	6	202,600	41,825	5	18,500	7,048	4
	11	106,320	14,377	5	17,100	9,440	4
	13	57,714	45,535	5	7,048	2,735	4
	18	77,080	7,792	5	9,453	4,592	4
	27	55,240	12,780	5	6,860	1,207	4
HLA-A KO	0.25	160,000	30,315	5	111,500	30,533	4
	1	206,800	38,493	5	153,000	24,427	4
	4	120,200	23,488	5	91,025	69,091	4
	6	81,100	16,903	5	91,408	106,141	4

T cell injection	Timepoint (days)	No NK cell injection			NK cell injection		
		Mean	SD	n	Mean	SD	n
	11	55,520	6,843	5	53,367	21,985	3
	13	30,716	23,658	5	33,233	13,615	3
	18	21,802	10,911	5	35,667	5,601	3
	27	20,600	808	4	46,900	4,937	3
CIITA KO	0.25	121,400	19,680	5	116,350	82,606	4
	1	168,200	32,760	5	120,225	43,535	4
	4	93,600	23,187	5	76,450	31,056	4
	6	71,298	40,161	5	52,500	35,590	4
	11	59,100	13,805	5	73,500	77,242	4
	13	43,870	22,810	5	31,760	30,831	4
	18	28,422	14,019	5	35,000	7,902	3
	27	18,780	3,505	5	69,067	31,194	3
HLA-A KO CIITA KO	0.25	259,250	59,824	4	363,000	113,731	4
	1	456,750	69,188	4	481,500	142,778	4
	4	170,500	26,665	4	200,750	70,415	4
	6	108,950	11,046	4	98,633	27,450	3
	11	97,350	19,982	4	93,867	32,173	3
	13	85,708	58,720	4	68,357	54,428	3
	18	20,923	22,172	4	98,633	27,450	3
	27	37,375	10,602	4	31,733	2,593	3

Example 9: HLA-A and CIITA Partial-Matching in an NK Cell *In Vivo* Killing Mouse Model

[00445] Female NOG-hIL-15 mice were engrafted with 1.5x10^^{6} primary NK cells followed by the injection of engineered T cells containing luciferase +/- HLA-A/CIITA KO with HD1 TCR 4 weeks later in order to determine 1) whether engrafted NK cells can readily lyse control T cells (B2M$^{-/-}$), and 2) whether the addition of a partial-matching edit (HLA-A & CIITA) provides a protective effect for T cells with the exogenous HD1 TCR from NK cell lysis *in vivo*.

9.1. Preparation of T cells containing luciferase +/-HLA-A/CIITA KO and HD1 TCR

[00446] T cells were isolated from peripheral blood of a healthy human donor with the following MHC I phenotype: HLA-A*02:01:01G, 03:01:01G, HLA-B*07:02:01G, HLA-C*07:02:01G. Briefly, a leukapheresis pack (Stemcell Technologies) was treated in ammonium chloride red blood cell lysis buffer (Stemcell Technologies; Cat. 07800) for 15 minutes to lyse red blood cells. Peripheral blood mononuclear cell (PBMC) count was determined post lysis, and T cell isolation was performed using EasySep Human T cell

isolation kit (Stemcell Technologies, Cat. 17951) according to manufacturer's protocol. Isolated CD3+ T cells were re-suspended in Cryostor CS10 media (Stemcell Technologies, Cat. 07930) and frozen down in liquid nitrogen until further use.

[00447] Frozen T cells were thawed at a cell concentration of 1.5x10^6 cells/ml into T cell activation media (TCAM) composed of OpTmizer TCGM as described in **Example 3** and further supplemented with 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), 5ng/ml IL-15 (Peprotech, Cat. 200-15). Cells were rested at 37 °C for 24 hours.

[00448] Twenty-four hours post thawing, T cells were counted and resuspended at 2x10^6 cells/ml in TCAM media and 1:50 of Transact was added. Cells were mixed and incubated for 20-30 mins at 37°C. LNP compositions containing mRNA encoding Cas9 (SEQ ID NO:802) and sgRNA G013675 (SEQ ID NO: 246), targeting CIITA were formulated with lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:38.5:10:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. LNP compositions at 5 ug/ml were incubated in OpTmizer TCAM and further supplemented with 5 ug/ml recombinant human ApoE3 (Peprotech, Cat. 350-02) for 15 minutes at 37 °C. Pre-incubated LNP compositions and T cells with Transact were mixed to yield final concentrations of 1x10^6 T cells/ml and 2.5 μg total RNA/mL of LNP in TCAM media with 2.5% human AB serum, 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), and 5 ng/ml IL-15 (Peprotech, Cat. 200-15). An additional group of cells were mock-edited with media containing ApoE3 but no LNP compositions. All cells were incubated at 37 °C for 24 hours.

[00449] After 48 hours post activation, all groups were transduced with EF1α-GFP-Luc lentivirus. Lentivirus was removed from -80 °C and thawed on ice. Cells were collected as per groups and centrifuged at 500Xg for 5 mins to wash off the LNP compositions and media. Cells were resuspended, individually according to their groups, at 2x10^6 cells/ml in TCAM media. 500 ul of the cell suspension was then transferred to a sterile Eppendorf tube (total 1x10^6 cells), and 100 ul of lentivirus was added. Cells were centrifuged at 1000XG for 60 minutes at 37 °C. After centrifugation, the cells were combined according to their groups and resuspended at 1x10^6 cells/ml of TCAM media containing final concentration of 2.5% human AB serum, 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), and 5 ng/ml IL-15 (Peprotech, Cat. 200-15) followed by incubating at 37 °C for 24 hours.

[00450] Seventy-two hours post activation, luciferase-transduced T cells were treated with LNP compositions to disrupt TRAC genes and further treated with HD1 AAV to insert the HD1 TCR at the TRAC locus. Cells were collected as per groups and centrifuged at 500Xg for 5 mins to wash off the lentivirus and media. The cells were then resuspended in TCAM media at $1x10^{\wedge 6}$ cells/ml in TCAM media. LNP compositions containing mRNA encoding Cas9 (SEQ ID NO:802) and sgRNA G013006 (SEQ ID NO: 243), targeting TRAC were formulated with lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:38.5:10:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. LNP compositions at 5 ug/ml were incubated in OpTmizer TCAM and further supplemented with 5 ug/ml recombinant human ApoE3 (Peprotech, Cat. 350-02) for 15 minutes at 37 °C. Pre-incubated LNP compositions and T cells with Transact were mixed to yield final concentrations of $1x10^{\wedge 6}$ T cells/ml and 2.5 µg total RNA/mL of LNP in TCAM with 2.5% human AB serum, 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), and 5 ng/ml IL-15 (Peprotech, Cat. 200-15). A vial of EF1α-HD1 AAV was thawed on benchtop and added to the TRAC LNP treated cells at $3x10^{\wedge 5}$ GC/cell. Cells were then incubated at 37 °C for 24hours.

[00451] Ninety-six hours post activation cells were then treated for a final round of editing either with TRBC LNP alone or in combination with HLA-A LNP. The B2M KO group was treated with B2M LNP. Cells were collected as per groups and centrifuged at 500Xg for 5 mins to wash off the LNP compositions and media. The cells were then resuspended in TCAM media at $1x10^{\wedge 6}$ cells/ml in TCAM media. Briefly, LNP compositions containing mRNA encoding Cas9 (SEQ ID NO:802) and sgRNA G018995 (sgRNA comprising SEQ ID NO: 13, as shown in Table 2) targeting HLA-A were formulated as described in **Example 1**. LNP compositions containing the Cas9 mRNA and sgRNA G000529 (SEQ ID NO: 245) targeting B2M and LNP compositions containing the Cas9 mRNA and sgRNA G016239 (SEQ ID NO: 247) targeting TRBC were formulated with lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:38.5:10:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. LNP compositions at 5 ug/ml were incubated in OpTmizer TCAM and further supplemented with 5 ug/ml recombinant human ApoE3 (Peprotech, Cat. 350-02) for 15 minutes at 37 °C. Pre-incubated LNP compositions and T cells with Transact were mixed to yield final concentrations of $1x10^{\wedge 6}$ T cells/ml and 2.5 µg total RNA/mL of LNP in TCAM with 2.5% human AB serum, 100 U/mL of recombinant

human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), and 5ng/ml IL-15 (Peprotech, Cat. 200-15). For simultaneous TRBC and HLA-A editing, LNP and ApoE3 were formulated at 4X the final concentration followed by adding TRBC LNP first to the T cells and incubating at 37 °C for 15 mins. After incubation preformulated HLA-A LNP compositions were added, the cells were incubated for 24 hours.

[00452] After the final round of editing, the cells were washed by spinning at 500XG for 5 mins and resuspended in TCGM media containing with 5% human AB serum, 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), and 5 ng/ml IL-15 (Peprotech, Cat. 200-15).

[00453] On day 5 post activation, edited T cells were sorted on GFP^+ cells using a BD FACS Aria Flow Sorter to enrich for luciferase-expressing cells. Sorted cells were rested overnight in TCGM media with cytokines in a 37 °C incubator. The next day, T cells were re-stimulated with T-cell TransAct™ at 1:100 dilution for 24 hours. Twenty-four hours after restimulation, TransAct™ was washed out and T cells were cultured and maintained in G-Rex plate for 15 days with regular changes in media and cytokines.

[00454] Fifteen days after first restimulation, editing levels were confirmed via flow cytometry, and cells were washed and resuspend in HBSS buffer for injections.

9.2. HLA-A and CIITA double knockout T cells show protection from NK killing

[00455] For the *in vivo* study, NK cells isolated from a leukopak by methods known in the art were washed with HBSS (Gibco, Cat. No. 14025-092) and resuspended at 10x10^6 cells/mL for injection in 150 µL HBSS. Thirty female NOG-hIL-15 mice (Taconic) were dosed by tail vein injection with 1.5x10^6 isolated NK cells. An addition 25 female NOG-hIL-15 served as NK-non-injected controls.

[00456] Twenty-eight days after NK cell injection, mice were injected with unedited or engineered T cells as described in **Table 21**. Briefly, 0.2 x 10^6 engineered T cells were injected 16 days post second activation after washing in PBS and resuspending in HBSS solution at a concentration of 6.0x10^6 cells/150 µL.

[00457] IVIS imaging of live mice was performed to identify luciferase-positive T cells by IVIS spectrum. IVIS imaging was done at 24 hours, 48 hours, 72 hours, 6 days, 10 days, 13 days, 17 days, 20 days, 24 days, 27 days, 31 days, 34 days, 38 days, 42 days, 44 days, 48 days, 55 days, 63 days, 72 days, 77 days, 85 days, and 91 days after T cell injection. Mice were prepared for imaging with an injection of D-luciferin i.p. at 10 µL/g body weight per the manufacturer's recommendation, about 150 µL per animal. Animals were anesthetized and

then placed in the IVIS imaging unit. The visualization was performed with the exposure time set to auto, field of view D, medium binning, and F/stop set to 1. **Table 22** and **FIG. 7A** shows radiance (photons/s/cm2/sr) from luciferase expressing T cells present at the various time points after injection out to 91 days. **FIG. 7B** shows radiance (photons/s/cm^2/sr) from luciferase expressing T cells present in the various mice groups after 31 days. *In vivo*, B2M edited cells showed sensitivity to NK killing, while the HLA-A, CIITA double edited cells showed protection from NK mediated lysis.

[00458] **Table 21 - T-Cell Engineering**

Group	Day 0	Day1	Day2	Day3	Day4	Day6	Day 7	Day 8	Day 16
HLA-A CIITA KO	Thaw	CIITA	GFP-Luc LV	TRAC+AAV	TRBC, HLA-A	Flow & Sort	Re-stim	Expand in G-Rex	Wash & Inject
B2M Control	Thaw	B2M	GFP-Luc LV	TRAC+AAV	TRBC	Flow & Sort	Re-stim	Expand in G-Rex	Wash & Inject
No Edit	Thaw	-	GFP-Luc LV	-	-	Flow & Sort	Re-stim	Expand in G-Rex	Wash & Inject

[00459] **Table 22 –Total Flux (photons/s) from luciferase expressing T cells in treated mice at intervals after T cell injection.**

T cell injection	Timepoint (days)	No NK cell injection			NK cell injection		
		Mean	SD	n	Mean	SD	n
No T cells	1	1170000	0	1	1060000	0	1
	2	884000	0	1	728000	0	1
	3	1090000	0	1	771000	0	1
	6	1040000	0	1	888000	0	1
	10	741000	0	1	799000	0	1
	13	1350000	0	1	751000	0	1
	17	1210000	0	1	709000	0	1
	20	1530000	0	1	1190000	0	1
	24	1280000	0	1	823000	0	1
	27	1430000	0	1	577000	0	1
	31	1310000	0	1	970000	0	1
	34	1840000	0	1	800000	0	1
	38	937000	0	1	750000	0	1
	42	1450000	0	1	757000	0	1
	44	1770000	0	1	797000	0	1
	48	1850000	0	1	666000	0	1
	55	1170000	0	1	723000	0	1
	63	1680000	0	1	799000	0	1
	72	1400000	0	1	840000	0	1
	77	1570000	0	1	801000	0	1

	85	1220000	0	1	770000	0	1
	91	1580000	0	1	905000	0	1
No edit	1	37560000	34014482.9	5	27882000	27141262.31	5
	2	40698000	22307084.5	5	28640000	14568047.23	5
	3	34210000	18847559.5	5	25692000	14362636.25	5
	6	51440000	10855551.6	5	37700000	34510288.32	5
	10	29460000	5028220.36	5	34060000	24420544.63	5
	13	17350000	8731122.49	5	42864000	47552123.82	5
	17	17380000	4065956.22	5	124180000	217126534.5	5
	20	35860000	9912012.91	5	329720000	644006666.9	5
	24	41400000	6393355.93	5	1784780000	3583692731	5
	27	70500000	28116809.9	5	9112600000	19172106869	5
	31	124260000	57196923	5	14383000000	27254468202	5
	34	313000000	256943574	5	17450000000	24859612829	5
	38	667800000	614512978	5	25316000000	26111305597	5
	42	1727400000	1703225998	5	21084000000	16956611690	5
	44	2101400000	2213844349	5	16975000000	13721121188	4
	48	5068000000	4995313854	5	15106666667	11613532337	3
	55	6386750000	5350377767	4	16303333333	11913187371	3
	63	8105750000	6722716632	4			
	72						
	77						
	85						
	91						
B2M KO	1	96334000	62882587.3	5	7192000	6901425.215	5
	2	138300000	57619007.3	5	7296000	2213194.524	5
	3	117980000	43943736.8	5	7342000	2837475.991	5
	6	104240000	34772230.3	5	7276000	2743998.907	5
	10	81120000	19876921.3	5	6124000	1967035.841	5
	13	45386000	24729233.3	5	5748000	3248448.861	5
	17	50600000	19718899.6	5	4390000	902607.3343	5
	20	38200000	12211470	5	2772000	947507.2559	5
	24	32180000	17561520.4	5	4566000	1182742.576	5
	27	35840000	15497354.6	5	3626000	1995903.304	5
	31	41380000	12243243	5	3344000	1295812.486	5
	34	40740000	13481394.6	5	3864000	506635.964	5
	38	33980000	15116117.2	5	3468000	1330139.09	5
	42	38840000	15452605	5	3504000	688534.676	5
	44	35280000	19116929.7	5	3266000	910291.1622	5

	48	31600000	17624982.3	5	3196000	726691.1311	5
	55	38920000	30824779	5	2654000	475794.0731	5
	63	29300000	22330584.4	5	2530000	274135.0032	5
	72	19070000	13309188.6	5	2522000	437344.258	5
	77	30680000	24960508.8	5	2650000	531554.3246	5
	85	24738000	22937833.8	5	1816000	410524.0553	5
	91	18234000	10913394.5	5	1736000	297707.9105	5
HLA-A KO CIITA KO	1	63960000	33085918.5	5	59320000	32265414.92	5
	2	55412000	31461432.3	5	49560000	9862707.539	5
	3	64686000	39918742.2	5	41264000	22521777.9	5
	6	88440000	22053865.9	5	33442000	18099663.53	5
	10	68320000	18250397.3	5	42040000	4585084.514	5
	13	57880000	8452041.17	5	37028000	20443236.53	5
	17	39320000	11283040.4	5	41400000	10968135.67	5
	20	40480000	12259363.8	5	37540000	8371260.359	5
	24	39900000	18287017.3	5	37740000	9070446.516	5
	27	37800000	14406422.2	5	31840000	11387185.78	5
	31	46160000	13751836.2	5	25020000	11377477.75	5
	34	39820000	8990383.75	5	28980000	5348551.206	5
	38	42620000	8249363.61	5	31000000	7146677.55	5
	42	30740000	10083798.9	5	16928000	9138868.639	5
	44	31740000	9619667.35	5	26580000	7343500.528	5
	48	30740000	9147021.37	5	28620000	3141178.123	5
	55	27600000	5482244.07	5	21340000	3673281.911	5
	63	24820000	6599015.08	5	12428000	3646082.83	5
	72	10918000	3813609.84	5	13094000	3349355.162	5
	77	24840000	4728953.37	5	14200000	3801973.172	5
	85	15520000	4283923.44	5	14580000	2920102.738	5
	91	17260000	5452797.45	5	11256000	2456141.283	5

Example 10: MHCI and MHCII KO *in-vivo* efficacy of HD1 T cells

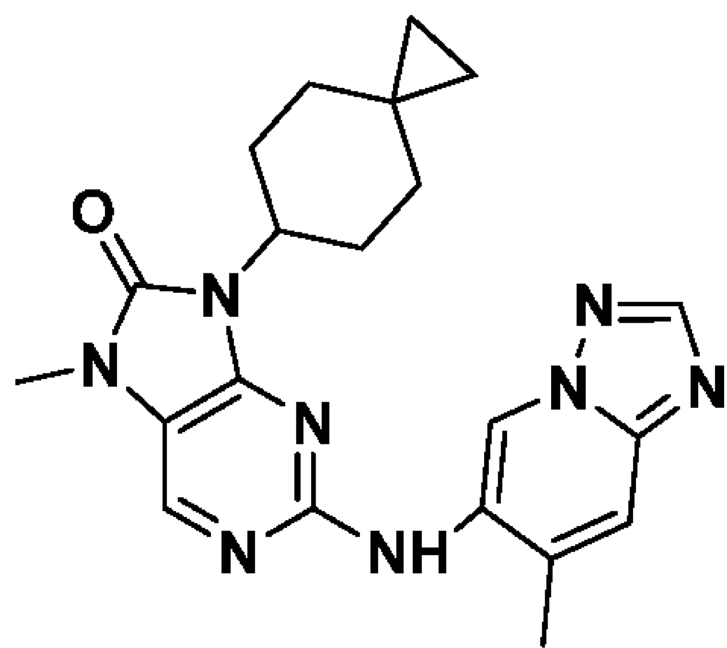
[00460] Female NOG-hIL-15 mice were engrafted with 0.2x10^6 human acute lymphoblastic leukemia (ALL) cell line 697-Luc2, followed by the injection of 10x10^6 engineered T cells with various edits in order to determine whether the edits provide a specific anti-tumor effect. Groups of T cells studied include: a control group of T cells with no edits (697 only); T cells with edits in TRAC and TRBC (TCR KO); T cells with edits in TRAC and TRBC and insertion of HD1 (TCR KO/WT1 insert); T cells with edits in TRAC and TRBC, insertion of HD1, and disruption in HLA-A (HLA-A KO); T cells with edits in TRAC and TRBC, insertion of HD1, and edits in HLA-A and in CIITA (AlloWT1); and T cells with edits in TRAC and TRBC and insertion of HD1 in the presence of a DNA PKi compound, and edits in HLA-A and in CIITA (AlloWT1+PKi Compound 1).

10.1. T cell Preparation

[00461] T cells from HLA-A2+ donor (110046967) were isolated from the leuokopheresis products of healthy donor (STEMCELL Technologies). T cells were isolated using EasySep Human T cell isolation kit (STEMCELL Technologies, Cat#17951) following manufacturer's protocol and cryopreserved using Cryostor CS10 (STEMCELL Technologies, Cat# 07930). The day before initiating T cell editing, cells were thawed and rested overnight in T cell activation media TCAM: CTS OpTmizer (Thermofisher #A3705001) supplemented with 2.5% human AB serum (Gemini #100-512), 1X GlutaMAX (Thermofisher #35050061), 10mM HEPES (Thermofisher #15630080), 200 U/mL IL-2 (Peprotech #200-02), IL-7 (Peprotech #200-07), IL-15 (Peprotech #200-15).

10.2 Multi-editing T cells with sequential LNP delivery

[00462] T cells were prepared by treating healthy donor cells sequentially with four LNP compositions co-formulated with Cas9 mRNA and sgRNA targeting either TRAC, TRBC, CIITA, and HLA-A. The lipid portion of the LNP compositions included Lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:38.5:10:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. A transgenic WT1-targeting TCR was site-specifically integrated into the TRAC cut site by delivering a homology-directed repair template using AAV indicated in Table 24, in combination with the small molecule inhibitor of DNA-dependent protein kinase to boost the tgTCR insertion rate. The inhibitor, referred to hereinafter as "DNAPKI Compound 1" is 9-(4,4-difluorocyclohexyl)-7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-7,9-dihydro-8H-purin-8-one, also depicted as:



[00463] DNAPKI Compound 1 was prepared as follows:

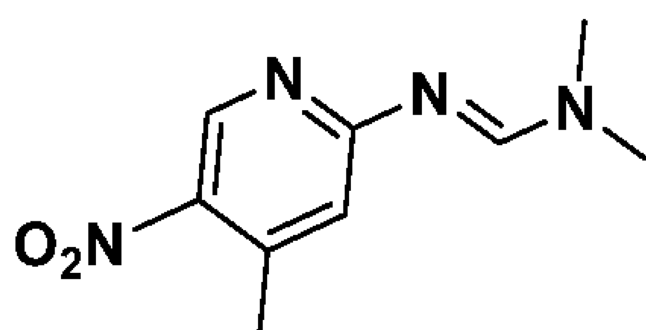
[00464] General Information

[00465] All reagents and solvents were purchased and used as received from commercial vendors or synthesized according to cited procedures. All intermediates and final compounds were purified using flash column chromatography on silica gel. NMR spectra were recorded

on a Bruker or Varian 400 MHz spectrometer, and NMR data were collected in CDCl3 at ambient temperature. Chemical shifts are reported in parts per million (ppm) relative to CDCl3 (7.26). Data for 1H NMR are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets m = multiplet), coupling constant, and integration. MS data were recorded on a Waters SQD2 mass spectrometer with an electrospray ionization (ESI) source. Purity of the final compounds was determined by UPLC-MS-ELS using a Waters Acquity H-Class liquid chromatography instrument equipped with SQD2 mass spectrometer with photodiode array (PDA) and evaporative light scattering (ELS) detectors.

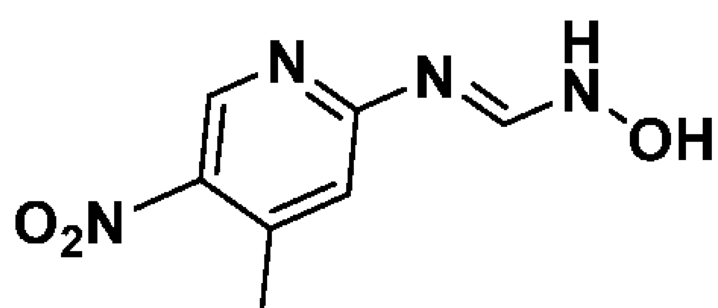
[00466] Example 1 - Compound 1

[00467] Intermediate 1a: (E)-N,N-dimethyl-N'-(4-methyl-5-nitropyridin-2-yl)formimidamide



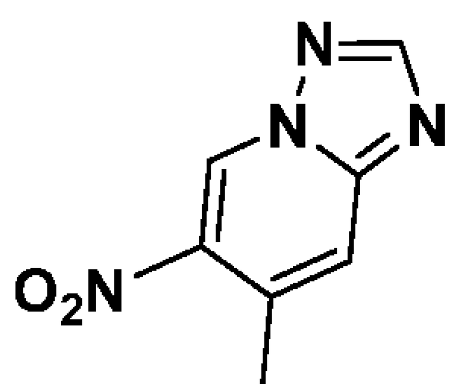
[00468] To a solution of 4-methyl-5-nitro-pyridin-2-amine (5 g, 1.0 equiv.) in toluene (0.3 M) was added DMF-DMA (3.0 equiv.). The mixture was stirred at 110 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue and purified by column chromatography to afford product as a yellow solid (59%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.82 (s, 1H), 8.63 (s, 1H), 6.74 (s, 1H), 3.21 (m, 6H).

[00469] Intermediate 1b: (E)-N-hydroxy-N'-(4-methyl-5-nitropyridin-2-yl)formimidamide



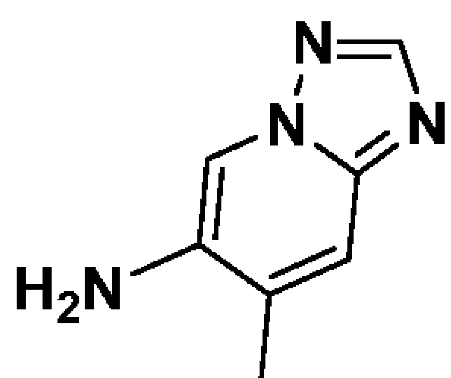
[00470] To a solution of Intermediate 1a (4 g, 1.0 equiv.) in MeOH (0.2 M) was added $NH_2OH{\cdot}HCl$ (2.0 equiv.). The reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was partitioned between H_2O and EtOAc, followed by 2x extraction with EtOAc. The organic phases were concentrated under reduced pressure to give a residue and purified by column chromatography to afford product as a white solid (66%). 1H NMR (400 MHz, $(CD_3)_2SO$) δ 10.52 (d, J = 3.8 Hz, 1H), 10.08 (dd, J = 9.9, 3.7 Hz, 1H), 8.84 (d, J = 3.8 Hz, 1H), 7.85 (dd, J = 9.7, 3.8 Hz, 1H), 7.01 (d, J = 3.9 Hz, 1H), 3.36 (s, 3 H).

[00471] Intermediate 1c: 7-methyl-6-nitro-[1,2,4]triazolo[1,5-a]pyridine



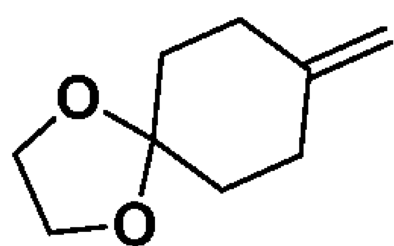
[00472] To a solution of Intermediate 1b (2.5 g, 1.0 equiv.) in THF (0.4 M) was added trifluoroacetic anhydride (1.0 equiv.) at 0 °C. The mixture was stirred at 25 °C for 18 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to afford product as a white solid (44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.49 (s, 1H), 7.69 (s, 1H), 2.78 (d, J = 1.0 Hz, 3H).

[00473] Intermediate 1d: 7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-amine



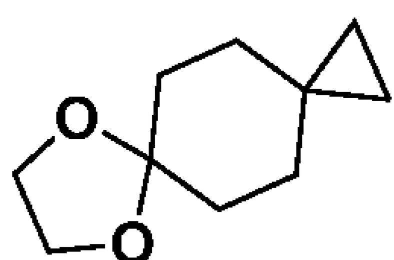
[00474] To a mixture of Pd/C (10% w/w, 0.2 equiv.) in EtOH (0.1 M) was added Intermediate 1c (1.0 equiv. and ammonium formate (5.0 equiv.). The mixture was heated at 105 °C for 2 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to afford product as a pale brown solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.41 (s, 2H), 8.07 (d, J = 9.0 Hz, 2H), 7.43 (s, 1H), 2.22 (s, 3H).

[00475] Intermediate 1e: 8-methylene-1,4-dioxaspiro[4.5]decane



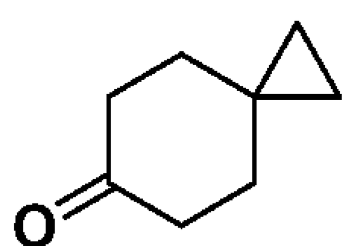
[00476] To a solution of methyl(triphenyl)phosphonium bromide (1.15 equiv.) in THF (0.6 M) was added *n*-BuLi (1.1 equiv.) at -78 °C dropwise, and the mixture was stirred at 0 °C for 1 h. Then, 1,4-dioxaspiro[4.5]decan-8-one (50 g, 1.0 equiv.) was added to the reaction mixture. The mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into aq. NH_4Cl at 0 °C, diluted with H_2O, and extracted 3x with EtOAc. The combined organic layers were concentrated under reduced pressure to give a residue and purified by column chromatography to afford product as a colorless oil (51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 1H), 3.96 (s, 4 H), 2.82 (t, J = 6.4 Hz, 4 H), 1.70 (t, J = 6.4 Hz, 4 H).

[00477] Intermediate 1f: 7,10-dioxadispiro[2.2.4^6.2^3]dodecane



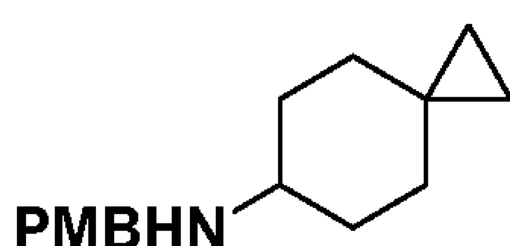
[00478] To a solution of Intermediate 4a (5 g, 1.0 equiv.) in toluene (3 M) was added $ZnEt_2$ (2.57 equiv.) dropwise at -40 °C and the mixture was stirred at -40 °C for 1 h. Then diiodomethane (6.0 equiv.) was added dropwise to the mixture at -40 °C under N_2. The mixture was then stirred at 20 °C for 17 h under N_2 atmosphere. The reaction mixture was poured into aq. NH_4Cl at 0 °C and extracted 2x with EtOAc. The combined organic phases were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered, and the filtrate was concentrated in vacuum. The residue was purified by column chromatography to afford product as a pale yellow oil (73%).

[00479] Intermediate 1g: spiro[2.5]octan-6-one



[00480] To a solution of Intermediate 4b (4 g, 1.0 equiv.) in 1:1 THF/H_2O (1.0 M) was added TFA (3.0 equiv.). The mixture was stirred at 20 °C for 2 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove THF, and the residue adjusted pH to 7 with 2 M NaOH (aq.). The mixture was poured into water and 3x extracted with EtOAc. The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered, and the filtrate was concentrated in vacuum. The residue was purified by column chromatography to afford product as a pale yellow oil (68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (t, J = 6.6 Hz, 4H), 1.62 (t, J = 6.6 Hz, 4H), 0.42 (s, 4H).

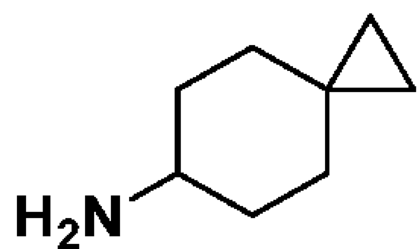
[00481] Intermediate 1h: N-(4-methoxybenzyl)spiro[2.5]octan-6-amine



[00482] To a mixture of Intermediate 4c (2 g, 1.0 equiv.) and (4-methoxyphenyl)methanamine (1.1 equiv.) in DCM (0.3 M) was added AcOH (1.3 equiv.). The mixture was stirred at 20 °C for 1 h under N_2 atmosphere. Then, $NaBH(OAc)_3$ (3.3 equiv.) was added to the mixture at 0 °C, and the mixture was stirred at 20 °C for 17 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove DCM, and the resulting residue was diluted with H_2O and extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to afford product as a gray solid (51%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.15 – 7.07 (m, 2H), 6.77 – 6.68 (m, 2H), 3.58 (s, 3H), 3.54 (s, 2H), 2.30 (ddt, J

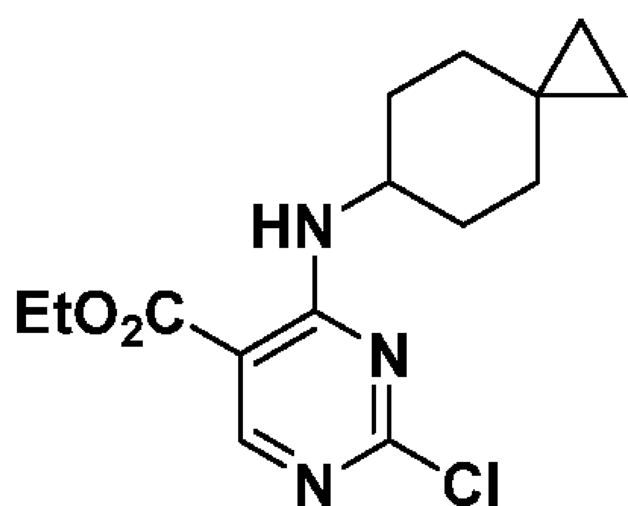
= 10.1, 7.3, 3.7 Hz, 1H), 1.69 – 1.62 (m, 2H), 1.37 (td, J = 12.6, 3.5 Hz, 2H), 1.12 – 1.02 (m, 2H), 0.87 – 0.78 (m, 2H), 0.13 – 0.04 (m, 2H).

[00483] Intermediate 1i: spiro[2.5]octan-6-amine



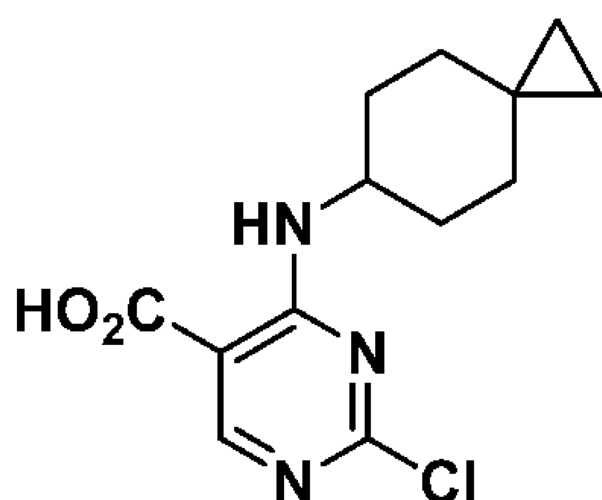
[00484] To a suspension of Pd/C (10% w/w, 1.0 equiv.) in MeOH (0.25 M) was added Intermediate 4d (2 g, 1.0 equiv.) and the mixture was stirred at 80 °C at 50 Psi for 24 h under H_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue that was purified by column chromatography to afford product as a white solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 2.61 (tt, J = 10.8, 3.9 Hz, 1H), 1.63 (ddd, J = 9.6, 5.1, 2.2 Hz, 2H), 1.47 (td, J = 12.8, 3.5 Hz, 2H), 1.21 – 1.06 (m, 2H), 0.82 – 0.72 (m, 2H), 0.14 – 0.05 (m, 2H).

[00485] Intermediate 1j: ethyl 2-chloro-4-(spiro[2.5]octan-6-ylamino)pyrimidine-5-carboxylate



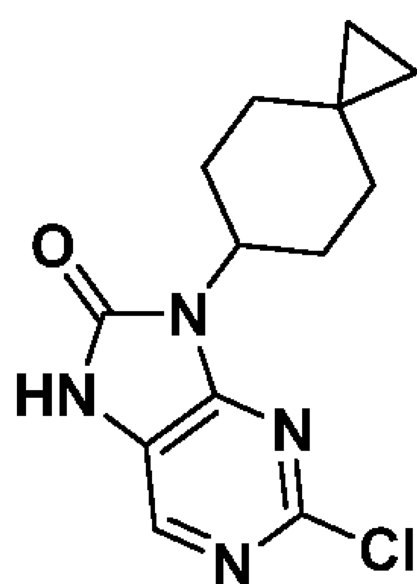
[00486] To a mixture of ethyl 2,4-dichloropyrimidine-5-carboxylate (2.7 g, 1.0 equiv.) and Intermediate 1i (1.0 equiv.) in ACN (0.5 – 0.6 M) was added K_2CO_3 (2.5 equiv.) in one portion under N_2. The mixture was stirred at 20 °C for 12 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography to afford product as a white solid (54%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.64 (s, 1H), 8.41 (d, J = 7.9 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.08 (d, J = 9.8 Hz, 1H), 1.90 (dd, J = 12.7, 4.8 Hz, 2H), 1.64 (t, J = 12.3 Hz, 2H), 1.52 (q, J = 10.7, 9.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H), 1.12 (d, J = 13.0 Hz, 2H), 0.40 – 0.21 (m, 4H).

[00487] Intermediate 1k: 2-chloro-4-(spiro[2.5]octan-6-ylamino)pyrimidine-5-carboxylic acid



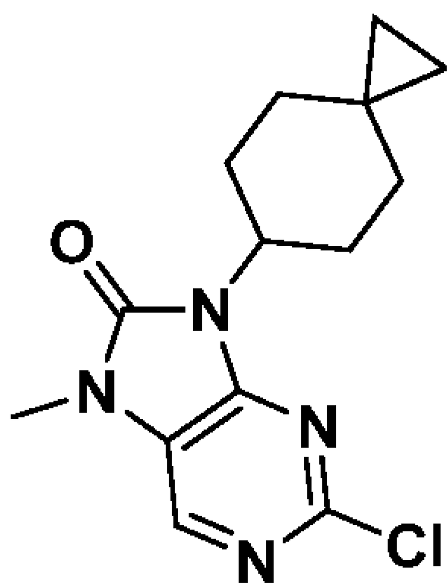
[00488] To a solution of Intermediate 1j (2 g, 1.0 equiv.) in 1:1 THF/H_2O (0.3 M) was added LiOH (2.0 equiv.). The mixture was stirred at 20 °C for 12 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was adjusted to pH 2 with 2 M HCl, and the precipitate was collected by filtration, washed with water, and tried under vacuum. Product was used directly in the next step without additional purification (82%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 13.54 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.35 (s, 1H), 3.82 (qt, J = 8.2, 3.7 Hz, 1H), 1.66 (dq, J = 12.8, 4.1 Hz, 2H), 1.47 – 1.34 (m, 2H), 1.33 – 1.20 (m, 2H), 0.86 (dt, J = 13.6, 4.2 Hz, 2H), 0.08 (dd, J = 8.3, 4.8 Hz, 4H).

[00489] Intermediate 1l: 2-chloro-9-(spiro[2.5]octan-6-yl)-7,9-dihydro-8H-purin-8-one



[00490] To a mixture of Intermediate 1k (1.5 g, 1.0 equiv.) and Et_3N (1.0 equiv.) in DMF (0.3 M) was added DPPA (1.0 equiv.). The mixture was stirred at 120 °C for 8 h under N_2 atmosphere. The reaction mixture was poured into water. The precipitate was collected by filtration, washed with water, and dried under vacuum to give a residue that was used directly in the next step without additional purification (67%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 11.68 (s, 1H), 8.18 (s, 1H), 4.26 (ddt, J = 12.3, 7.5, 3.7 Hz, 1H), 2.42 (qd, J = 12.6, 3.7 Hz, 2H), 1.95 (td, J = 13.3, 3.5 Hz, 2H), 1.82 – 1.69 (m, 2H), 1.08 – 0.95 (m, 2H), 0.39 (tdq, J = 11.6, 8.7, 4.2, 3.5 Hz, 4H).

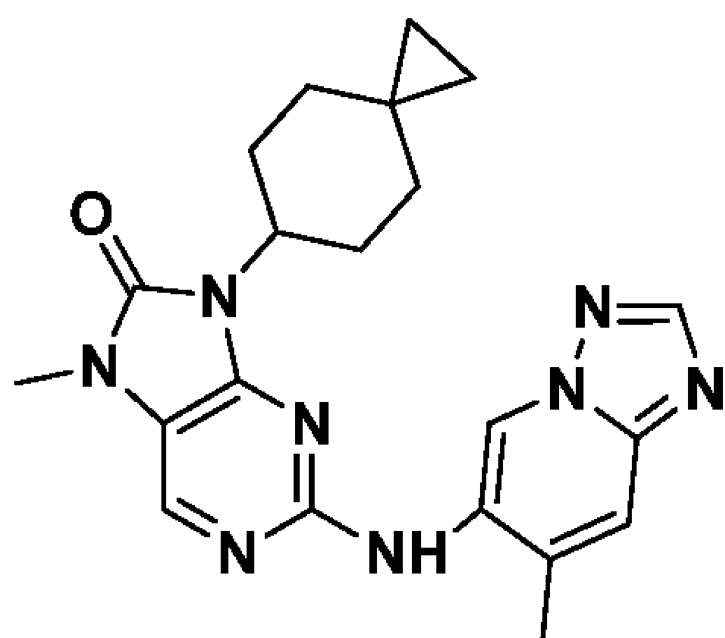
[00491] Intermediate 1m: 2-chloro-7-methyl-9-(spiro[2.5]octan-6-yl)-7,9-dihydro-8H-purin-8-one



[00492] To a mixture of Intermediate 1l (1.0 g, 1.0 equiv.) and NaOH (5.0 equiv.) in 1:1 THF/H_2O (0.3-0.5 M) was added MeI (2.0 equiv.). The mixture was stirred at 20 °C for 12 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to afford a residue that was purified by column chromatography to afford product as a pale

yellow solid (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 4.03 (tt, J = 12.5, 3.9 Hz, 1H), 3.03 (s, 3H), 2.17 (qd, J = 12.6, 3.8 Hz, 2H), 1.60 (td, J = 13.4, 3.6 Hz, 2H), 1.47 – 1.34 (m, 2H), 1.07 (s, 1H), 0.63 (dp, J = 14.0, 2.5 Hz, 2H), -0.05 (s, 4H).

[00493] Compound 1: 7-methyl-2-((7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino)-9-(spiro[2.5]octan-6-yl)-7,9-dihydro-8H-purin-8-one



[00494] To a mixture of Intermediate 1m (1.0 equiv.) and Intermediate 1d (1.0 equiv.), Pd(dppf)Cl_2 (0.2 equiv.), XantPhos (0.4 equiv.), and Cs_2CO_3 (2.0 equiv.) in DMF (0.2 – 0.3 M) was degassed and purged 3x with N_2, and the mixture was stirred at 130 °C for 12 h under N_2 atmosphere. The mixture was then poured into water and extracted 3x with DCM. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuum. The residue was purified by column chromatography to afford product as an off-white solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.09 (s, 1H), 8.73 (s, 1H), 8.44 (s, 1H), 8.16 (s, 1H), 7.78 (s, 1H), 4.21 (t, J = 12.5 Hz, 1H), 3.36 (s, 3H), 2.43 (s, 3H), 2.34 (dt, J = 13.0, 6.5 Hz, 2H), 1.93 – 1.77 (m, 2H), 1.77 – 1.62 (m, 2H), 0.91 (d, J = 13.2 Hz, 2H), 0.31 (t, J = 7.1 Hz, 2H). MS: 405.5 m/z [M+H].

[00495] The sequential edits occurred for each group as illustrated in **Table 23**.

[00496] Table 23 - T cell engineering

Group Name	Day 1	Day 2	Day 3	Day 4
TCR KO	TRBC		TRAC	
TCR KO/WT1 Insert	TRBC		TRAC/AAV	
WT1/HLA-A		HLA-A	TRAC/AAV	TRBC
AlloWT1	CIITA	HLA-A	TRAC/AAV	TRBC
AlloWT1+DNA PKi Compound 1	CIITA	HLA-A	TRAC/AAV +Compound 1 (0.25uM)	TRBC

10.3. LNP Treatment and Expansion of T cells

[00497] LNP compositions were formulated in ApoE-containing media and delivered to T cells as follows: on day 1, LNP compositions as indicated in Table 24 were incubated at a concentration of 5 ug/mL in TCAM containing 5 ug/mL rhApoE3 (Peprotech 350-02). Meanwhile, T cells were harvested, washed, and resuspended at a density of 2x10^6 cells/mL in TCAM with a 1:50 dilution of T Cell TransAct, human reagent (Miltenyi, 130-111-160). T cells and LNP-ApoE media were mixed at a 1:1 ratio and T cells plated in culture flasks overnight.

[00498] On day 2, LNP compositions as indicated in **Table 23** were incubated at a concentration of 25 ug/mL in TCAM containing 20 ug/mL rhApoE3 (Peprotech 350-02). LNP-ApoE solution was then added to the appropriate culture at a 1:10 ratio.

[00499] On day 3, TRAC-LNP compositions (**Table 23**) were incubated at a concentration of 5 ug/mL in TCAM containing 10 ug/mL rhApoE3 (Peprotech 350-02). Meanwhile, T cells were harvested, washed, and resuspended at a density of 1x10^6 cells/mL in TCAM. T cells and LNP-ApoE media were mixed at a 1:1 ratio, and T cells were plated in culture flasks. WT1 AAV was then added to the relevant groups at an MOI of 3x10^5 GC/cell. Compound 1 was added to the relevant groups at a final concentration of 0.25 uM.

[00500] On day 4, LNP compositions as indicated in **Table 23** were incubated at a concentration of 5 ug/mL in TCAM containing 5 ug/mL rhApoE3 (Peprotech 350-02). T cells were washed by centrifugation and resuspended at a density of 1x10^6 cells/mL LNP-ApoE solution was then added to the appropriate cultures at a 1:1 ratio.

[00501] On days 5 through 11, T cells were transferred to a GREX plate (Wilson Wolf) in T cell expansion media (TCEM: CTS OpTmizer (Thermofisher #A3705001) supplemented with 5% CTS Immune Cell Serum Replacement (Thermofisher #A2596101), 1X GlutaMAX (Thermofisher #35050061), 10 mM HEPES (Thermofisher #15630080), 200 U/mL IL-2

(Peprotech #200-02), IL-7 (Peprotech #200-07), IL-15 (Peprotech #200-15) and expanded. Briefly, T-cells were expanded for 6-days, with fresh cytokine supplementation every other day. Cells were counted using a Vi-CELL cell counter (Beckman Coulter) and fold expansion was calculated by dividing cell yield by the starting material.

10.4. Quantification of T cell editing by flow cytometry and NGS

[00502] Post expansion, edited T cells were stained in an antibody cocktail to determine HLA-A2 knockout (HLA-A2^{-}), HLA-DR-DP-DQ knockdown via CIITA knockout (HLA-DRDPDQ^{-}), WT1-TCR insertion (CD3^{+}Vb8^{+}), and the percentage of cells expressing residual endogenous (CD3^{+}Vb8^{-}). Cells were subsequently washed, analyzed on a Cytoflex LX instrument (Beckman Coulter) using the FlowJo software package. T cells were gated on size and CD8+ status, before editing and insertion rates were determined. Editing and insertion rates can be found in **Table 24** and **Figures 9A-9F**. The percent of fully edited AlloWT1-T cells expressing the WT1-TCR with knockout of HLA-A and CIITA was gated as % CD3^{+}Vb8^{+}HLA-A^{-}HLA-DRDPDQ^{-}. High levels of HLA-A and CIITA knockout, as well as WT1-TCR insertion and endogenous TCR KO were observed in edited samples. Notably, T cells receiving DNA PK inhibitor Compound 1 showed improved editing efficiencies

[00503] IVIS imaging of live mice was performed to identify luciferase-positive tumor cells by IVIS spectrum. IVIS imaging was done at 2 days, 6 days, 9 days, 13 days, 16 days, and 18 days after T cell injection. Mice were prepared for imaging with an injection of D-luciferin i.p. at 10 μL/g body weight per the manufacturer's recommendation, about 150 μL per animal. Animals were anesthetized and then placed in the IVIS imaging unit. The visualization was performed with the exposure time set to auto, field of view D, medium binning, and F/stop set to 1. **Table 25** and **Figure 10** show radiance (photons/s/cm2/sr) from luciferase expressing T cells present at the various time points after injection out to 18 days.

[00504] Table 24 -T cell editing efficiency

	CD8+	Endogenous TCR+	WT1 TCR+	HLA-A2-	HLA-DRDPDQ-	AlloWT1+
Unedited	26.9	95.4	4.39	0.66	35.7	0.00292
TCR KO	31.1	5.12	0.5	0.62	30.8	0.23
WT1	34.2	1.2	78.5	0.47	49.7	0.03
WT1/HLA-A	24.8	0.93	63.3	99.1	56.4	40.5
AlloWT1	28.8	0.51	69.3	98.7	96.2	66.1
AlloWT1 + Compound 1	29.2	0.23	89.8	99	96.5	86

[00505] **Table 25 – Total Flux (photons/s) from luciferase-expressing target cells in treated mice at intervals after T cell injection.**

		Mean	SD	n
IR Control	2	668000	0	1
	6	662000	0	1
	9	802000	0	1
	13	834000	0	1
	16	799000	0	1
	18	727000	0	1
697 Only	2	11695000	6766940.65	8
	6	11756250	6759771.63	8
	9	6542375000	4097940177	8
	13	34156125000	19588932739	8
	16	56000000000	14890936841	8
	18			
TCR KO	2	8696250	3615004.20	8
	6	8755000	3659211.47	8
	9	1985750000	1311102671	8
	13	39295000000	18556359711	8
	16	50442857143	12082474518	7
	18	35000000000	0	1
TCR KO/WT1 Insert	2	1395750	651356.99	8
	6	1418625	660585.66	8
	9	13293750	10040193.42	8
	13	416762500	340405656.90	8
	16	987625000	637380114.80	8
	18	2523750000	1518542699	8
HLA-A KO	2	1306375	514478.92	8
	6	1323750	504219.55	8
	9	1785000	691416.77	8
	13	9851428.57	13794971.82	7
	16	35832857.14	53937852.11	7
	18	53608571.43	65167479.22	7
AlloWT1	2	1085625	137185.94	8
	6	1100250	136031.25	8
	9	12085000	20455051.77	8
	13	43676250	87426018.67	8
	16	146917500	310795920.60	8
	18	31418750	33596200.65	8
AlloWT1 + DNAPki	2	1138000	429877.06	8
	6	1152750	420860.26	8
	9	1720000	654391.77	8
	13	3976250	5828721.83	8
	16	39420000	97704137.36	8
	18	80597500	162813409.10	8

10.5. Engineered T Cell Cytokine Release

[00506] Engineered T cells prepared as described in Example 10.1 and 10.2 were assayed for their cytokine release profiles. In vitro OCI-AML3 tumor cell killing assays were separately performed (data not shown) using the engineered T cells. The supernatants from the tumor cell killing assays were used to evaluate each engineered T cell's cytokine release profile.

[00507] Briefly, TCR KO T cells, Autologous WT1 T cells (TCR KO + WT1 TCR insertion), and Allogeneic WT1 T cells (as indicated in Table 24) were thawed and rested overnight in TCGM supplemented with IL-2, IL-7, and IL-15. The following day, a coculture assay was set up where each group of engineered T cells was co-cultured with OCI-AML3 target tumor. First, OCI-AML3 target tumor cells were pulsed with VLD peptide at different concentrations (500, 50, 5, 0.5, 0.05, and 0.005 nM) for 1 hr. Next, T cells from each group were counted and resuspended in TCGM media without cytokines and co-cultured with pulsed OCI-AML3 at 1:1 E:T ratio. The T cell numbers in the co-culture were normalized to the insertion rates to keep the E:T consistent among different groups. After 24 hours of co-culture, the supernatant from each co-culture sample was diluted 5x in Diluent 2 from the U-PLEX Immuno-Oncology Group 1 (hu) Assays kit (MSD, Cat No. K151AEL-2). 50 µL of diluted samples from each group were loaded onto the meso scale discovery (MSD) plate and incubated for 1 hour.

[00508] For each of the cytokines measured, biotinylated capture antibody from the U-PLEX Immuno-Oncology Group 1 (hu) Assays (MSD, Cat No. K151AEL-2) was added to the assigned linker according to the kit's protocol. The antibody-linker mixtures were vortexed and incubated at room temperature for 30 minutes. Post incubation, the plate was washed, sealed, and stored overnight.

[00509] The following day, calibrators containing standards for each of the cytokines (IL-2 and IFN-γ) to be assayed were reconstituted as per the manufacturer's instructions and diluted to create a 4-fold standard curve.

[00510] The plates were washed, and 50 µL of the detection antibody solution (prepared according to kit instructions) was added to each well of the MSD plate. The plate was incubated for 1 hour.

[00511] After incubation, the plate was washed and read immediately on the MSD instrument. Cytokine release is shown in **Tables 26-27** and **Figs. 11A-11B**.

[00512] **Table 26: IFN- γ**

IFN-γ						
Log[peptide (nM)]	TCR KO		AutoWT1		AlloWT1	
2.70	122.55	25.96	93417.51	7094.06	147620.65	9709.50
1.70	134.20	16.97	60680.24	2770.37	104018.15	10358.48
0.70	144.94	24.90	41863.52	1759.74	99896.25	7700.60
-0.30	146.14	58.09	4812.67	175.51	31820.97	1331.50
-1.30	155.20	11.49	77.72	23.65	1592.76	131.04
-2.30	110.63	22.03	69.41	3.27	351.29	23.17

[00513] **Table 27: IL-2**

IL-2						
Log[peptide (nM)]	TCR KO		AutoWT1		AlloWT1	
2.70	4.21	0.63	6031.67	373.56	7525.26	1116.85
1.70	4.17	0.76	3419.94	97.86	4450.71	861.82
0.70	5.28	0.25	1882.55	204.86	3780.66	381.75
-0.30	6.62	2.96	69.51	6.86	452.94	20.13
-1.30	5.87	1.47	4.88	1.07	10.91	2.80
-2.30	6.55	2.18	5.19	1.32	4.94	2.17

Example 11: Mixed Lymphocyte Reaction Assay

[00514] T cells were isolated from peripheral blood of a healthy human donor with the following MHC I phenotype: HLA-A*02:01:01G, 03:01:01G, HLA-B*07:02:01G, HLA-C*07:02:01G. Briefly, a leukapheresis pack (Stemcell Technologies) was treated in ammonium chloride RBC lysis buffer (Stemcell Technologies; Cat. 07800) for 15 minutes to lyse red blood cells. Peripheral blood mononuclear cell (PBMC) count was determined post lysis and T cell isolation was performed using EasySep Human T cell isolation kit (Stemcell Technologies, Cat. 17951) according to manufacturer's protocol. Isolated CD3+ T cells were re-suspended in Cryostor CS10 media (Stemcell Technologies, Cat. 07930) and frozen down in liquid nitrogen until further use.

[00515] Frozen T cells were thawed at a cell concentration of 1.5x10^6 cells/ml into T cell activation media (TCAM) composed of OpTmizer TCGM as described in Example 3 further supplemented with 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), 5 ng/ml IL-15 (Peprotech, Cat. 200-15). Cells were rested at 37°C for 24 hours.

[00516] Twenty-four hours post thawing T cells were counted and resuspended at 2x10^6 cells/ml in TCAM media and 1:50 v/v of TransAct (Miltenyi Biotec Cat. 30-111-160) was added.

1 x10^6 cells were added to each well of a 24-well tissue culture plate, keeping 2 wells for each group to be engineered and 2 wells as unedited controls (Groups engineered: Unedited or WT, B2M KO (also indicated as HLA-I or HLA class I), CIITA (also indicated as HLA class II or HLA-II) KO, B2M + CIITA DKO, HLA-A KO, HLA-A + CIITA DKO). The plate was transferred to a 37°C incubator. LNP compositions containing mRNA encoding cas9 (SEQ ID NO:802) and sgRNA G013675 (SEQ ID NO: 236), targeting CIITA were formulated with lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:38.5:10:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. LNP compositions at 5ug/ml were incubated in OpTmizer TCAM, further supplemented with 5 ug/ml recombinant human ApoE3 (Peprotech, Cat. 350-02) for 15 minutes at 37°C. In 6 out of the 12 wells, pre-incubated LNP and T cells with Transact were mixed to yield final concentrations of 1x10^6 T cells/ml and 2.5 μg total RNA/mL of LNP in TCAM media with 2.5% human AB serum, 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), 5ng/ml IL-15 (Peprotech, Cat. 200-15) (These would be 2 wells for the CIITA KO group, 2 wells for HLA-A + CIITA DKO group and 2 wells for the B2M + CIITA DKO group). All the additional wells were mock edited with media containing ApoE3 but no LNP compositions. All cells were incubated at 37°C for 24 hours.

[00517] 24 hours post activation, 2 previously untreated wells and 2 CIITA LNP containing wells were treated with LNP compositions for B2M (for B2M KO and B2M + CIITA DKO groups); and 2 previously untreated wells and 2 CIITA LNP containing wells were treated with LNP compositions for HLA-A (for HLA-A KO and HLA-A + CIITA DKO groups). LNP compositions containing the Cas9 mRNA and sgRNA G000529 (SEQ ID NO: 245) targeting B2M, and LNP compositions containing mRNA encoding cas9 (SEQ ID NO:802) and sgRNA G018995 (sgRNA comprising SEQ ID NO: 13, as shown in Table 2)

targeting HLA-A were formulated lipid A, cholesterol l, DSPC, and PEG2k-DMG in a 50:38.5:10:1.5 molar ratio, respectively. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. LNP compositions at 25ug/ml were incubated in OpTmizer TCAM, further supplemented with 20ug/ml recombinant human ApoE3 (Peprotech, Cat. 350-02) for 15 minutes at 37°C. The B2M and HLA-A LNP compositions, were added to the appropriate wells of the 24 well plate, as mentioned above, to yield final concentrations of 2.5 µg total RNA/mL of LNP in TCAM media with 2.5% human AB serum, 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), 5 ng/ml IL-15 (Peprotech, Cat. 200-15). An additional group of cells were mock edited with media containing ApoE3 but no LNP compositions, to serve as the unedited or WT control. All cells were incubated at 37°C for 24 hours.

[00518] 24 hours post the second round of editing, cells were washed by spinning at 500XG for 5mins and resuspended in TCEM media containing with 5% CTS™ Immune Cell SR (Gibco Cat. A2596101), 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml IL-7 (Peprotech, Cat. 200-07), 5ng/ml IL-15 (Peprotech, Cat. 200-15. The cells were cultured and maintained in G-Rex plate for 7 days with regular changes in media and cytokines, after which they were re-suspended in Cryostor CS10 media (Stemcell Technologies, Cat. 07930) and frozen down in liquid nitrogen until further use.

[00519] Six groups of donor T cells (wildtype unedited, B2M KO, HLA-A KO, CIITA KO, HLA-A + CIITA DKO, B2M + CIITA DKO) were thawed and resuspended in TCGM at 1x10^6/mL + 100 U/ml IL-2, 0.5 ng/mL IL-7 & IL-15 (Donor and Host HLA-genotypes are shown below in **Table 28**). Peripheral blood mononuclear cells (PBMCs) from 3 hosts (Autologous host, Allogeneic host (HLA-B and C matched host), and Positive control host (HLA-A, HLA-B and HLA-C mismatched) were thawed, resuspended in TCGM at 1x10^6/mL + 100 U/ml IL-2, 0.5 ng/mL IL-7 & IL-15. Donor and host cells were rested overnight in a 37 °C incubator. The following day, donor cell flasks were irradiated at 4000 rad and spun down, and each group was resuspended at 1x10^6/mL in TCGM without cytokines. Host PBMCs from the two hosts were depleted of $CD56^+$ cells using the CD56 MicroBeads (Miltenyi Biotec, Cat. No. 130-050-401). About 1x10^6 cells from each host were saved in 15 mL tubes for unlabeled flow controls. To label 18x10^6 cells of each host, a vial of Cell Trace Violet (Thermo Fisher, Cat. No. C34571) was brought to room temperature and reconstituted using 20 µL DMSO to generate a stock of 5 mM CTV. Host cells were resuspended at ~1x10^6/mL in phosphate buffered saline (Corning, Cat. No. 21-040-CV) and

transferred to another 50 mL conical tube. After adding 18 µL CTV into the tubes to stain host cells, the tubes were transferred to a 37 °C incubator for 15 minutes. Following that, the tubes were topped up to 40 mL with TCGM without cytokines to absorb any unbound dye. The labelled host cells were then spun down at 500xg for 5 minutes and resuspended in TCGM without cytokines at 1x10^6/mL. 50,000 cells per 50 µL per well of host PBMCs were plated per well from appropriate hosts. In the wells requiring 4x host cells (control samples to normalize the data), 200,000 host cells were plated per 200 µL per well. In the host cells labelled "host + TransAct" (proliferation positive control), 50,000 cells per 50 µL per well of host PBMCs were seeded followed by the addition of 1 µL of T Cell TransAct™, human (Miltenyi Biotec, Cat. No. 130-111-160), and the volume of these wells was made up to 200 µL with cytokine free TCGM. The irradiated donor cells were plated according to the plate layout at 150,000 cells per 150 µL per well. For flow controls, 50,000 cells from one donor and host each were plated together. The volume in all wells was filled to 200 µL with TCGM without cytokines.

[00520] On day 5 post co-culture, half the media (~100 µL) from each well was replaced with fresh media (TCGM without cytokines).

[00521] On day 8 post co-culture, the assay plate was stained and analyzed by flow cytometry. For the purpose of staining, the plate was spun at 600xg for 3 minutes, flicked to remove media, and 100 µL of a 1:100 v/v solution of Fc blocker (Biolegend, Cat # 422302) in FACS buffer was added to each well. Cells were resuspended in the Fc blocker, and the plate was incubated at room temperature for 5 minutes. An antibody cocktail was prepared such that each antibody was present at a 1:100 v/v dilution, and 100 µL of this antibody mixture was added to each sample well. The plate was protected from light by covering with an aluminum foil and incubated at 2-8 ºC for 20-30 minutes. After staining, the plate was spun at 600xg for 3 minutes, flicked to remove media and washed with 200 µL of FACS buffer. The plate was washed again, and the cell pellets were resuspended in 70 µL of a 1:200 v/v solution of the viability dye 7-AAD (BD Pharmingen, Cat# 51-68981E). Unstained wells were resuspended in 70 µL of FACS buffer. The plate was run on fast mode (60 seconds per well) on Cytoflex flow cytometer. The results, shown in **Tables 29A and 29B** and **Figures 8A and 8B** (figures show a subset of data for Wildtype, B2M KO, and HLA-A + CIITA DKO), demonstrate that the HLA-A + CIITA DKO cells elicit minimal CD4 and CD8 responses in the allogeneic host (HLA-B and C matched), which were comparable to the response elicited by B2M + CIITA DKO cells. Results for each group have been normalized to that of the proliferation of the 4x host group, for the respective host.

[00522] Table 28 – Genotypes of T cell donor and PBMC Hosts

	HLA-A	HLA-B	HLA-C	HLA-DR	HLA-DQ	HLA-DP
T cell Donor and Autologous Host	A*02:01:01G, 03:01:01G	B*07:02:01G	C*07:02:01G	DRB1*15:01:01G, DRB5*01:01:01G	DQA1*01:02:01G, DQB1*06:02:01G	DPA1*01:03:01G, 02:07:01G, DPB1*04:01:01G, 19:01:01G
B, C matched Host	A*02:01:01G	B*07:02:01G, 44:02:01G	C*05:01:01G, 07:02:01G	DRB1*13:01:01G, 15:01:01G, DRB3*01:01:02G, DRB5*01:01:01	DQB1*06:02:01G, 06:03:01G, DQA1*01:02:01G, 01:03:01G	DPB1*02:01:02G, 04:02:01G, DPA1*01:03:01G
HLA mis-matched Host	A*11:01:01G, 24:02:01G	B*40:01:01G	C*03:04:01G	DRB1*08:01:01G, 13:02:01G, DRB3*03:01:01G	DQB1*04:02:01G, 06:04:01G	DPB1*03:01:01G, 05:01:01G

[00523] Table 29A – Proliferation of Host CD4+ T Cells

Group	Autologous Host		Allogeneic Host		Positive Control Host	
	Average % Normalized Proliferation	SD % Normalized Proliferation	Average % Normalized Proliferation	SD % Normalized Proliferation	Average % Normalized Proliferation	SD % Normalized Proliferation
WT	-13.76	3.05	5.93	1.72	39.07	3.68
B2M KO	-13.50	2.66	-3.22	5.10	42.47	3.20
CIITA KO	-12.62	4.27	-7.00	5.54	-8.83	14.93
B2M + CIITA KO	-11.98	2.76	-5.15	5.21	-14.20	4.64
HLA-A KO	-9.14	7.96	7.67	12.41	41.83	5.01
HLA-A + CIITA KO	-11.33	2.03	-3.00	4.47	-3.97	6.57

[00524] Table 29B – Proliferation of Host CD8+ T Cells

Group	Autologous Host		Allogeneic Host		Positive Control Host	
	Average % Normalized Proliferation	SD % Normalized Proliferation	Average % Normalized Proliferation	SD % Normalized Proliferation	Average % Normalized Proliferation	SD % Normalized Proliferation
WT	7.53	6.95	35.71	12.28	74.00	1.42
B2M KO	-8.87	3.75	20.41	0.95	31.97	11.70
CIITA KO	1.43	5.24	6.17	4.89	56.07	8.53

B2M + CIITA KO	9.63	14.50	-0.05	4.59	0.47	5.23
HLA-A KO	22.40	23.65	25.31	16.59	71.83	2.25
HLA-A + CIITA KO	17.57	12.00	5.14	2.88	58.13	7.02

Example 12: Sequential Delivery of Multiple LNP Compositions for Multiple Gene Disruptions and Insertions

[00525] T cells were engineered with a series of gene disruptions and insertions. Healthy donor cells were treated sequentially with four LNP compositions, each LNP composition co-formulated with mRNA encoding Cas9 (SEQ ID NO: 802) and sgRNA targeting either TRAC (G013006) (SEQ ID NO: 243), TRBC (G016239) (SEQ ID NO: 247), CIITA (G013675) (SEQ ID NO: 246), or HLA-A (G018995) (sgRNA comprising SEQ ID NO: 13, as shown in Table 2). LNP compositions were formulated according to the Groups indicated in **Table 30** with either lipid A, cholesterol, DSPC, and PEG2k-DMG in a 35:47.5:15:2.5 molar ratio (Groups 1 and 2), respectively or lipid A, cholesterol, DSPC, and PEG2k-DMG in a 50:35:10:1.5 molar ratio (Group 3), respectively at the indicated doses. Groups 1 and 2 differ in LNP concentration. The lipid nucleic acid assemblies were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6, and a ratio of gRNA to mRNA of 1:2 by weight. A transgenic WT1 targeting TCR was site-specifically integrated into the TRAC cut site by delivering a homology directed repair template using AAV. LNP compositions were prepared each day and delivered to T cells as described in **Table 30**.

12.1 T cell Preparation

[00526] T cells from three HLA-A*02:01+ serotypes were isolated from the leukopheresis products of two healthy donors (STEMCELL Technologies). T cells were isolated using EasySep Human T cell isolation kit (STEMCELL Technologies, Cat#17951) following manufacturer's protocol and cryopreserved using Cryostor CS10 (STEMCELL Technologies, Cat# 07930). The day before initiating T cell editing, cells were thawed and rested overnight in T cell activation media (TCAM: CTS OpTmizer, Thermofisher #A3705001) supplemented with 2.5% human AB serum (Gemini #100-512), 1X GlutaMAX (Thermofisher #35050061), 10 mM HEPES (Thermofisher #15630080), 200 U/mL IL-2 (Peprotech #200-02), IL-7 (Peprotech #200-07), and IL-15 (Peprotech #200-15).

12.2 LNP Treatment and Expansion of T cells

[00527] LNP compositions were thawed and diluted on each day in ApoE containing media and delivered to T cells as follows.

[00528] Table 30 – Order of Editing for T Cell Engineering

Group	Day 1 Edit (LNP formulation & final concentration)	Day 2 Edit (LNP formulation & final concentration)	Day 3 Edit (LNP formulation & final concentration)	Day 4 Edit (LNP formulation & final concentration)
Group 1	CIITA KO (Lipid A: 35:47.5:15:2.5, 0.65 μg/mL)	HLA-A KO (Lipid A: 35:47.5:15:2.5, 0.65 μg/mL)	TRAC KI (Lipid A: 35:47.5:15:2.5, 0.65 μg/mL)	TRBC KO (Lipid A: 35:47.5:15:2.5, 0.65 μg/mL)
Group 2	CIITA KO (Lipid A: 35:47.5:15:2.5, 2.5 μg/mL)	HLA-A KO (Lipid A: 35:47.5:15:2.5, 2.5 μg/mL)	TRAC KI (Lipid A: 35:47.5:15:2.5, 2.5 μg/mL)	TRBC KO (Lipid A: 35:47.5:15:2.5, 2.5 μg/mL)
Group 3	CIITA KO (Lipid A: 50:35.5:10:1.5, 2.5 μg/mL)	HLA-A KO (Lipid A: 50:35.5:10:1.5, 2.5 μg/mL)	TRAC KI (Lipid A: 50:35.5:10:1.5, 2.5 μg/mL)	TRBC KO (Lipid A: 50:35.5:10:1.5, 2.5 μg/mL)
Unedited	None	None	None	None

[00529] On day 1, LNP compositions as indicated in **Table 30** were incubated in TCAM containing 5 μg/mL rhApoE3 (Peprotech 350-02). Meanwhile, T cells were harvested, washed, and resuspended at a density of 2x10^6 cells/mL in TCAM with a 1:50 dilution of T Cell TransAct, human reagent (Miltenyi, 130-111-160). T cells and LNP-ApoE media were mixed at a 1:1 ratio and T cells plated in culture flasks overnight.

[00530] On day 2, LNP compositions as indicated in **Table 30** were incubated at a concentration of 25 μg/mL in TCAM containing 20 μg/mL rhApoE3 (Peprotech 350-02). LNP-ApoE solution was then added to the appropriate culture at a 10:1 ratio.

[00531] On day 3, as indicated in **Table 30** TRAC-LNP compositions were incubated in TCAM containing 5 μg/mL rhApoE3 (Peprotech 350-02). Meanwhile, T cells were harvested, washed, and resuspended at a density of 1x10^6 cells/mL in TCAM. T cells and LNP-ApoE media were mixed at a 1:1 ratio, and T cells were plated in culture flasks. WT1 AAV was then added to each group at a MOI of 3x10^5 GC/cell. The DNA-PK inhibitor "Compound 1" was added to each group at a concentration of 0.25 μM

[00532] On day 4, LNP compositions as indicated in **Table 30** were incubated in TCAM containing 5 μg/mL rhApoE3 (Peprotech 350-02). Meanwhile, T cells were harvested,

washed, and resuspended at a density of 1x10^6 cells/mL in TCAM. T cells and LNP-ApoE media were mixed at a 1:1 ratio and T cells plated in culture flasks.

[00533] On days 5-13, T cells were transferred to a 24-well GREX plate (Wilson Wolf, 80192) in T cell expansion media (TCEM: CTS OpTmizer, Thermofisher #A3705001) supplemented with 5% human AB serum (Gemini #100-512], 1X GlutaMAX (Thermofisher #35050061], 10 mM HEPES (Thermofisher #15630080), 200 U/mL IL-2 (Peprotech #200-02), IL-7 (Peprotech #200-07), IL-15 (Peprotech #200-15) and expanded per manufacturers' protocols. Briefly, T-cells were expanded for 8-days, with media exchanges every 2-3 days.

[00534] Post expansion, edited T cells were assayed by flow cytometry to determine HLA-A*02:01 knockout, HLA-DR-DP-DQ knockdown via CIITA knockout, WT1-TCR insertion ($CD3^+Vb8^+$), and the percentage of cells expressing residual endogenous ($CD3^+Vb8^-$). T Cells were incubated with an antibody cocktail targeting the following molecules: Vb8 (Biolegend, Cat. 348104), HLA-A2 (Biolegend, Cat. 343320), HLA-DRDPDQ (Biolegend, Cat. 361712), CD4 (Biolegend, Cat. 300538), CD8 (Biolegend, Cat. 301046), CD3 (Biolegend, Cat. 317336), CCR7 (Biolegend, Cat. 353214), CD62L (Biolegend, Cat. 304820), CD45RA (Biolegend, Cat. 304134), CD45RO (Biolegend, Cat. 304230), CD56 (Biolegend, Cat. 318328), and Viakrome (Beckman Coulter, Cat. C36628). Cells were subsequently washed, processed on a Cytoflex LX instrument (Beckman Coulter) and analyzed using the FlowJo software package. T cells were gated on size and CD4/CD8 status, before editing and insertion rates were determined. The percentage of cells expressing relevant cell surface proteins following sequential T cell engineering are shown in **Table 31** and **Figure 12A** for CD8+ T cells respectively. The percent of T cells with all intended edits (insertion of the WT1-TCR, combined with knockout of HLA-A and CIITA) was gated as % $CD3^+Vb8^+$ $HLA\text{-}A^-HLA\text{-}DRDPDQ^-$ and is shown in **Figure 12B**. High levels of HLA-A and CIITA knockout, as well as WT1-TCR insertion were observed in edited samples from all groups yielding >75% of fully edited CD8+ T cells. The lower dosage (0.65 µg/mL) used with Lipid A 35:15:47.5:2.5 composition showed similar potency in editing T cells across all targets as the Lipid A 50:10:35.5:1.5 formulation at a higher dose (2.5µg/mL).

[00535] **Table 31. Editing rates in CD8+ T cells**

	Group 1			Group 2			Group 3			Unedited		
Edit	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Fully Edited (Vb8+,CD3+,HLA-DRPDPDQ-,HLA-A*02:01-)	79.6	4.7	3.0	80.5	4.2	3.0	76.8	1.9	3.0	0.2	0.2	3.0

	Group 1			Group 2			Group 3			Unedited		
HLA-A KO (HLA-A*02:01-)	97.1	3.6	3.0	96.4	4.7	3.0	96.4	4.4	3.0	3.6	3.8	3.0
CIITA KO (HLA-DRDPDQ-)	99.3	0.4	3.0	97.7	2.1	3.0	98.7	0.9	3.0	na	na	na
TCR KO (CD3-)	99.3	0.1	3.0	99.7	0.1	3.0	98.7	1.1	3.0	1.8	1.4	3.0
WT1 TCR Insertion (Vb8+)	82.6	2.0	3.0	85.6	0.8	3.0	81.1	2.1	3.0	0.2	0.2	3.0

Example 13: Cytotoxic Susceptibility of Engineered T Cells

[00536] Engineered T cells were assayed for cytotoxic susceptibility when targeted by natural killer (NK) cells.

[00537] NK cells (Stemcell Technologies) were thawed and resuspended at a cell concentration of 1x10^6 cells/ml into T cell growth media (TCGM) composed of OpTmizer TCGM and further supplemented with 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/mL IL-7 (Peprotech, Cat. 200-07), 5 ng/mL IL-15 (Peprotech, Cat. 200-15). Cells were incubated at 37 °C for 24 hours.

[00538] Twenty-four hours post thaw, the NK cells were labelled with 0.5 µM Cell Trace Violet (CTV) as follows: a vial of CTV (CellTrace™ Violet Cell Proliferation Kit, for flow cytometry, Cat. C34571) was reconstituted in DMSO from the kit to give a 5 mM stock concentration. Two µL of CTV stock was diluted with 18 µL Phosphate-Buffered Saline (PBS) (Corning, Cat. 21-040-CV) to obtain a concentration of 0.5 mM. NK cells were centrifuged at 500 x g for 5 minutes, the media was aspirated, and cells were resuspended in PBS at a concentration of 1 x 10^6 cells/mL such that the final concentration of CTV dye was 0.5 µM. The cells were mixed with CTV dye solution incubated at 37 °C for 20 minutes. Unbound dye was quenched by the addition of TCGM and incubated for 5 minutes. The cells were centrifuged at 500 x g for 5 minutes. Cells are resuspended in TCGM supplemented with 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/mL IL-7 (Peprotech, Cat. 200-07), 5 ng/mL IL-15 (Peprotech, Cat. 200-15) at a concentration of 2 x 10^6 cells/mL. To test a range of effector:target (E:T) ratios, CTV-labelled NK cells were aliquoted in 100 µL of media in a 6-point, 2-fold serial dilution with the highest number of cells being 2 x 10^5 cells. Media-only samples were included as negative controls.

[00539] T cells were engineered using BC22n and UGI mRNA using G023523 (SEQ ID NO: 1016) targeting HLA-A as a test sample and with G023519 (SEQ ID NO: 816) targeting B2M as a positive control for NK killing.

[00540] T cells were prepared from a leukopak using the EasySep Human T Cell Isolation Kit (Stem Cell Technology, Cat. 17951) following the manufacturers protocol. T cells were cryopreserved in Cryostor CS10 freezing media (Cat. 07930) for future use. Upon thaw, T cells were plated at a density of 1.0 x 10^6 cells/mL in T cell R10 media composed of RPMI 1640 (Corning, Cat. 10-040-CV) containing 10% (v/v) of fetal bovine serum, 2 mM Glutamax (Gibco, Cat. 35050-061), 22 µM of 2-Mercaptoethanol, 100 uM non-essential amino acids (Corning, Cat. 25-025-Cl), 1 mM sodium pyruvate, 10 mM HEPES buffer, 1% of Penicillin-Streptomycin, plus 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02). T cells were activated with Dynabeads® Human T-Activator CD3/CD28 (Gibco, Cat. 11141D). Cells were expanded in T cell media for 72 hours prior to mRNA transfection.

[00541] Solutions containing mRNA encoding BC22n (SEQ ID NO: 972) or UGI (SEQ ID NO: 1005) were prepared in sterile water. 50 µM targeting sgRNAs were removed from their storage plates and denatured for 2 minutes at 95 °C before cooling on ice. Seventy-two hours post activation, T cells were harvested, centrifuged, and resuspended at a concentration of 12.5 x 10^6 T cells/mL in P3 electroporation buffer (Lonza). For each well to be electroporated, 1 x 10^5 T cells were mixed with 200 ng of editor mRNA (BC22n), 200 ng of UGI mRNA, and 20 pmols of sgRNA in a final volume of 20 µL of P3 electroporation buffer. This mix was electroporated using the manufacturer's pulse code.

[00542] Unedited T cells were assayed as a negative control for NK killing. Other controls for flow cytometry included CTV-labelled NK cells without T cells; a "unstained" sample combining unlabelled NK cells and T cells; and a 1:1 mix of unlabeled heat killed and non-heat killed NK cells and T cells stained with 7AAD. T cells were resuspended at a density of 2 x 10^5 cells in TCGM composed of OpTmizer TCGM and further supplemented with 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/mL IL-7 (Peprotech, Cat. 200-07), and 5 ng/mL IL-15 (Peprotech, Cat. 200-15). Twenty thousand T cells were added to each well of NK cells and media controls. Cells were incubated at 37 °C for 24 hours.

[00543] At 24 hours, half of the volume of the cells from the LD heat killed well were heat killed and transferred back to the same well in the assay plate. Cells were centrifuged and resuspended in 80 µL of a 1:200 v/v solution of 7-AAD (BD Biosciences, Cat. 559925) in FACS buffer (PBS + 2% FBS (Gibco, Cat. A31605-02) + 2mM EDTA (Invitrogen, Cat. 15-575-020)). Data for specific lysis of T cells were acquired by flow cytometry using a Cytoflex LX instrument (Beckman Coulter) and analyzed using the FlowJo software package.

Gates were first drawn on the CTV negative population to gate out the NK cells, followed by gating on singlets after which a gate was drawn on the 7-AAD negative population to gate for the live T cells. The percent lysis of T cells was calculated by subtracting the live cell percentage from 100. T cells edited using BC22n and HLA-A guide G023523 (SEQ ID NO: 1016) were protected from NK cell mediated cytotoxicity as shown in **Table 32** and **Fig. 13**.

[00544] **Table 32 – Mean percentage lysis of engineered T cells exposed to HLA-B and C matched NK cells**

E:T	Unedited			G023519 B2M			G023523 HLA-A		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
10	19.65	2.33	2	69.60	4.81	2	22.23	1.10	3
5	18.80	1.59	3	61.10	0.85	2	21.35	0.49	2
2.5	22.27	6.62	3	47.95	0.49	2	22.10	1.27	2
1.25	18.47	1.27	3	39.20	2.98	3	21.00	0.81	3
0.63	19.30	0.66	3	30.20	NA	1	19.75	0.35	2
0.31	20.70	5.02	3	40.60	NA	1	20.27	1.67	3
0	19.77	2.01	3	26.57	2.73	3	18.30	1.41	3

Example 14: Editing human T cells with BC22n, UGI and 91-mer sgRNAs

[00545] The base editing efficacy of 91-mer sgRNA as assessed by receptor knockout was compared to that of a 100-mer sgRNA format with the same guide sequence.

[00546] The tested 91-mer sgRNA include a 20-nucleotide guide sequence (as represented by N) and a guide scaffold as follows: mN*mN*mN*NNNNNNNNNNNNNNNNNGUUUUAGAmGmCmUmAmGmAmAmAmU mAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCG GmUmGmC*mU (SEQ ID NO: 1003), where A, C, G, U, and N are adenine, cytosine, guanine, uracil, and any ribonucleotide, respectively, unless otherwise indicated. An m is indicative of a 2'O-methyl modification, and an * is indicative of a phosphorothioate linkage between the nucleotides. Unmodified and modified versions of the guide is provided in Table 6 (Sequence Table).

Example 14.1. T cell preparation

[00547] Healthy human donor apheresis was obtained commercially (Hemacare), and cells were washed, re-suspended in CliniMACS® PBS/EDTA buffer (Miltenyi Biotec Cat. 130-070-525) and processed in a MultiMACS™ Cell 24 Separator Plus device (Miltenyi Biotec). T cells were isolated via positive selection using a Straight from Leukopak® CD4/CD8

MicroBead kit, human (Miltenyi Biotec Cat. 130-122-352). T cells were aliquoted and cryopreserved for future use in Cryostor® CS10 (StemCell Technologies Cat. 07930).

[00548] Healthy human donor apheresis was obtained commercially (Hemacare), and cells were washed, re-suspended in CliniMACS® PBS/EDTA buffer (Miltenyi Biotec Cat. 130-070-525) and processed in a MultiMACS™ Cell 24 Separator Plus device (Miltenyi Biotec). T cells were isolated via positive selection using a Straight from Leukopak® CD4/CD8 MicroBead kit, human (Miltenyi Biotec Cat. 130-122-352). T cells were aliquoted and cryopreserved for future use in Cryostor® CS10 (StemCell Technologies Cat. 07930).

[00549] Upon thaw, T cells were plated at a density of 1.0 x 10^6 cells/mL in T cell growth media (TCGM) composed of CTS OpTmizer T Cell Expansion SFM and T Cell Expansion Supplement (ThermoFisher Cat. A1048501), 5% human AB serum (GeminiBio, Cat. 100-512) 1X Penicillin-Streptomycin, 1X Glutamax, 10 mM HEPES, 200 U/mL recombinant human interleukin-2 (Peprotech, Cat. 200-02), 5 ng/ml recombinant human interleukin 7 (Peprotech, Cat. 200-07), and 5 ng/ml recombinant human interleukin 15 (Peprotech, Cat. 200-15). T cells were rested in this media for 24 hours, at which time they were activated with T Cell TransAct™, human reagent (Miltenyi, Cat. 130-111-160) added at a 1:100 ratio by volume. T cells were activated for 48 hours prior to LNP treatments.

Example 14.2. T cell LNP treatment and expansion

[00550] Forty-eight hours post-activation, T cells were harvested, centrifuged at 500 g for 5 min, and resuspended at a concentration of 1 x 10^6 T cells/mL in T cell plating media (TCPM): a serum-free version of TCGM containing 400 U/mL recombinant human interleukin-2 (Peprotech, Cat. 200-02), 10 ng/ml recombinant human interleukin 7 (Peprotech, Cat. 200-07), and 10 ng/ml recombinant human interleukin 15 (Peprotech, Cat. 200-15). 50 µL of T cells in TCPM (5 x 10^4 T cells) were added per well to be treated in flat-bottom 96-well plates.

[00551] LNPs were prepared as described in Example 1 at a ratio of 35:47.5:15:2.5 (Lipid A/ cholesterol/DSPC/PEG2k-DMG). The LNPs were formulated with a lipid amine to RNA phosphate (N:P) molar ratio of about 6. LNPs encapsulated a single RNA species, either a sgRNA as described in Table 34, BC22n mRNA (SEQ ID No: 972), or UGI mRNA (SEQ ID No. 1005).

[00552] **Table 33 - 100-mer and 91-mer sgRNAs**.

Gene target	100-mer	91-mer
HLA-A	G021209 (SEQ ID NO: 381)	G023523 (SEQ ID NO: 1016)

[00553] Prior to T cell treatment, LNPs encapsulating a sgRNA were diluted to 6.64 µg/mL in T cell treatment media (TCTM): a version of TCGM containing 20 ug/mL rhApoE3 in the absence of interleukins 2, 5 or 7. These LNPs were incubated at 37°C for 15 minutes and serially diluted 1:4 using TCTM, which resulted in an 8-point dilution series ranging from 6.64 µg/mL to zero. Similarly, single-cargo LNPs with BC22n mRNA (SEQ ID NO: 972) or UGI mRNA (SEQ ID NO: 1005) were diluted in TCTM to 3.32 and 1.67 µg/mL, respectively, incubated at 37°C for 15 minutes, and mixed 1:1 by volume with sgRNA LNPs serially diluted in the previous step. Last, 50 µL from the resulting mix was added to T cells in 96-well plates at a 1:1 ratio by volume. T cells were incubated at 37 °C for 24 hours, at which time they were harvested, centrifuged at 500 g for 5 min, resuspended in 200 µL of TCGM and returned to the incubator.

Example 14.4. Evaluation of receptor knockout by flow cytometry

[00554] The set of sgRNAs targeting the HLA-A gene were evaluated by flow cytometry instead of NGS due to the hyperpolymorphic nature of the HLA-A locus.

[00555] Seven days post LNP treatment, T cells were assayed by flow cytometry to evaluate receptor knockout. T cells were incubated with a fixable viability dye (Beckman Coulter, Cat. C36628) and an antibody cocktail targeting HLA-A2 (Biolegend, Cat. 343304). Cells were subsequently washed, analyzed on a Cytoflex LX instrument (Beckman Coulter) using the FlowJo software package. T cells were gated on size, viability and CD8 positivity before expression of any markers was determined. The resulting data was plotted on GraphPad Prism v. 9.0.2 and analyzed using a variable slope (four parameter) non-linear regression.

[00556] As shown in **Tables 34 and 35** and **Fig. 14**, the 91-mer sgRNA tested outperformed the 100-mer version. Targets with a lower potency (i.e., higher EC50) in the 100-mer format (HLA-A) seem to benefit the most from usage of 91-mer sgRNAs.

[00557] **Table 34 – Mean percentage of CD8+ T cells that are negative for HLA-A2 surface receptors following treatment sgRNA targeting HLA-A, in the 100-mer or 91-mer formats.**

sgRNA (ng)	HLA-A (HLA-A2-)			
	100-mer		91-mer	
	Mean	SD	Mean	SD
166.00	98.8	0.1	99.6	0.2
41.50	93.6	0.8	99.2	0.4
10.38	70.2	1.0	93.8	1.4
2.59	34.0	2.1	63.2	3.0
0.65	12.1	1.3	28.5	1.2
0.16	3.3	0.2	8.3	0.6
0.04	0.9	0.3	2.6	0.5
0.00	0.1	0.0	0.3	0.2

[00558] **Table 35 – Amount (pmol) of sgRNA that lead to a 50% loss of receptor expression in the surface of CD8+ T cells (EC50s). The far right column shows the fold-increase in potency achieved by 91-mer sgRNA when compared to the 100-mer with the same guide sequence.**

Gene target	100-mer		91-mer		EC50 shift (100-mer/91-mer)
	sgRNA ID	EC50 (pmols)	sgRNA ID	EC50 (pmols)	
HLA-A	G021209	0.150	G023523	0.053	2.81

Example 15: Correlation between HLA-A Editing by NGS and Protein KO by Flow Cytometry

[00559] Frozen T cells from three T cell donors, the first heterozygous for HLA-A*02:01:01G, 03:01:01G, the second homozygous for HLA-A*02:01:01G, and the third homozygous for HLA-A*03:01:01G, were thawed at a cell concentration of 1.5 x $10^{\wedge 6}$ cells/mL into T cell growth media (TCGM) composed of CTS OpTmizer media (Gibco, Cat. # A10485-01) with 2.5 percent GemCell Plus Human AB Serum (Gemini, Cat. # 100-512), and 10 mL each of GlutaMAX 100X (Gibco, Cat. # 35050061), HEPES (Gibco, Cat. # 15630080) and Pen/Strep (Gibco, Cat. # 15140-122), further supplemented with 100 U/mL of recombinant human interleukin-2 (Peprotech, Cat. # 200-02), 5 ng/mL IL-7 (Peprotech, Cat. # 200-07), 5 ng/mL IL-15 (Peprotech, Cat. # 200-15), and rested overnight in a 37 °C incubator.

[00560] Twenty-four (24) hours post thaw, cells were activated using T cell TransActTM (Miltenyi Biotec, Cat. # 130-111-160) at 1:100 dilution at 37 °C for 24 hours. Cells were plated at 1 x $10^{\wedge 5}$ cells per 100 µL per well and then transfected with a serial dilution of LNP-formulated guides, starting from 5 µg/mL as the highest dose and down to 0.04 µg/mL.

[00561] On Day 5 post transfection, cells from each donor were spun and collected for NGS assay. Genomic DNA was extracted using QuickExtract DNA extraction solution. PCR1 was performed to amplify the gene-specific sequences, while PCR2 was performed to amplify the common adaptor for sequencing (NEB Cat. # N0494). PCR samples were cleaned using AMPure XP Beads (Beckman Coulter Cat. # A63881) before sequencing by NGS.

[00562] On Day 8 post transfection, the assay plate was stained and analyzed by flow cytometry. For the purpose of staining, the plate was spun at 500 x g for 5 minutes, flicked to remove media, and 100 µL of a 1:100 v/v solution of Fc blocker (Biolegend, Cat. # 422302) in FACS buffer was added to each well. Cells were resuspended in the Fc blocker, and the plate was incubated at room temperature for 5 minutes. An antibody cocktail was prepared such that each antibody (HLA-A2 Monoclonal Antibody (BB7.2), APC, eBioscience, Cat. # 17-9876-42 and HLA-A3 Monoclonal Antibody (GAP.A3), PE, eBioscience, Cat. # 12-5754-42) was present at a 1:100 v/v dilution, and 100 µL of this antibody mixture was added to each sample well. The plate was protected from light by covering with an aluminum foil and incubated at 2-8 ºC for 20-30 minutes. After staining, the plate was spun at 600 x g for 3 minutes, flicked to remove media, and washed with 200 µL of FACS buffer. The plate was washed again, and the cell pellets were resuspended in 100 µL of FACS buffer. The plate was run on fast mode (60 seconds per well) on a Cytoflex flow cytometer. Data analysis was conducted on FlowJo.

[00563] High correlation between protein knockout and editing was observed in all three donors, and for three unique primer sets, as shown in **Tables 36-38** and **Figs. 15A-15C**.

Table 36: HLA-A gene editing correlation to protein knockout in Donor A

LNP Concentration	NGS Primer 1 (% Edit)	NGS Primer 2 (% Edit)	NGS Primer 3 (% Edit)	Protein KO
5	92.7	91.9	93.5	89.15
2.5	93.6	94.4	92.7	88.35
1.25	93.2	94	92.8	87.55

LNP Concentration	NGS Primer 1 (% Edit)	NGS Primer 2 (% Edit)	NGS Primer 3 (% Edit)	Protein KO
0.63	72.9	79.3	74.3	68.45
0.31	41.8	41.8	46.1	27.6
0.17	12.9	18.5	15.8	7.23
0.08	4.7	7.8	1.9	1.44
0.04	2	1.7	6.8	0.30

Table 37: HLA-A gene editing correlation to protein knockout in Donor B

LNP Concentration	NGS Primer 1 (% Edit)	NGS Primer 2 (% Edit)	NGS Primer 3 (% Edit)	Protein KO
5	97.9	97.5	97.9	92.3
2.5	97.2	96.9	97.2	92.6
1.25	96.4	96.1	96.5	91.25
0.63	82.1	81.9	82	71.35
0.31	42.4	43.6	44.7	24.5
0.17	20.3	20.2	21.2	5.65
0.08	7.4	8.6	8.4	0.94
0.04	2.1	2.7	2.3	0.15

Table 38: HLA-A gene editing correlation to protein knockout in Donor C

LNP Concentration	NGS Primer 1 (% Edit)	NGS Primer 2 (% Edit)	NGS Primer 3 (% Edit)	Protein KO
5	96.6	95.3	96.6	99.295
2.5	97.3	97.4	97.3	99.165
1.25	95.7	95.8	97.4	98.9
0.63	77.9	78.1	79.4	91
0.31	37.7	38.5	37.7	54.25
0.17	16.3	16	16.7	23.35
0.08	7	6.8	6.5	9.22
0.04	3.1	2.5	2.6	3.108

Example 16. Additional Embodiments

[00564] The following numbered embodiments provide additional support for and descriptions of the embodiments herein.

[00565] Embodiment 1 is 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 the cell is homozygous for HLA-B and homozygous for HLA-C.

[00566] Embodiment 2 is 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 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.

[00567] Embodiment 3 is the engineered cell of any of the preceding embodiments, 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.

[00568] Embodiment 4 is the engineered cell of any of the preceding embodiments, wherein the cell has reduced or eliminated expression of HLA-A1.

[00569] Embodiment 5 is the engineered cell of any of the preceding embodiments, wherein the cell has reduced or eliminated expression of HLA-A2.

[00570] Embodiment 6 is the engineered cell of any of the preceding embodiments, wherein the cell has reduced or eliminated expression of HLA-A3.

[00571] Embodiment 7 is the engineered cell of any of the preceding embodiments, wherein the cell has reduced or eliminated expression of HLA-A11.

[00572] Embodiment 8 is the engineered cell of any of the preceding embodiments, wherein the cell has reduced or eliminated expression of HLA-A24.

[00573] Embodiment 9 is the engineered cell of any of the preceding embodiments, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942864-chr6: 29942903.

[00574] Embodiment 10 is the engineered cell of any of the preceding embodiments, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-chr6:29943609.

[00575] Embodiment 11 is the engineered cell of any of the preceding embodiments, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942864-29942884; chr6:29942868-29942888; chr6:29942876-29942896; chr6:29942877-29942897; and chr6:29942883-29942903.

[00576] Embodiment 12 is the engineered cell of any of the preceding embodiments, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-29943548; chr6:29943529-29943549; chr6:29943530-29943550; chr6:29943537-29943557; chr6:29943549-29943569; and chr6:29943589-29943609.

[00577] Embodiment 13 is the engineered cell of any of the preceding embodiments, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942876-29942897.

[00578] Embodiment 14 is the engineered cell of any of the preceding embodiments, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-chr629943550.

[00579] Embodiment 15 is the engineered cell of any of the preceding embodiments, wherein 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.

[00580] Embodiment 16 is the engineered cell of any of the preceding embodiments, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from: chr6:29943528-29943548, chr6:29943529-29943549, and chr6:29943530-29943550.

[00581] Embodiment 17 is 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 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.

[00582] Embodiment 18 is an engineered human cell, which has reduced or eliminated surface expression of HLA-A relative to an unmodified cell, comprising a genetic modification in an HLA-A gene, 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.

[00583] Embodiment 19 is the engineered cell of any one of embodiments 17-18, wherein the cell is homozygous for HLA-B and homozygous for HLA-C.

[00584] Embodiment 20 is the engineered cell of any one of embodiments 17-19, wherein the genetic modification comprises at least 2, at least 3, at least 4, 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, or wherein the genetic modification comprises at least 5 contiguous nucleotides within the genomic coordinates.

[00585] Embodiment 21 is the engineered cell of any one of embodiments 17-20, wherein the genetic modification comprises at least 6, 7, 8, 9, or 10 contiguous nucleotides within the genomic coordinates.

[00586] Embodiment 22 is the engineered cell of any one of embodiments 17-21, wherein the genetic modification comprises at least one C to T substitution or at least one A to G substitution within the genomic coordinates.

[00587] Embodiment 23 is the engineered cell of any one of the preceding embodiments, 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; or (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.

[00588] Embodiment 24 is the engineered cell of any one of the preceding embodiments, 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.

[00589] Embodiment 25 is the engineered cell of any one of the preceding embodiments, 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.

[00590] Embodiment 26 is the engineered cell of any one of the preceding embodiments, 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-chr629943550.

[00591] Embodiment 27 is the engineered cell of any one of the preceding embodiments, 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 chr6:29942864-29942884.

[00592] Embodiment 28 is the engineered cell of any one of the preceding embodiments, 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 chr6:29942868-29942888.

[00593] Embodiment 29 is the engineered cell of any one of the preceding embodiments, 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 chr6:29942876-29942896.

[00594] Embodiment 30 is the engineered cell of any one of the preceding embodiments, 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 chr6:29942877-29942897.

[00595] Embodiment 31 is the engineered cell of any one of the preceding embodiments, 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 chr6:29942883-29942903.

[00596] Embodiment 32 is the engineered cell of any one of the preceding embodiments, 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 chr6:29943126-29943146.

[00597] Embodiment 33 is the engineered cell of any one of the preceding embodiments, 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 chr6:29943528-29943548.

[00598] Embodiment 34 is the engineered cell of any one of the preceding embodiments, 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 chr6:29943529-29943549.

[00599] Embodiment 35 is the engineered cell of any one of the preceding embodiments, 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 chr6:29943530-29943550.

[00600] Embodiment 36 is the engineered cell of any one of the preceding embodiments, 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 chr6:29943537-29943557.

[00601] Embodiment 37 is the engineered cell of any one of the preceding embodiments, 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 chr6:29943549-29943569.

[00602] Embodiment 38 is the engineered cell of any one of the preceding embodiments, 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 chr6:29943589-29943609.

[00603] Embodiment 39 is the engineered cell of any one of the preceding embodiments, 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 and chr6:29944026-29944046.

[00604] Embodiment 40 is the engineered cell of any one of embodiments 23-39, wherein the HLA-A genomic target sequence comprises at least 10 contiguous nucleotides within the genomic coordinates.

[00605] Embodiment 41 is the engineered cell of any one of embodiments 23-40, wherein the HLA-A genomic target sequence comprises at least 15 contiguous nucleotides within the genomic coordinates.

[00606] Embodiment 42 is the engineered cell of any one of embodiments 23-41, wherein the HLA-A genomic target sequence comprises at least 17, 19, 18, or 20 contiguous nucleotides within the genomic coordinates.

[00607] Embodiment 43 is the engineered cell of any one of embodiments 23-41, wherein the gene editing system comprises a transcription activator-like effector nuclease (TALEN).

[00608] Embodiment 44 is the engineered cell of any one of embodiments 23-41, wherein the gene editing system comprises a zinc finger nuclease.

[00609] Embodiment 45 is the engineered cell of any one of embodiments 23-41, wherein the gene editing system comprises an RNA-guided DNA-binding agent or a nucleic acid encoding an RNA-guided DNA binding agent.

[00610] Embodiment 46 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid comprises a Cas9 protein.

[00611] Embodiment 47 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is S. pyogenes Cas9.

[00612] Embodiment 48 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is N. meningitidis Cas9, optionally Nme2Cas9.

[00613] Embodiment 49 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is S. thermophilus Cas9.

[00614] Embodiment 50 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is S. aureus Cas9.

[00615] Embodiment 51 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is Cpf1 from F. novicida.

[00616] Embodiment 52 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is Cpf1 from Acidaminococcus sp.

[00617] Embodiment 53 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is Cpf1 from Lachnospiraceae bacterium ND2006.

[00618] Embodiment 54 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is a C to T base editor.

[00619] Embodiment 55 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is an A to G base editor.

[00620] Embodiment 56 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid comprises a APOBEC3A deaminase (A3A) and an RNA-guided nickase.

[00621] Embodiment 57 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is Cas12a.

[00622] Embodiment 58 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is CasX.

[00623] Embodiment 59 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is Nme2Cas9.

[00624] Embodiment 60 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is Mad7 nuclease.

[00625] Embodiment 61 is the engineered cell of embodiment 45, wherein the RNA-guided DNA-binding agent or the RNA-guided DNA-binding agent encoded by the nucleic acid is an ARCUS nucleases.

[00626] Embodiment 62 is the engineered cell of any one of embodiments 17-61, wherein the cell is homozygous for HLA-B and homozygous for HLA-C.

[00627] Embodiment 63 is the engineered cell of any one of the preceding embodiments, 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.

[00628] Embodiment 64 is the engineered cell of any one of the preceding embodiments, 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.

[00629] Embodiment 65 is the engineered cell of any one of the preceding embodiments, 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.

[00630] Embodiment 66 is the engineered cell of any one of the preceding embodiments, 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.

[00631] Embodiment 67 is the engineered cell of any one of the preceding embodiments, wherein the HLA-B and HLA-C alleles are HLA-B*07:02 and HLA-C*07:02.

[00632] Embodiment 68 is the engineered cell of any one of the preceding embodiments, wherein the HLA-B and HLA-C alleles are HLA-B*08:01 and HLA-C*07:01.

[00633] Embodiment 69 is the engineered cell of any one of the preceding embodiments, wherein the HLA-B and HLA-C alleles are HLA-B*44:02 and HLA-C*05:01.

[00634] Embodiment 70 is the engineered cell of any one of the preceding embodiments, wherein the HLA-B and HLA-C alleles are HLA-B*35:01 and HLA-C*04:01.

[00635] Embodiment 71 is the engineered cell of any one of the preceding embodiments, wherein the cell has reduced expression of MHC class II protein on the surface of the cell.

[00636] Embodiment 72 is the engineered cell of any one of the preceding embodiments, 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.

[00637] Embodiment 73 is the engineered cell of any one of the preceding embodiments, wherein the cell has a genetic modification in the CIITA gene.

[00638] Embodiment 74 is the engineered cell of any one of the preceding embodiments, wherein the cell has reduced expression of TRAC protein on the surface of the cell.

[00639] Embodiment 75 is the engineered cell of any one of the preceding embodiments, wherein the cell has reduced expression of TRBC protein on the surface of the cell.

[00640] Embodiment 76 is the engineered cell of any one of the preceding embodiments, wherein the engineered cell further comprises an exogenous nucleic acid.

[00641] Embodiment 77 is the engineered cell of any one of the preceding embodiments, 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.

[00642] Embodiment 78 is the engineered cell of embodiment 77, wherein the targeting receptor is a CAR.

[00643] Embodiment 79 is the engineered cell of embodiment 77, wherein the targeting receptor is a TCR.

[00644] Embodiment 80 is the engineered cell of embodiment 77, wherein the targeting receptor is a WT1 TCR.

[00645] Embodiment 81 is the engineered cell of embodiment 77, wherein the engineered cell comprises a ligand for the receptor.

[00646] Embodiment 82 is the engineered cell of any one of the preceding embodiments, wherein the engineered cell further comprises an exogenous nucleic acid encoding a polypeptide that is secreted by the engineered cell.

[00647] Embodiment 83 is the engineered cell of any one of the preceding embodiments, wherein the engineered cell is an immune cell.

[00648] Embodiment 84 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a primary cell.

[00649] Embodiment 85 is the engineered cell of any one of the preceding embodiments, wherein the engineered cell is a monocyte, macrophage, mast cell, dendritic cell, or granulocyte.

[00650] Embodiment 86 is the engineered cell of any one of the preceding embodiments, wherein the engineered cell is a lymphocyte.

[00651] Embodiment 87 is the engineered cell of any one of the preceding embodiments, wherein the cell is a T cell.

[00652] Embodiment 88 is the engineered cell of any one of the preceding embodiments, wherein the cell is a CD8+ T cell.

[00653] Embodiment 89 is the engineered cell of any one of the preceding embodiments, wherein the cell is a CD4+ T cell.

[00654] Embodiment 90 is the engineered cell of any one of the preceding embodiments, wherein the cell is a B cell.

[00655] Embodiment 91 is the engineered cell of any one of the preceding embodiments, wherein the cell is a natural killer (NK) cell.

[00656] Embodiment 92 is the engineered cell of any one of the preceding embodiments, wherein the cell is a macrophage.

[00657] Embodiment 93 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a B cell.

[00658] Embodiment 94 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a plasma B cell.

[00659] Embodiment 95 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is memory B cell.

[00660] Embodiment 96 is the engineered cell of any one of the preceding embodiments, wherein the cell is a stem or progenitor cell.

[00661] Embodiment 97 is the engineered cell of any one of the preceding embodiments, wherein the stem or progenitor cell is an HSC or an iPSC.

[00662] Embodiment 98 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is an activated cell.

[00663] Embodiment 99 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a non-activated cell.

[00664] Embodiment 100 is the engineered cell of any one of the preceding embodiments, wherein the genetic modification comprises at least 2, at least 3, at least 4, 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, or wherein the genetic modification comprises at least 5 contiguous nucleotides within the genomic coordinates.

[00665] Embodiment 101 is the engineered cell of any one of the preceding embodiments, wherein the genetic modification comprises at least 6, 7, 8, 9, or 10 contiguous nucleotides within the genomic coordinates.

[00666] Embodiment 102 is the engineered cell of any one of the preceding embodiments, wherein the genetic modification comprises an indel.

[00667] Embodiment 103 is the engineered cell of any of the preceding embodiments, wherein the genetic modification comprises at least one C to T substitution or at least one A to G substitution within the genomic coordinates.

[00668] Embodiment 104 is a pharmaceutical composition comprising the engineered cell of any one of the preceding embodiments.

[00669] Embodiment 105 is a population of cells comprising the engineered cell of any one of the preceding embodiments.

[00670] Embodiment 106 is a pharmaceutical composition comprising the population of cells of embodiment 105.

[00671] Embodiment 107 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 65% HLA-A negative as measured by flow cytometry.

[00672] Embodiment 107.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 65% of the population of cells comprises the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00673] Embodiment 108 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 70% HLA-A negative as measured by flow cytometry.

[00674] Embodiment 108.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 70% of the population of cells comprises the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00675] Embodiment 109 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 80% HLA-A negative as measured by flow cytometry.

[00676] Embodiment 109.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 80% of the population of cells comprises the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00677] Embodiment 110 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 90% HLA-A negative as measured by flow cytometry.

[00678] Embodiment 110.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 90% of the population of cells comprises the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00679] Embodiment 111 is the population of embodiment 105or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 92% HLA-A negative as measured by flow cytometry.

[00680] Embodiment 111.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 92% of the population of cells comprises the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00681] Embodiment 112 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 93% HLA-A negative as measured by flow cytometry.

[00682] Embodiment 112.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 93% of the population of cells comprises the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00683] Embodiment 113 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 94% HLA-A negative as measured by flow cytometry.

[00684] Embodiment 113.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 94% of the population of cells comprises the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00685] Embodiment 114 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 95% HLA-A negative as measured by flow cytometry.

[00686] Embodiment 114.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 95% of the population of cells comprises

the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00687] Embodiment 115 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 96% HLA-A negative as measured by flow cytometry.

[00688] Embodiment 115.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 96% of the population of cells comprises the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00689] Embodiment 116 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 97% HLA-A negative as measured by flow cytometry.

[00690] Embodiment 116.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 97% of the population of cells comprises the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00691] Embodiment 117 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 98% HLA-A negative as measured by flow cytometry.

[00692] Embodiment 117.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 98% of the population of cells comprises the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00693] Embodiment 118 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein the population of cells is at least 99% HLA-A negative as measured by flow cytometry.

[00694] Embodiment 118.1 is the population of embodiment 105 or pharmaceutical composition of embodiment 106, wherein at least 99% of the population of cells comprises the genetic modification in the HLA-A gene, as measured by next-generation sequencing (NGS).

[00695] Embodiment 119 is the population or pharmaceutical composition of any one of embodiments 105-118, wherein the population of cells is at least 94% CIITA negative as measured by flow cytometry.

[00696] Embodiment 120 is the population or pharmaceutical composition of any one of embodiments 105-118, wherein the population of cells is at least 95% CIITA negative as measured by flow cytometry.

[00697] Embodiment 121 is the population or pharmaceutical composition of any one of embodiments 105-118, wherein the population of cells is at least 96% CIITA negative as measured by flow cytometry.

[00698] Embodiment 122 is the population or pharmaceutical composition of any one of embodiments 105-118, wherein the population of cells is at least 97% CIITA negative as measured by flow cytometry.

[00699] Embodiment 123 is the population or pharmaceutical composition of any one of embodiments 105-118, wherein the population of cells is at least 98% CIITA negative as measured by flow cytometry.

[00700] Embodiment 124 is the population or pharmaceutical composition of any one of embodiments 105-118, wherein the population of cells is at least 99% CIITA negative as measured by flow cytometry.

[00701] Embodiment 125 is the population or pharmaceutical composition of any one of embodiments 105-124, wherein the population of cells is at least 95% endogenous TCR protein negative as measured by flow cytometry.

[00702] Embodiment 126 is the population or pharmaceutical composition of any one of embodiments 105-124, wherein the population of cells is at least 97% endogenous TCR protein negative as measured by flow cytometry.

[00703] Embodiment 127 is the population or pharmaceutical composition of any one of embodiments 105-124, wherein the population of cells is at least 98% endogenous TCR protein negative as measured by flow cytometry.

[00704] Embodiment 128 is the population or pharmaceutical composition of any one of embodiments 105-124, wherein the population of cells is at least 99% endogenous TCR protein negative as measured by flow cytometry.

[00705] Embodiment 129 is the population or pharmaceutical composition of any one of embodiments 105-124, wherein the population of cells is at least 99.5% endogenous TCR protein negative as measured by flow cytometry.

[00706] Embodiment 130 is a method of administering the engineered cell, population of cells, pharmaceutical composition of any one of the preceding embodiments to a subject in need thereof.

[00707] Embodiment 131 is a method of administering the engineered cell, population of cells, or pharmaceutical composition of any one of the preceding embodiments to a subject as an adoptive cell transfer (ACT) therapy.

[00708] Embodiment 132 is a method of treating a disease or disorder comprising administering the engineered cell, population of cells, or pharmaceutical composition of any one of the preceding embodiments to a subject in need thereof.

[00709] Embodiment 133 is 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.

[00710] Embodiment 134 is 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.

[00711] Embodiment 135 is the method of embodiment 133 or 134, wherein the RNA-guided DNA binding agent comprises a Cas9 protein.

[00712] Embodiment 136 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is S. pyogenes Cas9.

[00713] Embodiment 137 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is N. meningitidis Cas9.

[00714] Embodiment 138 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is S. thermophilus Cas9.

[00715] Embodiment 139 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is S. aureus Cas9.

[00716] Embodiment 140 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is Cpf1 from F. novicida.

[00717] Embodiment 141 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is Cpf1 from Acidaminococcus sp.

[00718] Embodiment 142 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is Cpf1 from Lachnospiraceae bacterium ND2006.

[00719] Embodiment 143 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is a C to T base editor.

[00720] Embodiment 144 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is a A to G base editor.

[00721] Embodiment 145 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent comprises a APOBEC3A deaminase (A3A) and an RNA-guided nickase.

[00722] Embodiment 146 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is Cas12a.

[00723] Embodiment 147 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is CasX.

[00724] Embodiment 148 is the method of embodiment 133 or 134, wherein the RNA-guided DNA-binding agent or nucleic acid encoding the RNA-guided DNA binding agent is Nme2Cas9.

[00725] Embodiment 149 is the method of any one of embodiments 133-148, further comprising reducing or eliminating the surface expression of MHC class II protein in the cell relative to an unmodified cell, for example 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.

[00726] Embodiment 150 is the method of any one of embodiments 133-149, further comprising contacting the cell with a CIITA guide RNA.

[00727] Embodiment 151 is the method of any one of embodiments 133-150, further comprising reducing or eliminating the surface expression of a TCR protein in the cell relative to an unmodified cell.

[00728] Embodiment 152 is the method of any one of embodiments 133-151, further comprising contacting the cell with an exogenous nucleic acid.

[00729] Embodiment 153 is the method of embodiment 152, further comprising contacting the cell with an exogenous nucleic acid encoding a targeting receptor.

[00730] Embodiment 154 is the method of embodiment 152, further comprising contacting the cell with an exogenous nucleic acid encoding a polypeptide that is secreted by the cell.

[00731] Embodiment 155 is the method of embodiment 152, further comprising contacting the cell with a DNA-dependent protein kinase inhibitor (DNAPKi).

[00732] Embodiment 156 is the method of embodiment 155, wherein the DNAPKi is Compound 1.

[00733] Embodiment 157 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is an allogeneic cell.

[00734] Embodiment 158 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a primary cell.

[00735] Embodiment 159 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a CD4+ T cell.

[00736] Embodiment 160 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a CD8+ T cell.

[00737] Embodiment 161 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a memory T cell.

[00738] Embodiment 162 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a B cell.

[00739] Embodiment 163 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a plasma B cell.

[00740] Embodiment 164 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a memory B cell.

[00741] Embodiment 165 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a natural killer (NK) cell.

[00742] Embodiment 166 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a macrophage.

[00743] Embodiment 167 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is stem cell.

[00744] Embodiment 168 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a pluripotent stem cell (PSC).

[00745] Embodiment 169 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a hematopoietic stem cell (HSC).

[00746] Embodiment 170 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is an induced pluripotent stem cell (iPSC).

[00747] Embodiment 171 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a mesenchymal stem cell (MSC).

[00748] Embodiment 172 The engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a neural stem cell (NSC).

[00749] Embodiment 173 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a limbal stem cell (LSC).

[00750] Embodiment 174 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a progenitor cell, e.g. an endothelial progenitor cell or a neural progenitor cell.

[00751] Embodiment 175 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a tissue-specific primary cell.

[00752] Embodiment 176 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a chosen from: chondrocyte, myocyte, and keratinocyte.

[00753] Embodiment 177 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is an activated cell.

[00754] Embodiment 178 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cell is a non-activated cell.

[00755] Embodiment 179 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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.

[00756] Embodiment 180 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 a full-length IgG antibody.

[00757] Embodiment 181 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 a single chain antibody.

[00758] Embodiment 182 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 a neutralizing antibody.

[00759] Embodiment 183 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 enzyme.

[00760] Embodiment 184 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 a cytokine.

[00761] Embodiment 185 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 a fusion protein.

[00762] Embodiment 186 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 comprises a soluble receptor.

[00763] Embodiment 187 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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).

[00764] Embodiment 188 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 genetically modified TCR.

[00765] Embodiment 189 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 WT1 TCR.

[00766] Embodiment 190 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 CAR.

[00767] Embodiment 191 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 universal CAR.

[00768] Embodiment 192 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, 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 proliferation-inducing ligand (APRIL).

[00769] Embodiment 193 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the cells are engineered with a gene editing system.

[00770] Embodiment 194 is the engineered cell, population of cells, pharmaceutical composition, or method of embodiment 193, wherein the gene editing system comprises a transcription activator-like effector nuclease (TALEN).

[00771] Embodiment 195 is the engineered cell, population of cells, pharmaceutical composition, or method of embodiment 193, wherein the gene editing system comprises a zinc finger nuclease.

[00772] Embodiment 196 is the engineered cell, population of cells, pharmaceutical composition, or method of embodiment 193, 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.

[00773] Embodiment 197 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA is provided to the cell in a vector.

[00774] Embodiment 198 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the RNA-guided DNA binding agent is provided to the cell in a vector, optionally in the same vector as the HLA-A guide RNA.

[00775] Embodiment 199 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the exogenous nucleic acid is provided to the cell in a vector.

[00776] Embodiment 200 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the vector is a viral vector.

[00777] Embodiment 201 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the vector is a non-viral vector.

[00778] Embodiment 202 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the vector is a lentiviral vector.

[00779] Embodiment 203 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the vector is a retroviral vector.

[00780] Embodiment 204 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the vector is an AAV.

[00781] Embodiment 205 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the guide RNA is provided to the cell in a lipid nucleic acid assembly composition, optionally in the same lipid nucleic acid assembly composition as an RNA-guided DNA binding agent.

[00782] Embodiment 206 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the exogenous nucleic acid is provided to the cell in a lipid nucleic acid assembly composition.

[00783] Embodiment 207 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the lipid nucleic acid assembly composition is a lipid nanoparticle (LNP).

[00784] Embodiment 208 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the exogenous nucleic acid is integrated into the genome of the cell.

[00785] Embodiment 209 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the exogenous nucleic acid is integrated into the genome of the cell by homologous recombination (HR).

[00786] Embodiment 210 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the exogenous nucleic acid is integrated into a safe harbor locus in the genome of the cell.

[00787] Embodiment 211 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 13 or wherein the HLA-A guide RNA comprises SEQ ID NO: 14.

[00788] Embodiment 212 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 15.

[00789] Embodiment 213 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 16.

[00790] Embodiment 214 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 17.

[00791] Embodiment 215 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 18.

[00792] Embodiment 216 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 26.

[00793] Embodiment 217 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 37.

[00794] Embodiment 218 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 38.

[00795] Embodiment 219 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 39.

[00796] Embodiment 220 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 41.

[00797] Embodiment 221 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 43.

[00798] Embodiment 222 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 45.

[00799] Embodiment 223 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises SEQ ID NO: 62.

[00800] Embodiment 224 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises at least one modification.

[00801] Embodiment 225 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises at least one modification, wherein the at least one modification includes a 2'-O-methyl (2'-O-Me) modified nucleotide.

[00802] Embodiment 226 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises at least one modification, comprising a phosphorothioate (PS) bond between nucleotides.

[00803] Embodiment 227 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises at least one modification, comprising a 2'-fluoro (2'-F) modified nucleotide.

[00804] Embodiment 228 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide

RNA comprises at least one modification, comprising a modification at one or more of the first five nucleotides at the 5' end of the guide RNA.

[00805] Embodiment 229 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises at least one modification, comprising a modification at one or more of the last five nucleotides at the 3' end of the guide RNA.

[00806] Embodiment 230 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises at least one modification, comprising a PS bond between the first four nucleotides of the guide RNA.

[00807] Embodiment 231 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises at least one modification, comprising a PS bond between the last four nucleotides of the guide RNA.

[00808] Embodiment 232 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises at least one modification, comprising a 2'-O-Me modified nucleotide at the first three nucleotides at the 5' end of the guide RNA.

[00809] Embodiment 233 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, wherein the HLA-A guide RNA comprises at least one modification, comprising a 2'-O-Me modified nucleotide at the last three nucleotides at the 3' end of the guide RNA.

[00810] Embodiment 234 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, for use to express a TCR with specificity for a polypeptide expressed by cancer cells.

[00811] Embodiment 235 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, for use in administering to a subject as an adoptive cell transfer (ACT) therapy.

[00812] Embodiment 236 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, for use in treating a subject with cancer.

[00813] Embodiment 237 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, for use in treating a subject with an infectious disease.

[00814] Embodiment 238 is the engineered cell, population of cells, pharmaceutical composition, or method of any one of the preceding embodiments, for use in treating a subject with an autoimmune disease

[00815] Embodiment 239 is a cell bank comprising: (a) the engineered cells of any one of the preceding embodiments, or the engineered cells produced by the method of any one of the preceding embodiments; and (b) a catalogue comprising information documenting the HLA-B and HLA-C alleles of the donor cells in the cell bank.

[00816] Embodiment 240 is the cell bank of embodiment 239, 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.

[00817] Embodiment 241 is a method of administering an engineered cell to a recipient subject in need thereof, the method comprising: (a) determining the HLA-B and HLA-C alleles of the recipient subject; (b) selecting an engineered cell or cell population of any one of the preceding embodiments, or engineered cell or cell population produced by the method of any one of the preceding embodiments, wherein the engineered cell comprises at least one of the same HLA-B or HLA-C alleles as the recipient subject; (c) administering the selected engineered cell to the recipient subject.

[00818] Embodiment 242 is the method of embodiment 241, wherein the subject has the HLA-B and HLA-C alleles of the engineered cell.

[00819] Embodiment 243 is the engineered cell, composition, pharmaceutical composition, or method of any one of the preceding embodiments, for use in administering to a partially matched subject for an adoptive cell transfer (ACT) therapy, wherein the partially matched subject has the HLA-B and HLA-C alleles of the engineered cell or cell population.

[00820] Embodiment 244 is the engineered cell, composition, pharmaceutical composition, or method of any one of embodiments 130-132, 235-238, 241-243, wherein the engineered cell or cell population comprises HLA-B and HLA-C alleles shared with the subject.

[00821] Embodiment 245 is the engineered cell, composition, pharmaceutical composition, or method of any one of the preceding embodiments 130-132, 235-238, 241-243, wherein the HLA-B and HLA-C alleles of the engineered cell or cell population consist of alleles that match one or more HLA-B and HLA-C alleles of the subject.

[00822] Embodiment 246 is the engineered cell, composition, pharmaceutical composition, or method of any one of the preceding embodiments 130-132, 235-238, 241-

243, wherein the HLA-B and HLA-C alleles of the engineered cell or cell population consist of alleles that match one or both HLA-B and/or one or both HLA-C alleles of the subject.

We claim:

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

2. 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 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.

3. The engineered cell of claim 1 or 2, 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.

4. The engineered cell of any one of claims 1-3, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942864-chr6: 29942903.

5. The engineered cell of any one of claims 1-4, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528-chr6:29943609.

6. The engineered cell of any one of claims 1-5, 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; and chr6:29942883-29942903.

7. The engineered cell of any one of claims 1-6, wherein 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.

8. The engineered cell of any one of claims 1-7, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29942876-29942897.

9. The engineered cell of any one of claims 1-8, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chr6:29943528- 29943550.

10. The engineered cell of any one of claims 1-9, wherein 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.

11. The engineered cell of any one of claims 1-10, wherein the genetic modification comprises at least one nucleotide within the genomic coordinates chosen from: chr6:29943528-29943548, chr6:29943529-29943549, and chr6:29943530-29943550.

12. 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 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.

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

14. The engineered cell of claim 12 or 13, wherein the cell is homozygous for HLA-B and homozygous for HLA-C.

15. The engineered cell of any one of claims 12-14, wherein the genetic modification comprises at least 5, 6, 7, 8, 9, or 10 contiguous nucleotides within the genomic coordinates.

16. The engineered cell of any one of claims 12-15, wherein the genetic modification comprises at least one C to T substitution or at least one A to G substitution within the genomic coordinates.

17. The engineered cell of any one of claims 1-16, 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; or

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.

18. The engineered cell of any one of claims 1-17, 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.

19. The engineered cell of any one of claims 1-18, 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.

20. The engineered cell of any one of claims 1-19, 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.

21. The engineered cell of any one of claims 1-20, 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.

22. The engineered cell of any one of claims 17-21, 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.

23. The engineered cell of any one of claims 12-22, wherein the cell is homozygous for HLA-B and homozygous for HLA-C.

24. The engineered cell of any one of claims 1-23, 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.

25. The engineered cell of any one of claims 1-24, 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.

26. The engineered cell of any one of claims 1-25, 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.

27. The engineered cell of any one of claims 1-26, 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.

28. The engineered cell of any one of claims 1-27, wherein the HLA-B and HLA-C alleles are HLA-B*07:02 and HLA-C*07:02.

29. The engineered cell of any one of claims 1-28, wherein the HLA-B and HLA-C alleles are HLA-B*08:01 and HLA-C*07:01.

30. The engineered cell of any one of claims 1-29, wherein the HLA-B and HLA-C alleles are HLA-B*44:02 and HLA-C*05:01.

31. The engineered cell of any one of claims 1-30, wherein the HLA-B and HLA-C alleles are HLA-B*35:01 and HLA-C*04:01.

32. The engineered cell of any one of claims 1-31, wherein the cell has reduced expression of MHC class II protein on the surface of the cell.

33. The engineered cell of any one of claims 1-32, 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.

34. The engineered cell of any one of claims 1-33, wherein the cell has a genetic modification in the CIITA gene.

35. The engineered cell of any one of claims 1-34, wherein the cell has reduced expression of TRAC protein or TRBC protein on the surface of the cell.

36. The engineered cell of any one of claims 1-35, 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.

37. The engineered cell of claim 36, wherein the targeting receptor is a CAR or a TCR.

38. The engineered cell of any one of claims 1-37, wherein the engineered cell further comprises an exogenous nucleic acid encoding a polypeptide that is secreted by the engineered cell.

39. The engineered cell of any one of claims 1-38, wherein the engineered cell is an immune cell.

40. The engineered cell of any one of claims 1-39, wherein the engineered cell is a primary cell.

41. The engineered cell of any one of claims 1-40, wherein the engineered cell is a monocyte, macrophage, mast cell, dendritic cell, or granulocyte.

42. The engineered cell of any one of claims 1-41, wherein the engineered cell is a lymphocyte.

43. The engineered cell of any one of claims 1-42, wherein the cell is a T cell.

44. The engineered cell of any one of claims 1-43, 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.

45. The engineered cell of any one of claims 1-44, wherein the genetic modification comprises an indel.

46. The engineered cell of any one of claims 1-45, wherein the genetic modification comprises at least one C to T substitution or at least one A to G substitution within the genomic coordinates.

47. A pharmaceutical composition comprising the engineered cell of any one of claims 1-46.

48. A population of cells comprising the engineered cell of any one of claims 1-47.

49. A pharmaceutical composition comprising the population of cells of claim 48.

50. The population of claim 48 or pharmaceutical composition of claim 49, 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.

51. The population or pharmaceutical composition of any one of claims 48-50,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.

52. The population or pharmaceutical composition of any one of claims 48-51, 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.

53. A method of administering the engineered cell, population of cells, or pharmaceutical composition of any one of claims 1-53 to a subject in need thereof.

54. A method of administering the engineered cell, population of cells, or pharmaceutical composition of any one of claims 1-53 to a subject as an adoptive cell transfer (ACT) therapy.

55. A method of treating a disease or disorder comprising administering the engineered cell, population of cells, or pharmaceutical composition of any one of claims 1-53 to a subject in need thereof.

56. 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.

57. 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.

58. The method of claim 56 or 57, wherein the RNA-guided DNA binding agent comprises a Cas9 protein.

59. The method of claim 56 or 57, wherein the RNA-guided DNA-binding agent or nucleic acid encoding 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.*

60. The method of claim 56 or 57, wherein the RNA-guided DNA-binding agent or nucleic acid encoding 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.

61. The method of any one of claims 56-60, 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.

62. The method of any one of claims 56-61, further comprising contacting the cell with a CIITA guide RNA.

63. The method of any one of claims 56-62, further comprising reducing or eliminating the surface expression of a TCR protein in the cell relative to an unmodified cell.

64. The method of any one of claims 56-63, further comprising contacting the cell with an exogenous nucleic acid.

65. The method of claim 64, wherein the exogenous nucleic acid encodes a targeting receptor or a polypeptide that is secreted by the cell.

66. The method of claim 64, further comprising contacting the cell with a DNA-dependent protein kinase inhibitor (DNAPKi), optionally wherein the DNAPKi is Compound 1.

67. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-66, wherein the cell is an allogeneic cell.

68. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-67, wherein the cell is a primary cell.

69. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-68, wherein the cell is a T cell, optionally wherein the T cell is a CD4+ T cell, a CD8+ T cell, or a memory T cell.

70. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-68, wherein the cell is a B cell, optionally wherein the B cell is a plasma B cell or a memory B cell.

71. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-68, wherein the cell is a stem cell, 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)..

72. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-71, 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.

73. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-72, 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 a full-length IgG antibody, a single chain antibody, or a neutralizing antibody.

74. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-73, 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 a cytokine.

75. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-74, 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).

76. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-75, wherein the cell is engineered with a gene editing system.

77. The engineered cell, population of cells, pharmaceutical composition, or method of claim 76, wherein the gene editing system comprises a transcription activator-like effector nuclease (TALEN) or a zinc finger nuclease.

78. The engineered cell, population of cells, pharmaceutical composition, or method of claim 76, 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.

79. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 56-78, 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.

80. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 56-79, wherein the guide RNA or the exogenous nucleic acid is provided to

the cell in a lipid nucleic acid assembly composition, optionally in the same lipid nucleic acid assembly composition as an RNA-guided DNA binding agent.

81. The engineered cell, population of cells, pharmaceutical composition, or method of claim 80, wherein the lipid nucleic acid assembly composition is a lipid nanoparticle (LNP).

82. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 56-81, wherein 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.

83. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 56-82, wherein 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.

84. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 56-83, wherein the HLA-A guide RNA comprises at least one modification.

85. The engineered cell, population of cells, pharmaceutical composition, or method of claim 84, 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).

86. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-85, for use to express a TCR with specificity for a polypeptide expressed by cancer cells.

87. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-85, for use in administering to a subject as an adoptive cell transfer (ACT) therapy.

88. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-85, for use in treating a subject with cancer, an infectious disease, or an autoimmune disease.

89. A cell bank comprising:

a. the engineered cell of any one of claims 1-46 and 67-88, or the engineered cell produced by the method of any one of claims 56 and 58-88; and
b. a catalogue comprising information documenting the HLA-B and HLA-C alleles of the donor cells in the cell bank.

90. The cell bank of claim 89, 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.

91. A method of administering an engineered cell to a recipient subject in need thereof, the method comprising:

a. determining the HLA-B and HLA-C alleles of the recipient subject;
b. selecting the engineered cell or population of cells of any one of 1-46, 48, 50-52, and 67-88, or the engineered cell produced by the method of any one of claims 56 and 58-88, wherein the engineered cell comprises at least one of the same HLA-B or HLA-C alleles as the recipient subject;
c. administering the selected engineered cell to the recipient subject.

92. The method of claim 91, wherein the subject has the HLA-B and HLA-C alleles of the engineered cell.

93. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 1-92, for use in administering to a partially matched subject for an adoptive cell transfer (ACT) therapy, wherein the partially matched subject has the HLA-B and HLA-C alleles of the engineered cell or population of cells.

94. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 53-55, 87-88, and 91-93, wherein the engineered cell or population of cells comprises HLA-B and HLA-C alleles shared with the subject.

95. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 53-55, 87-88, and 91-93, 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.

96. The engineered cell, population of cells, pharmaceutical composition, or method of any one of claims 53-55, 87-88, and 91-93, 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.

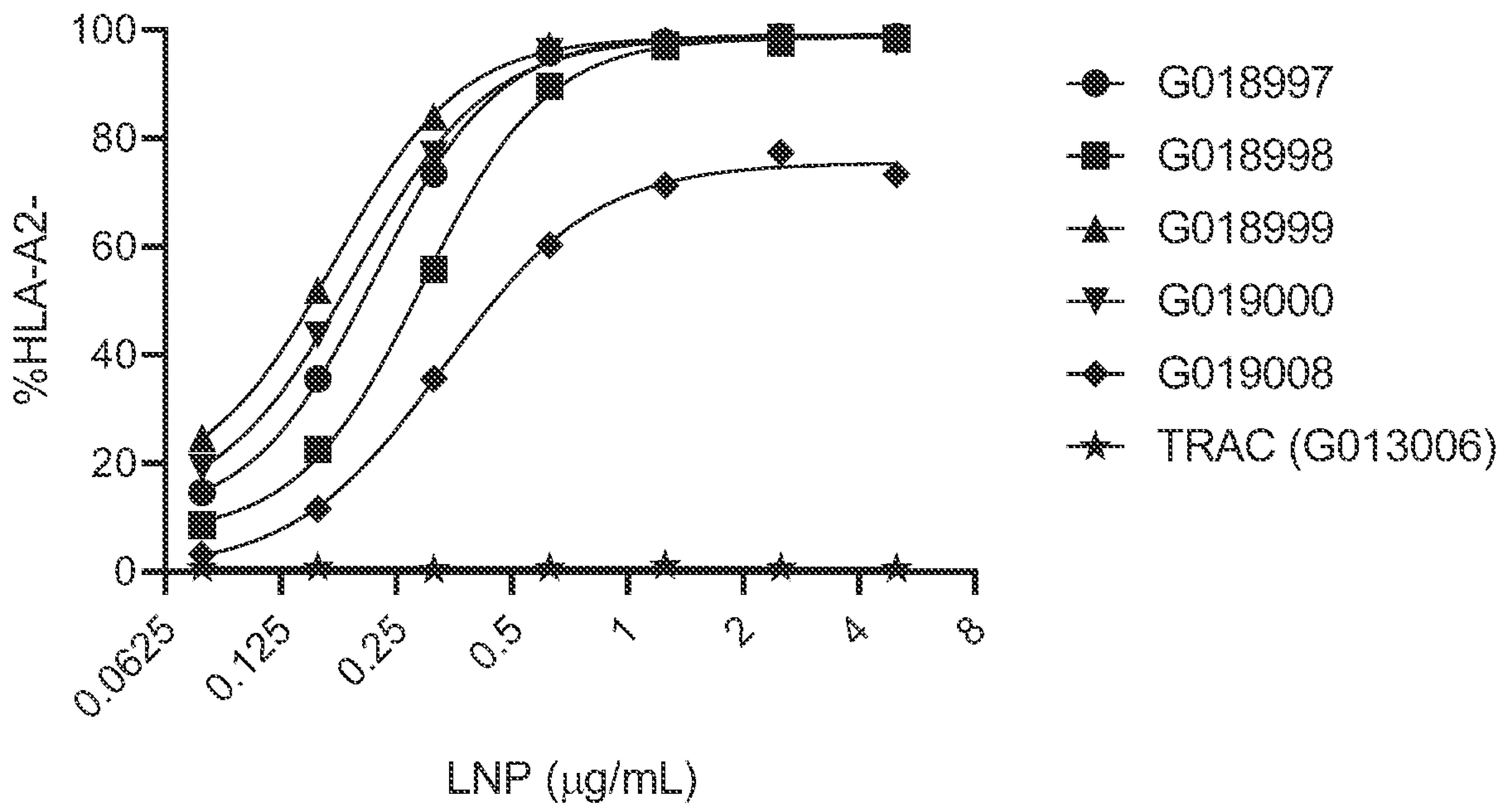


FIG. 1A

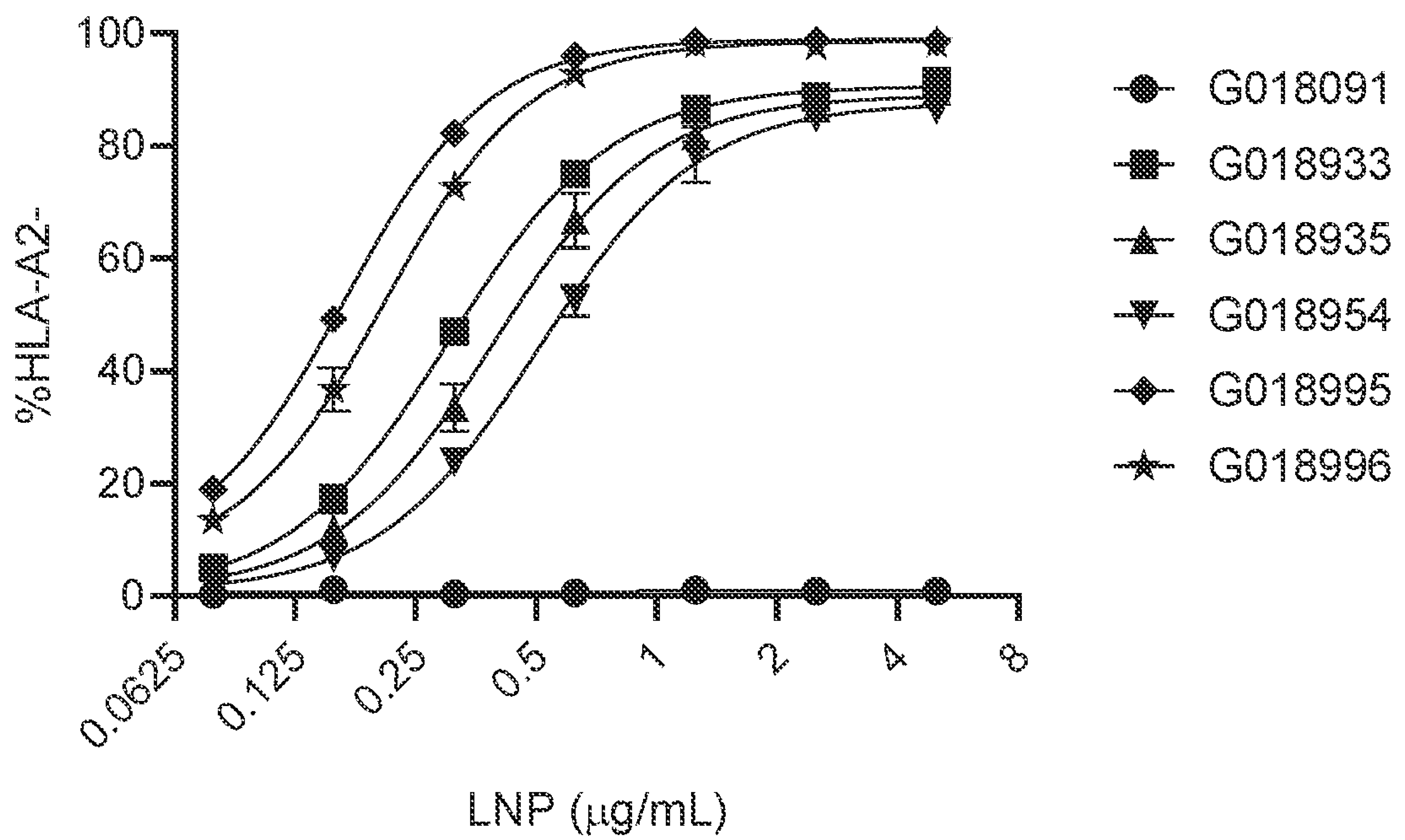


FIG. 1B

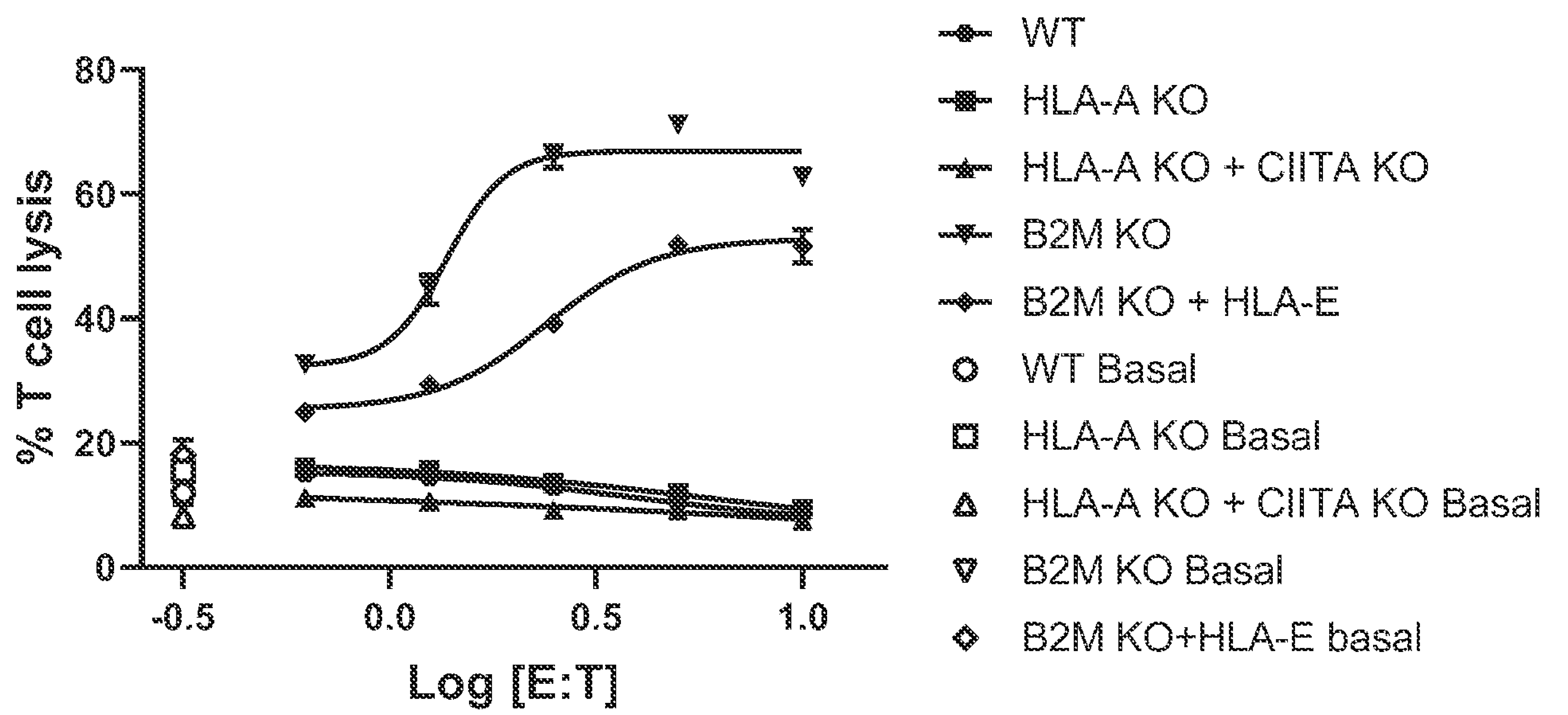


FIG. 2

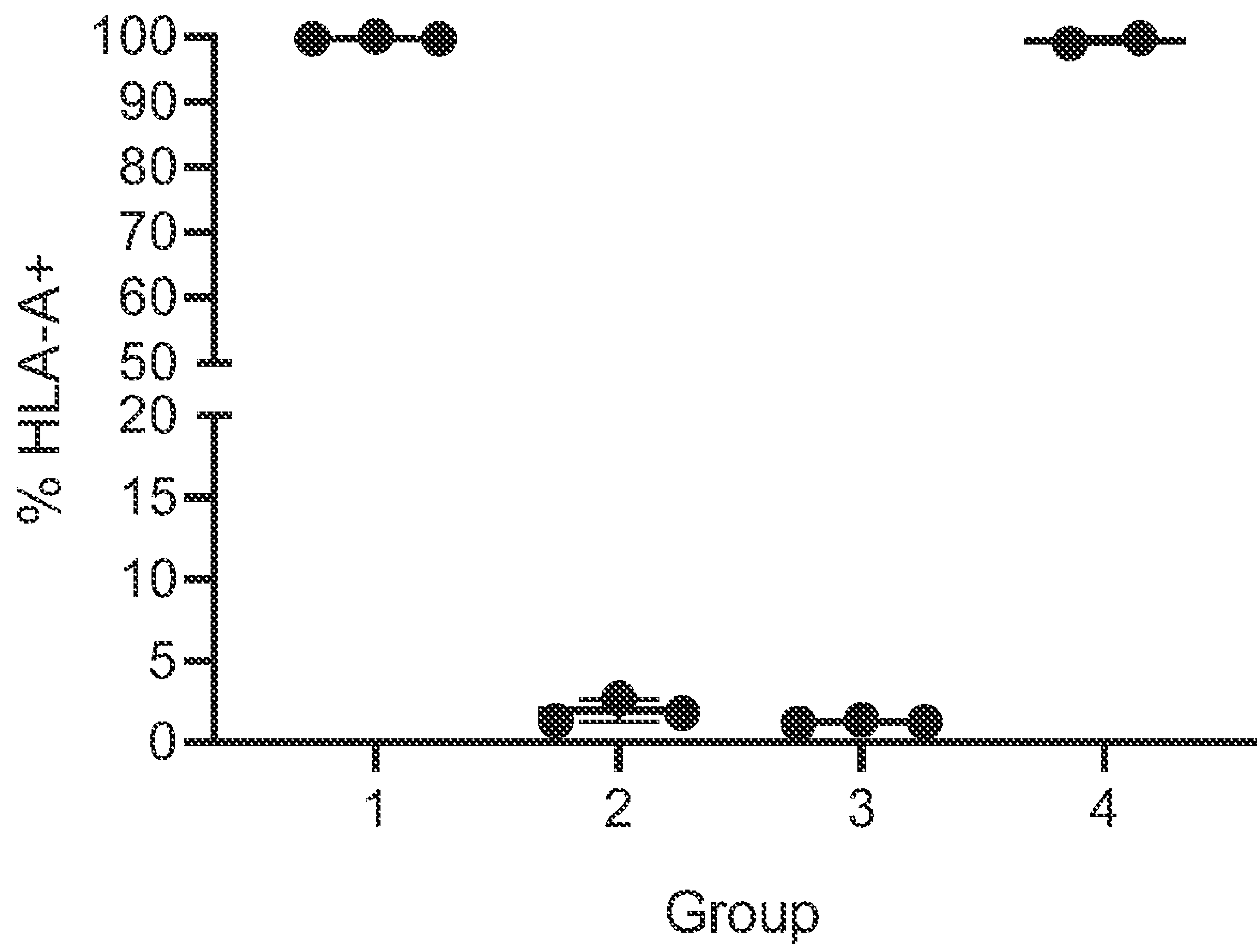


FIG. 3A

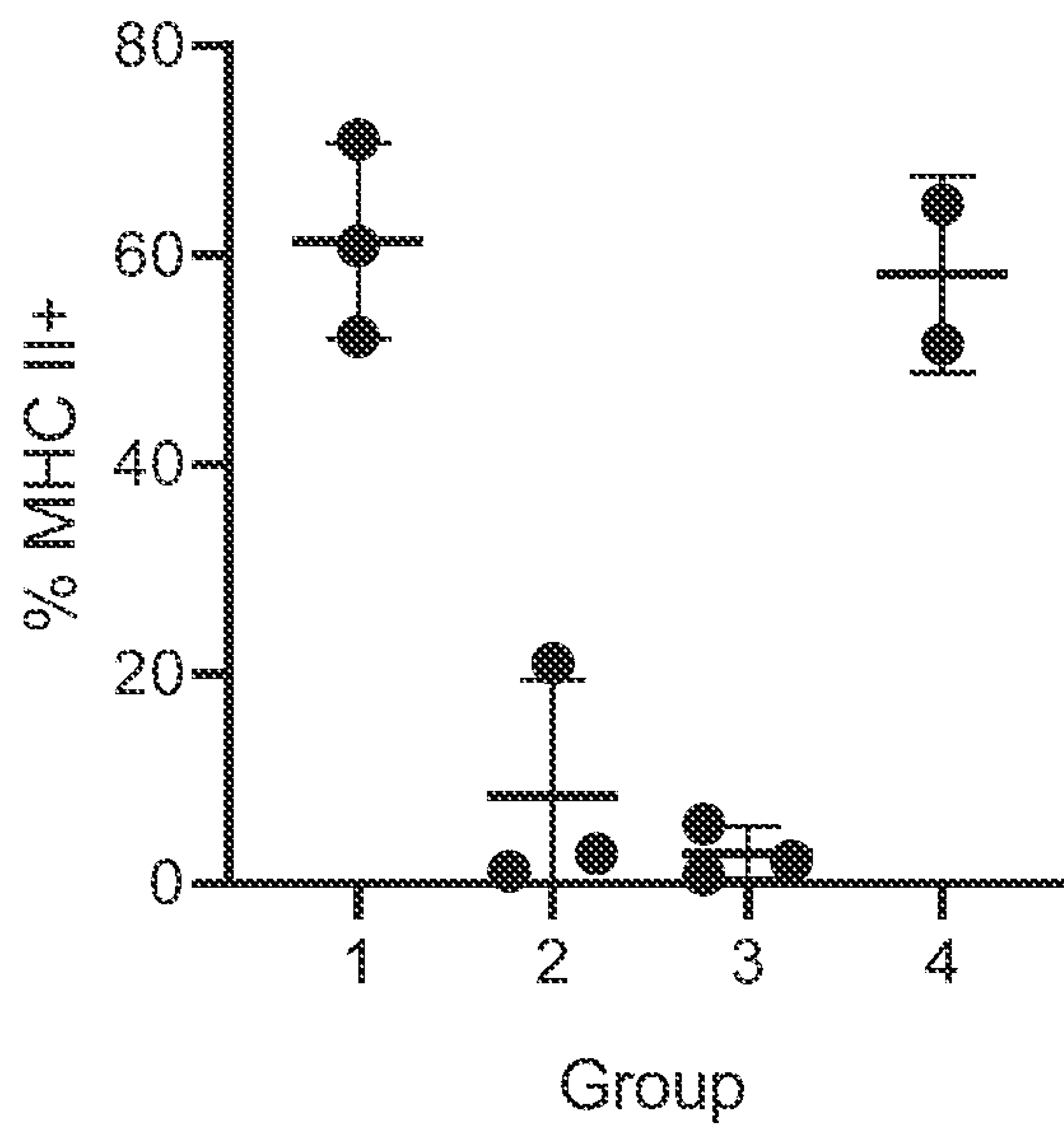


FIG. 3B

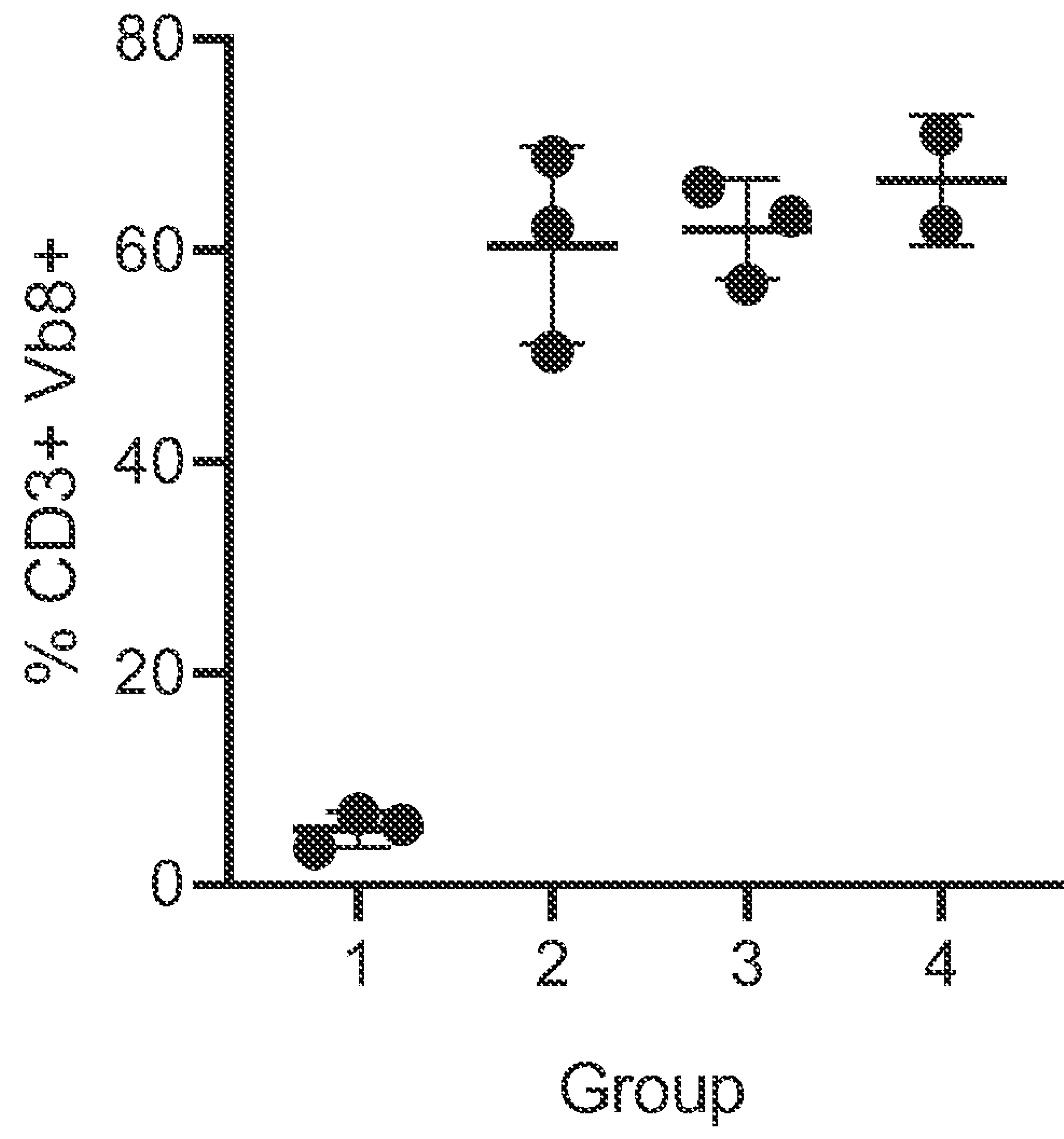


FIG. 3C

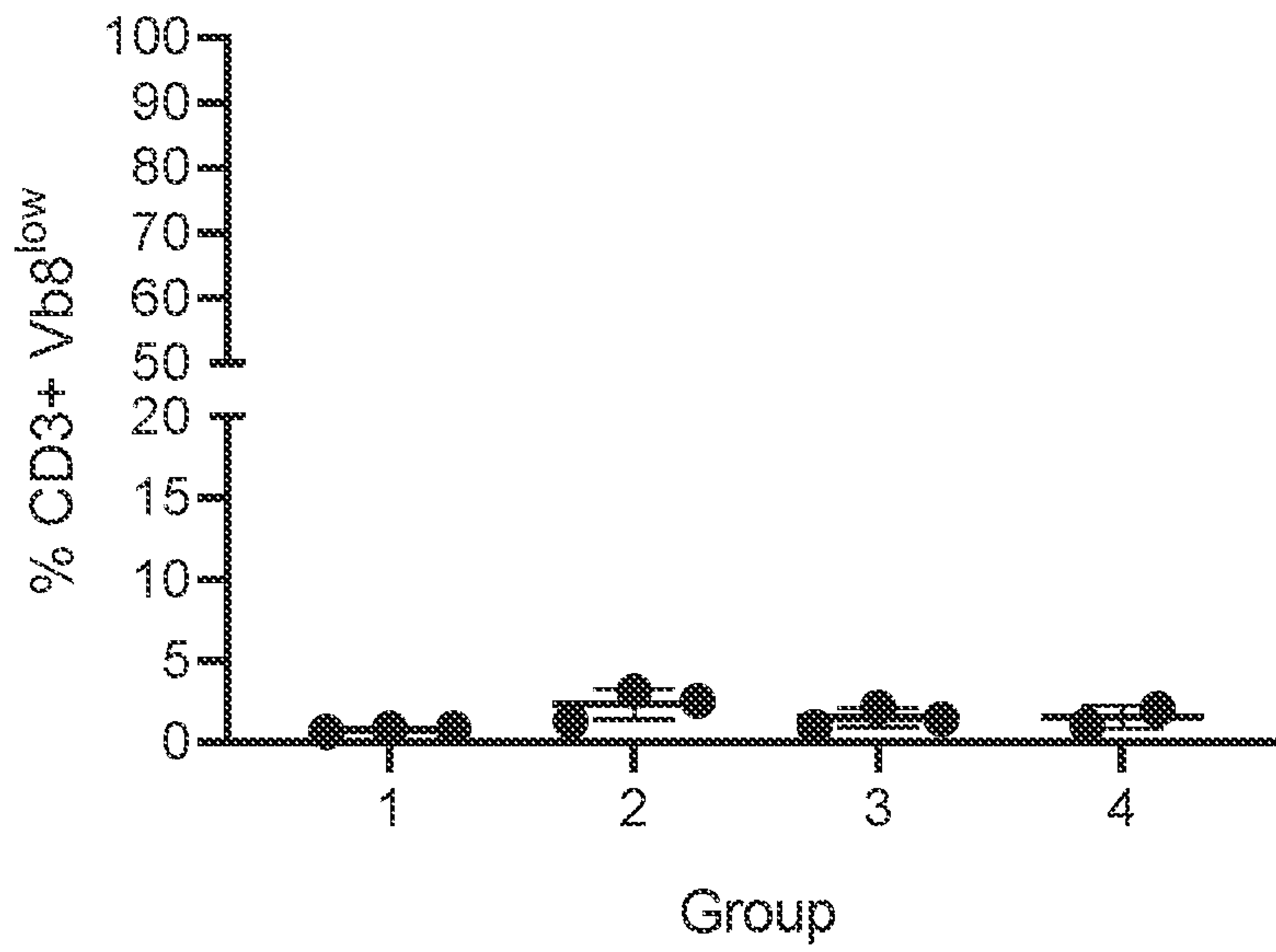


FIG. 3D

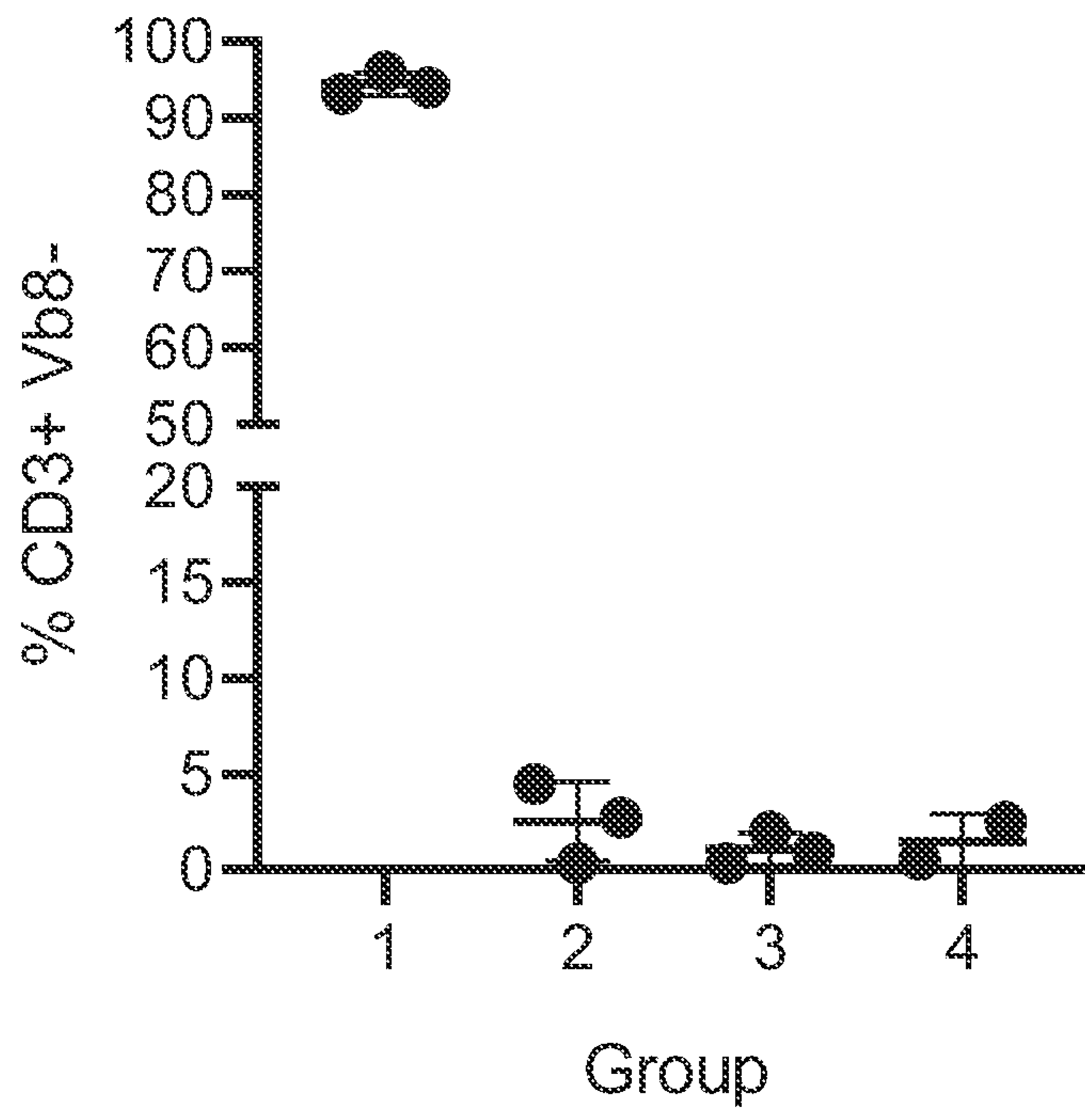


FIG. 3E

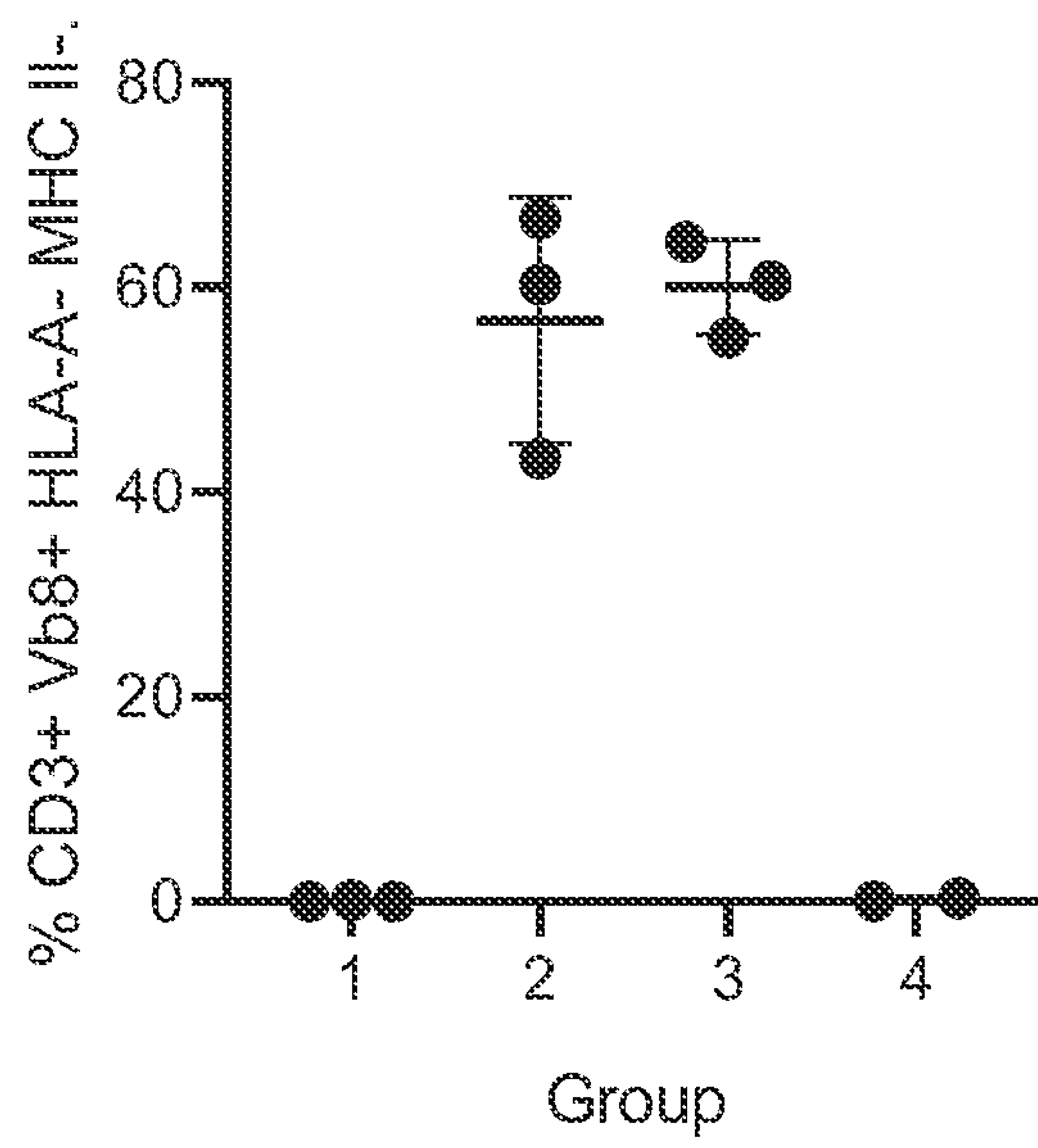


FIG. 3F

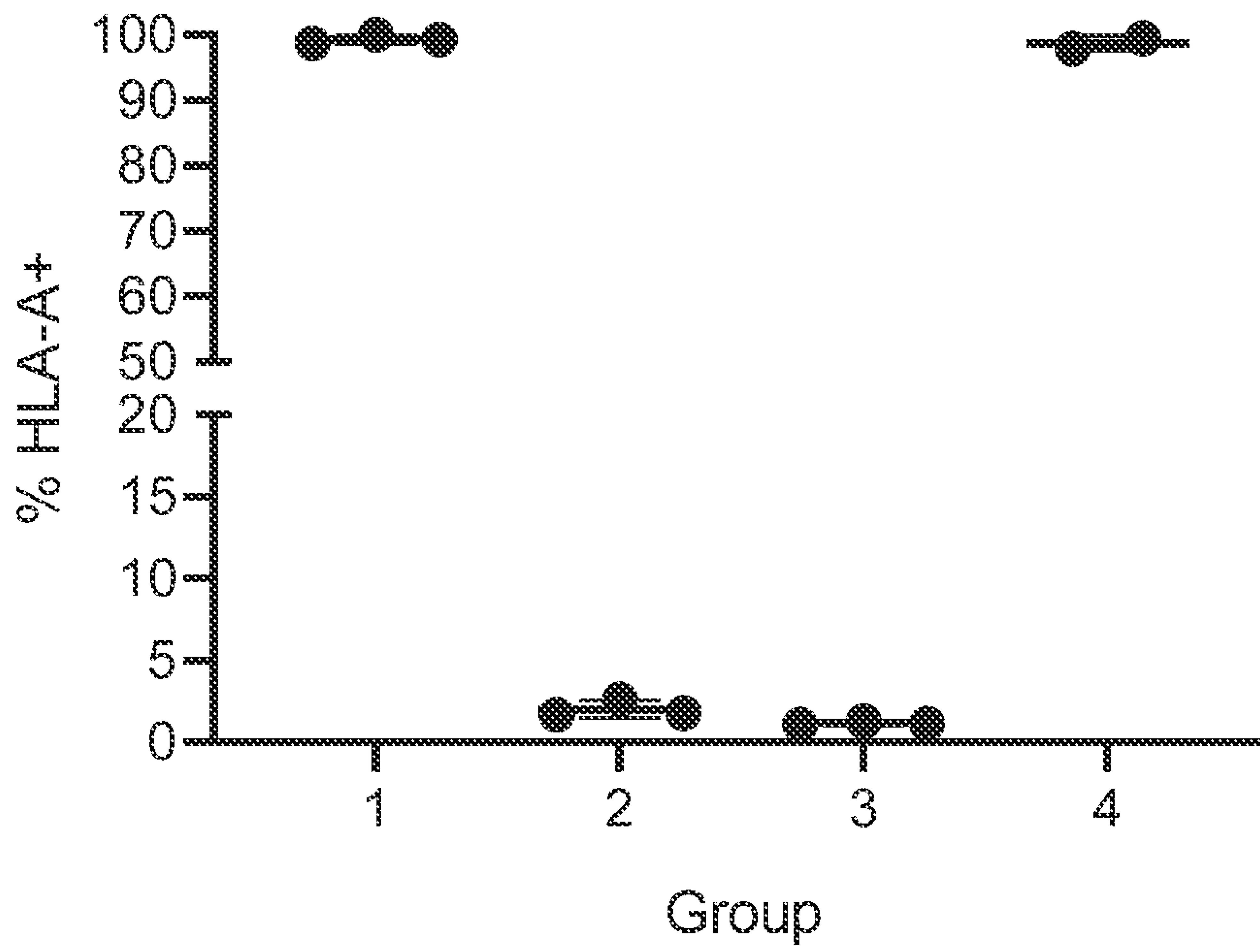


FIG. 4A

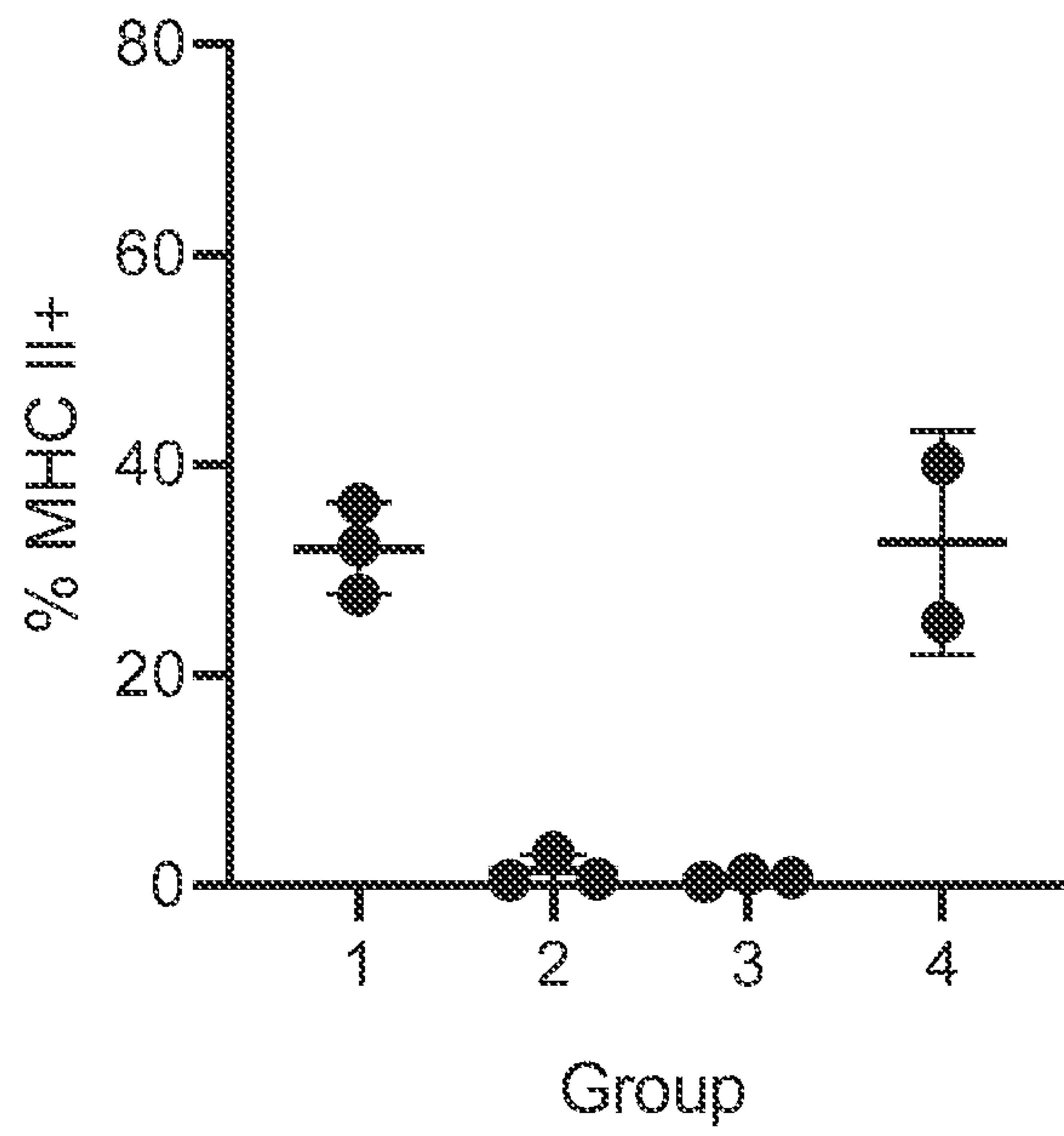


FIG. 4B

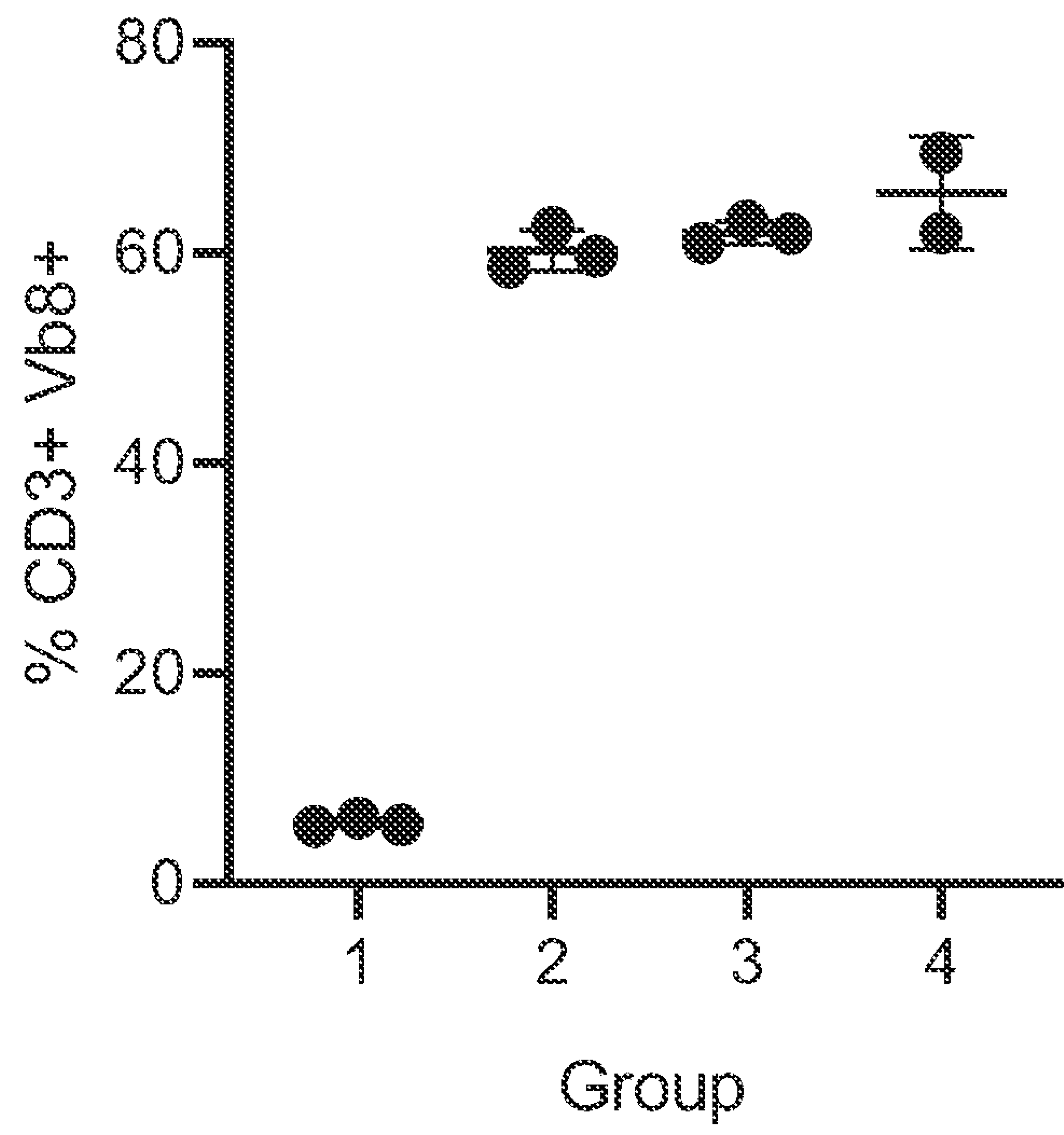


FIG. 4C

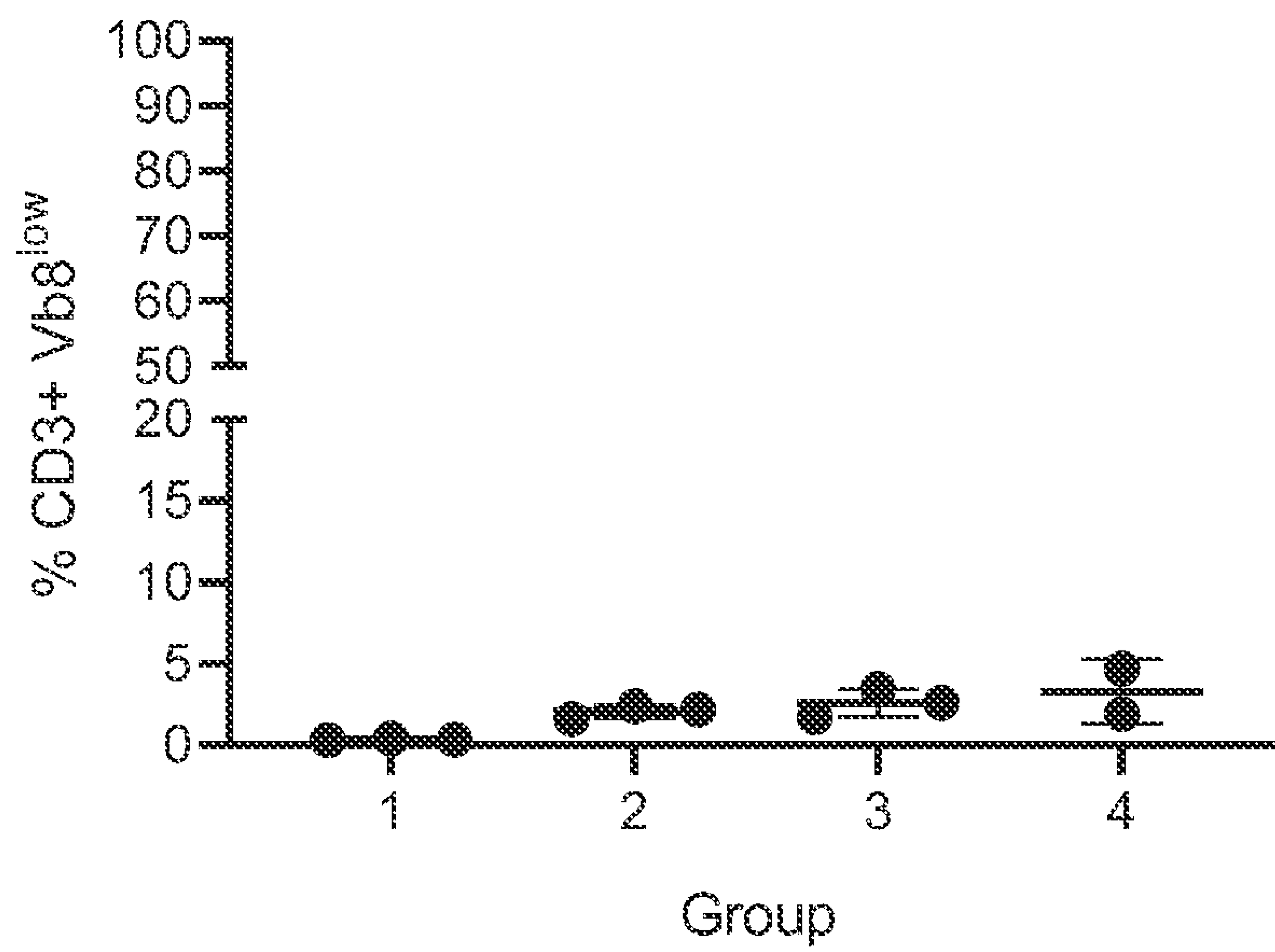


FIG. 4D

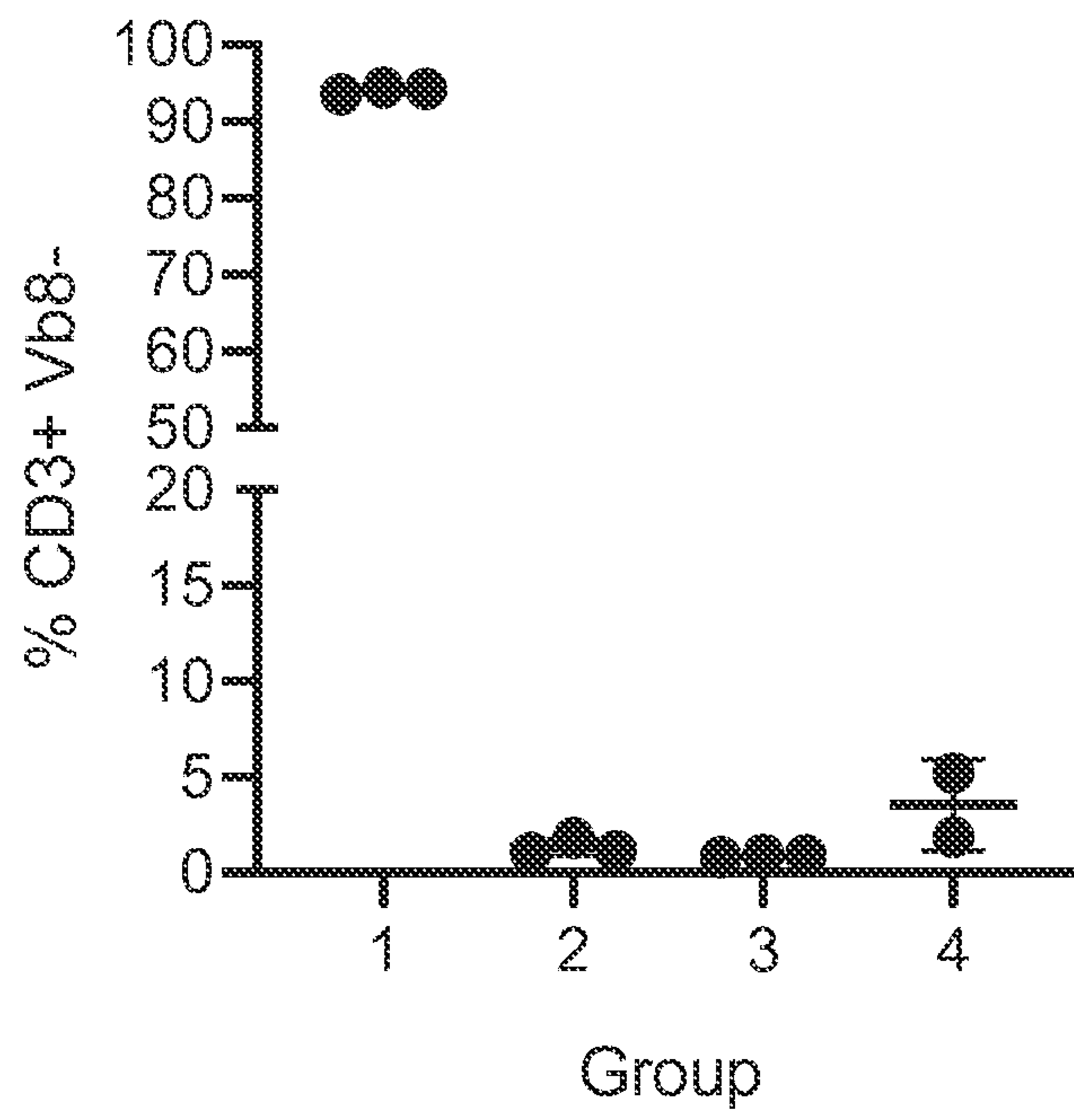


FIG. 4E

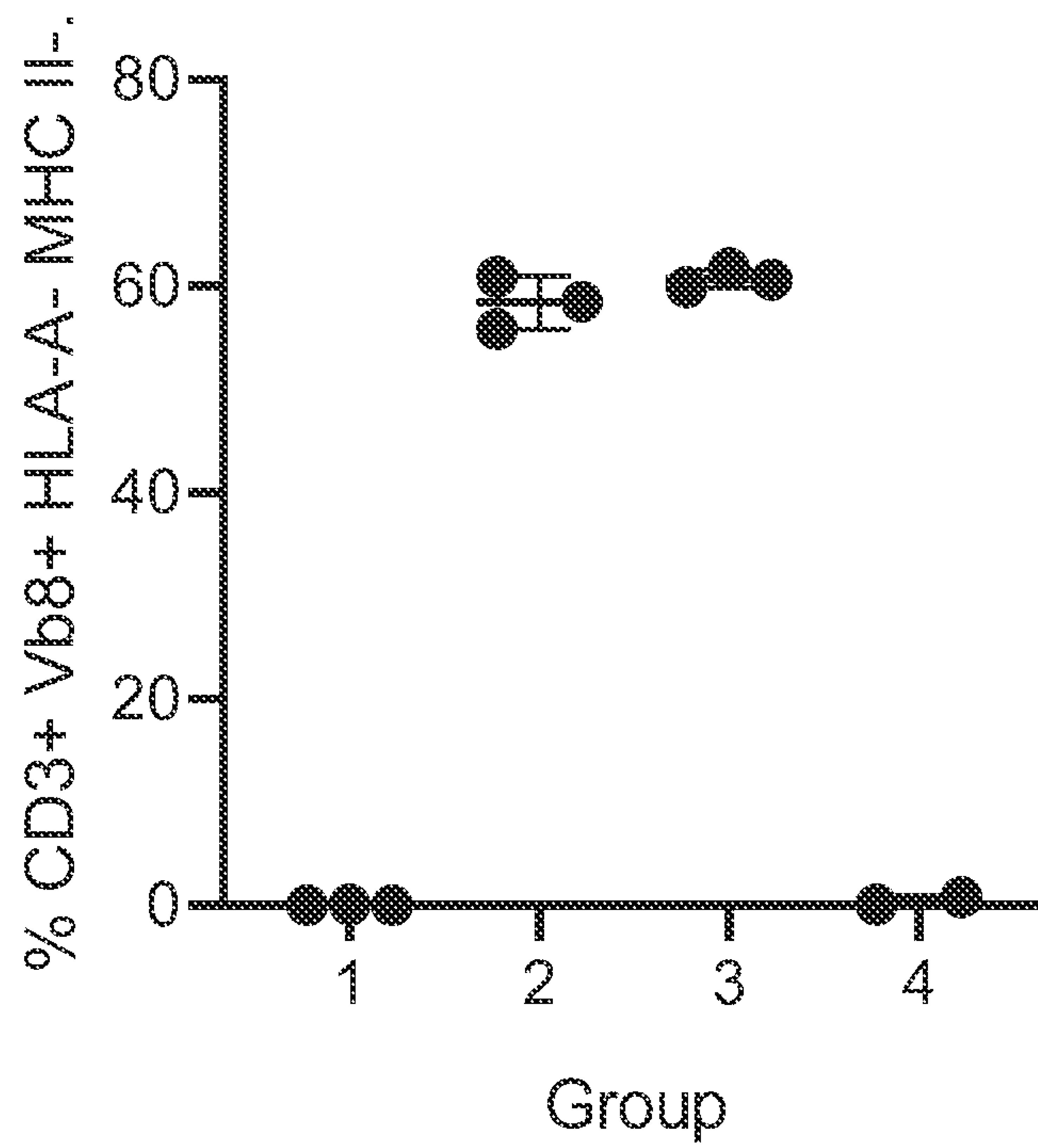


FIG. 4F

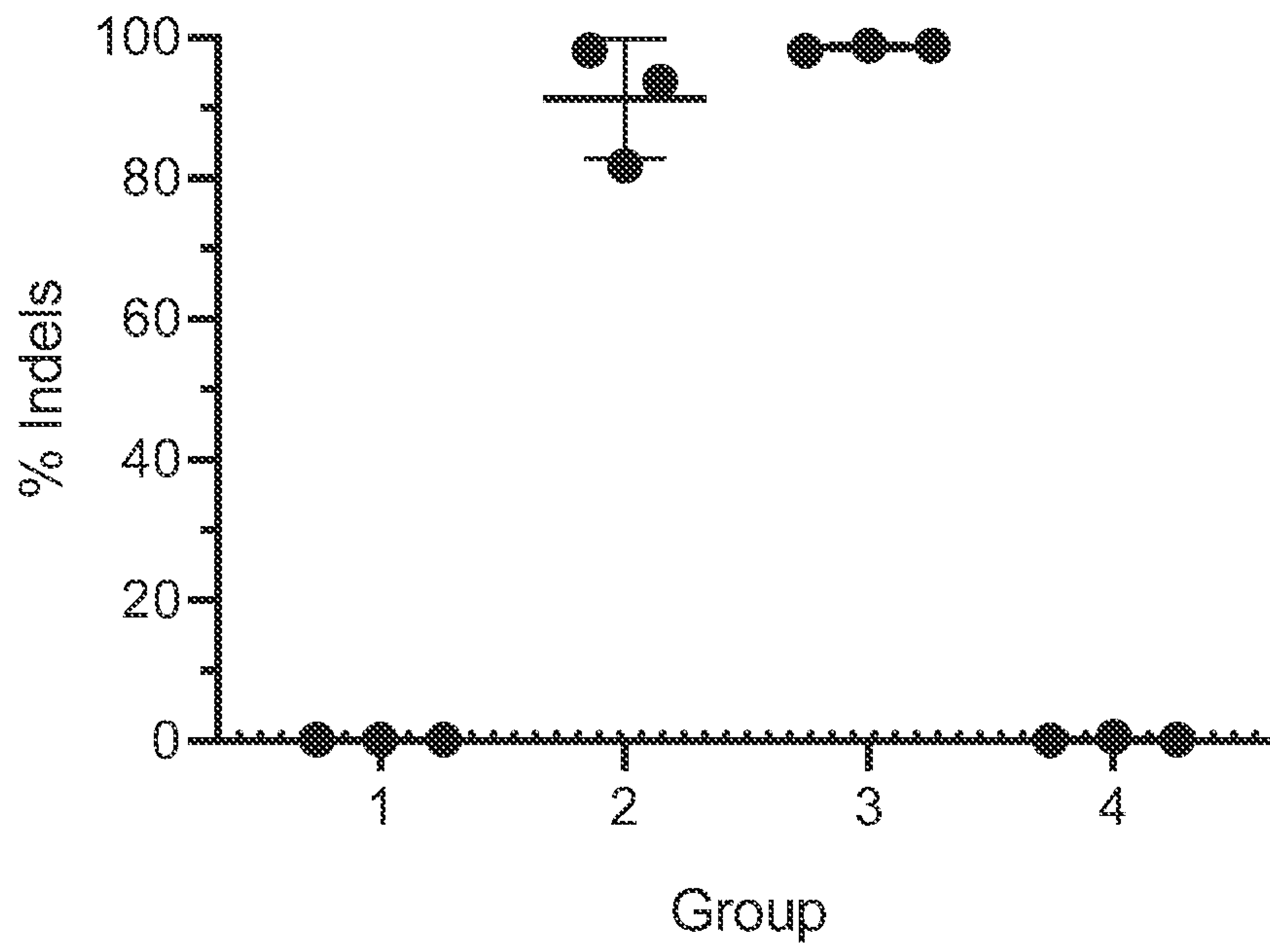


FIG. 5A

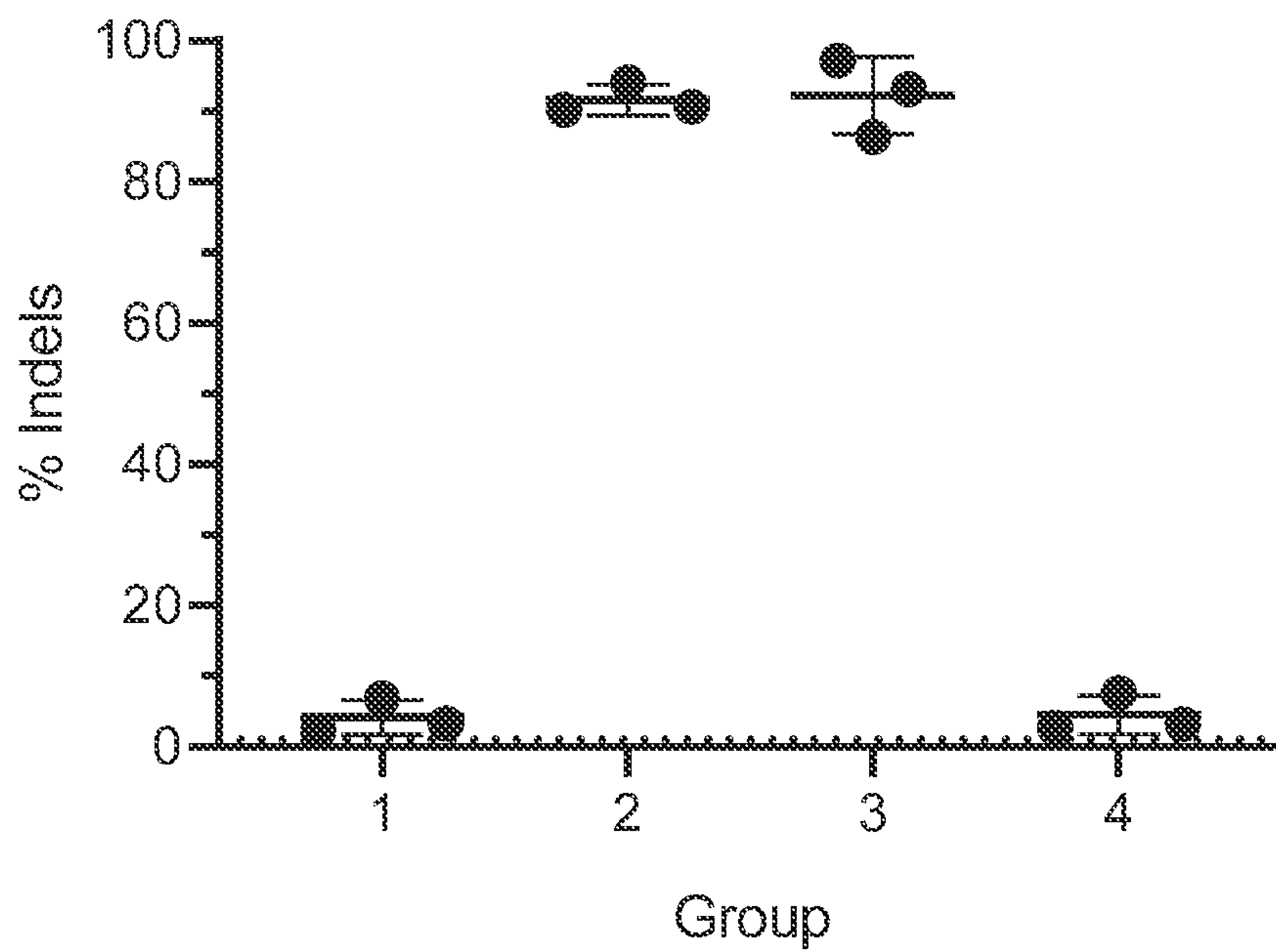


FIG. 5B

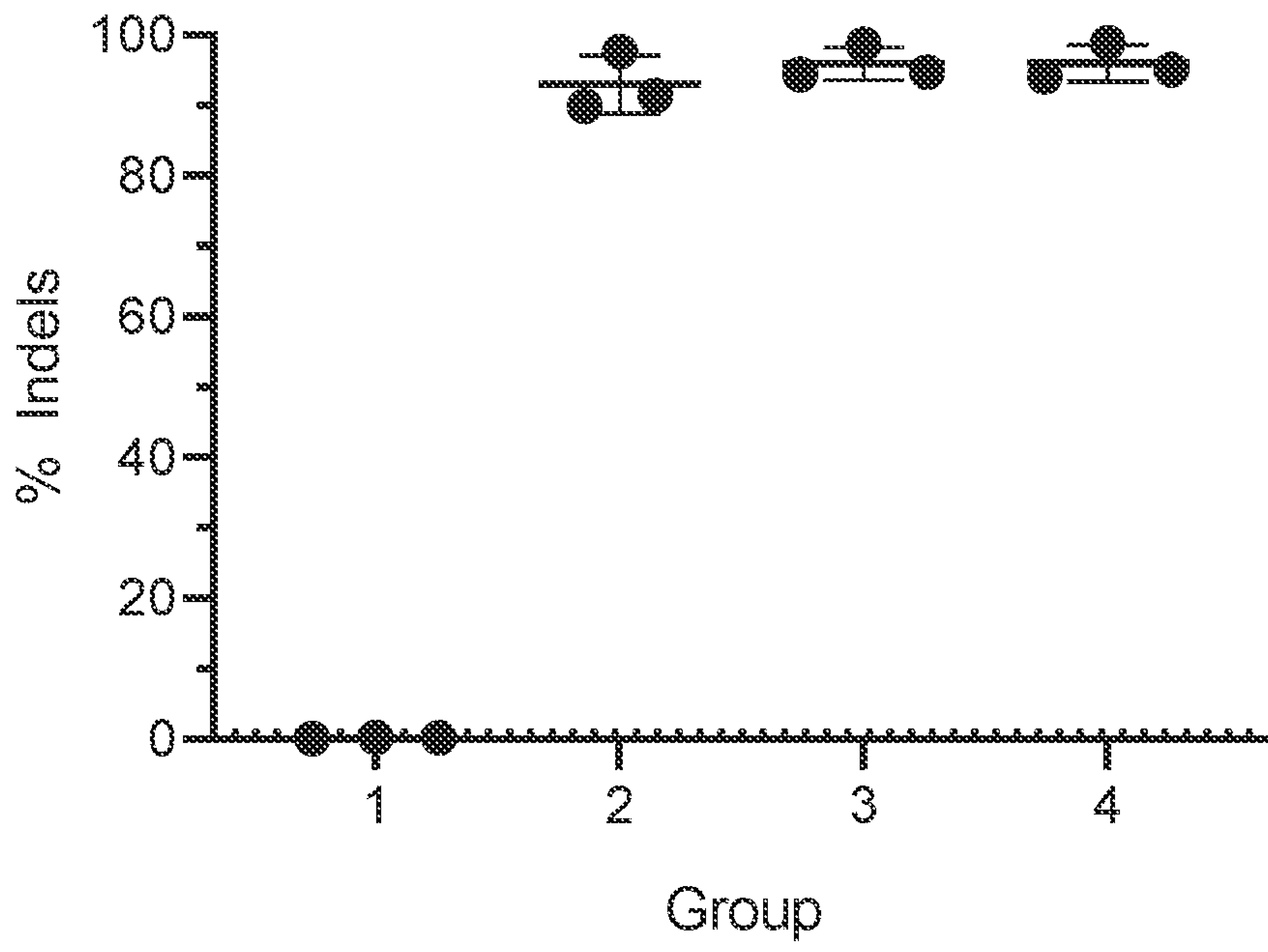


FIG. 5C

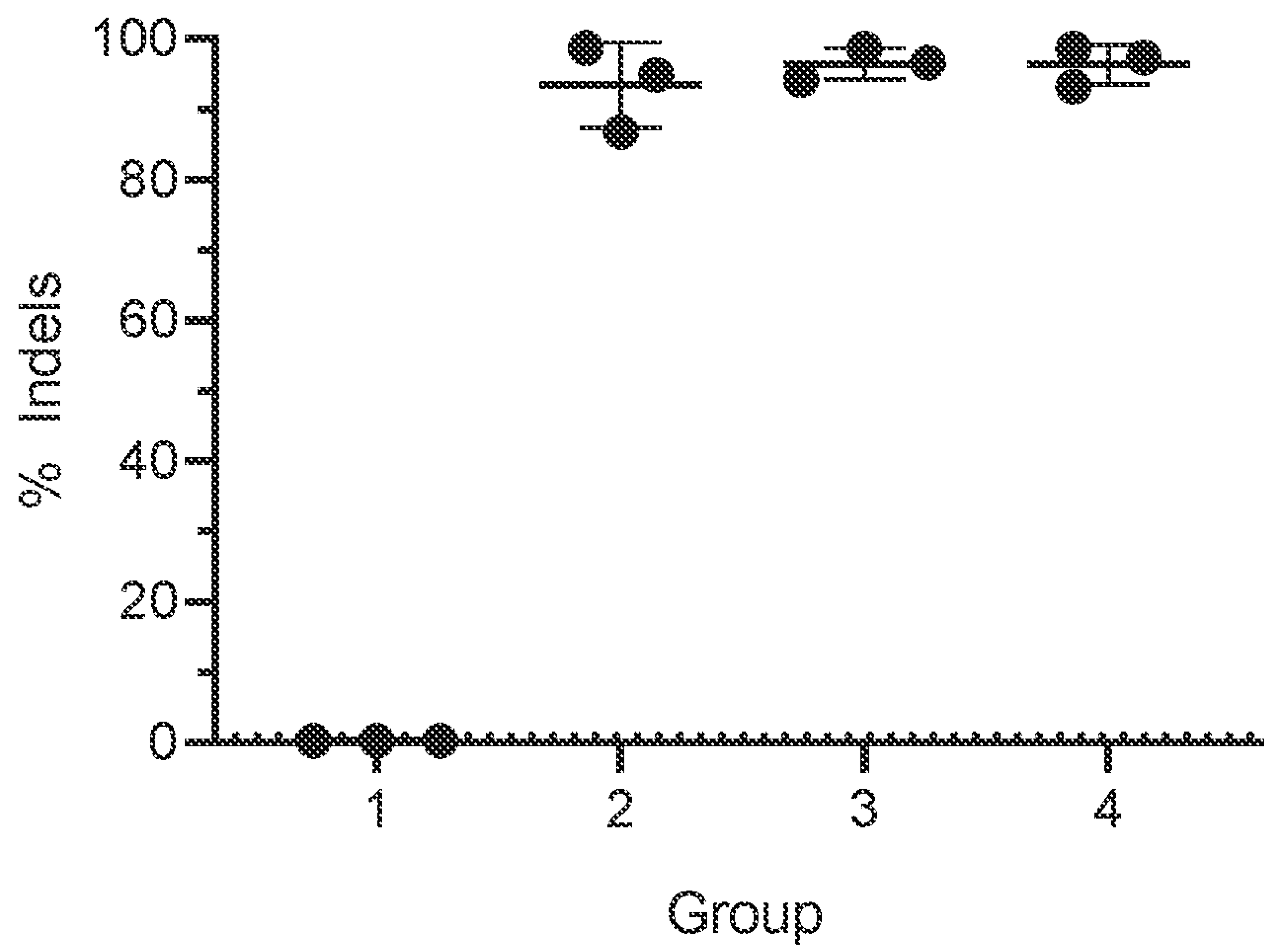


FIG. 5D

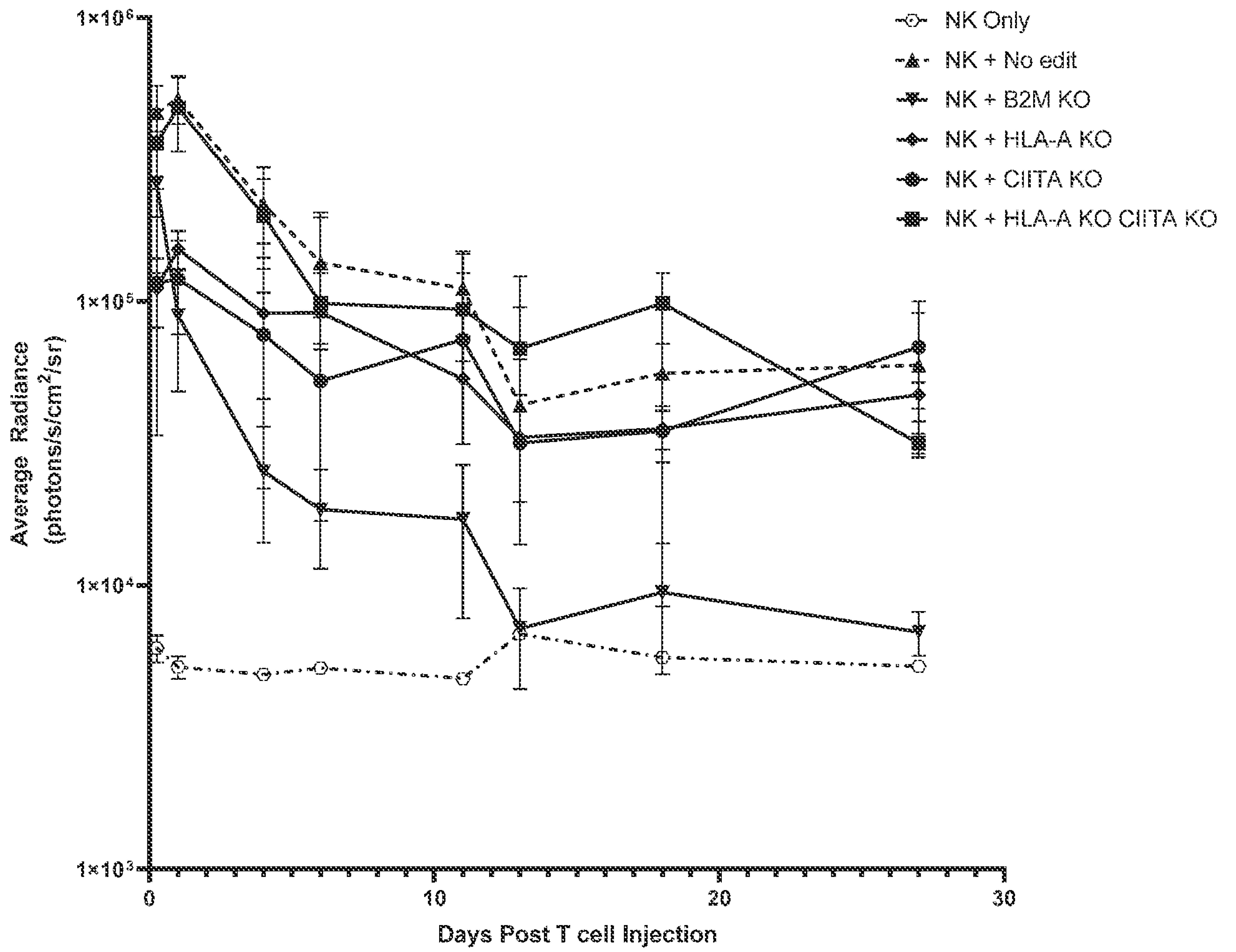


FIG. 6A

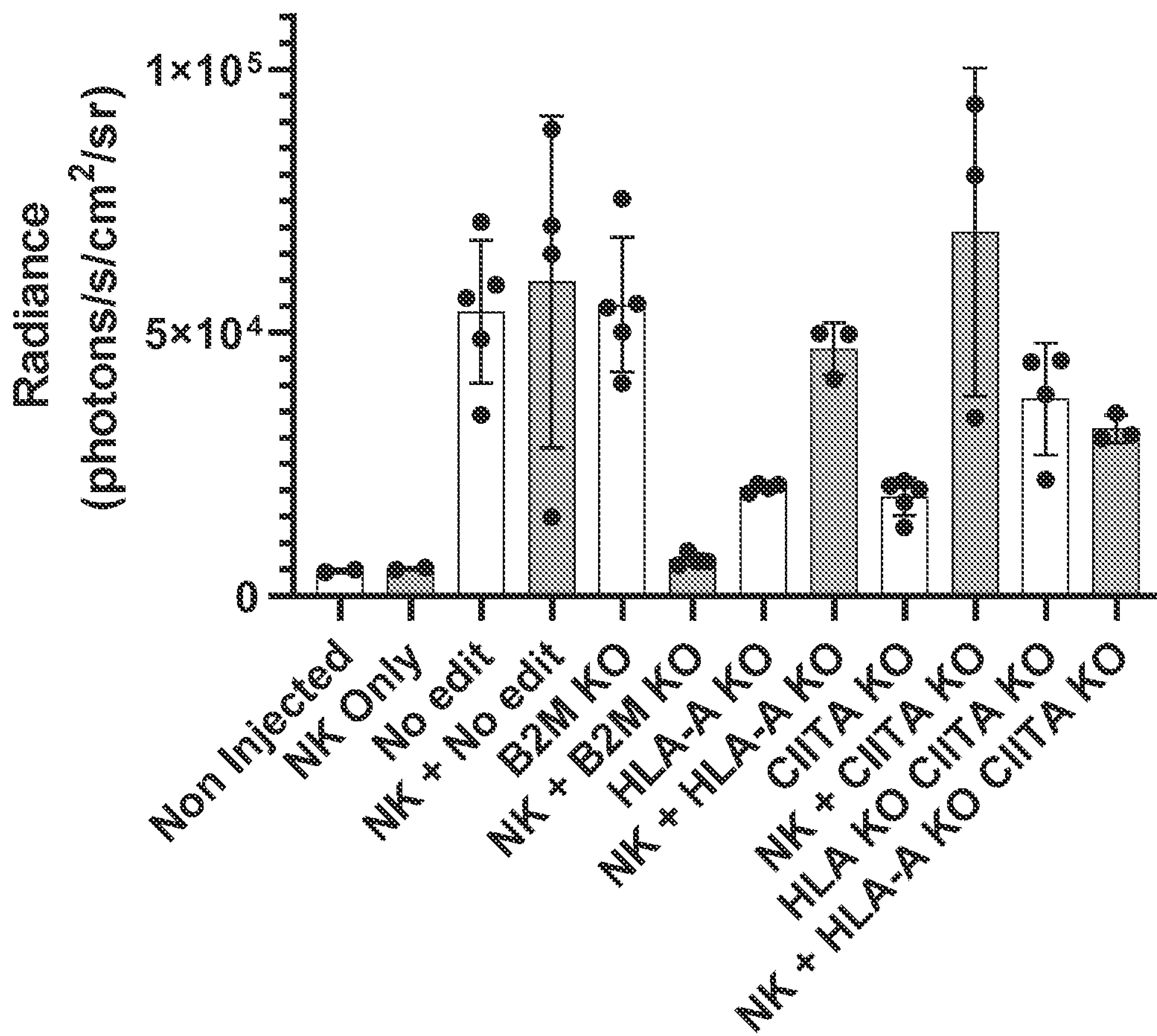


FIG. 6B

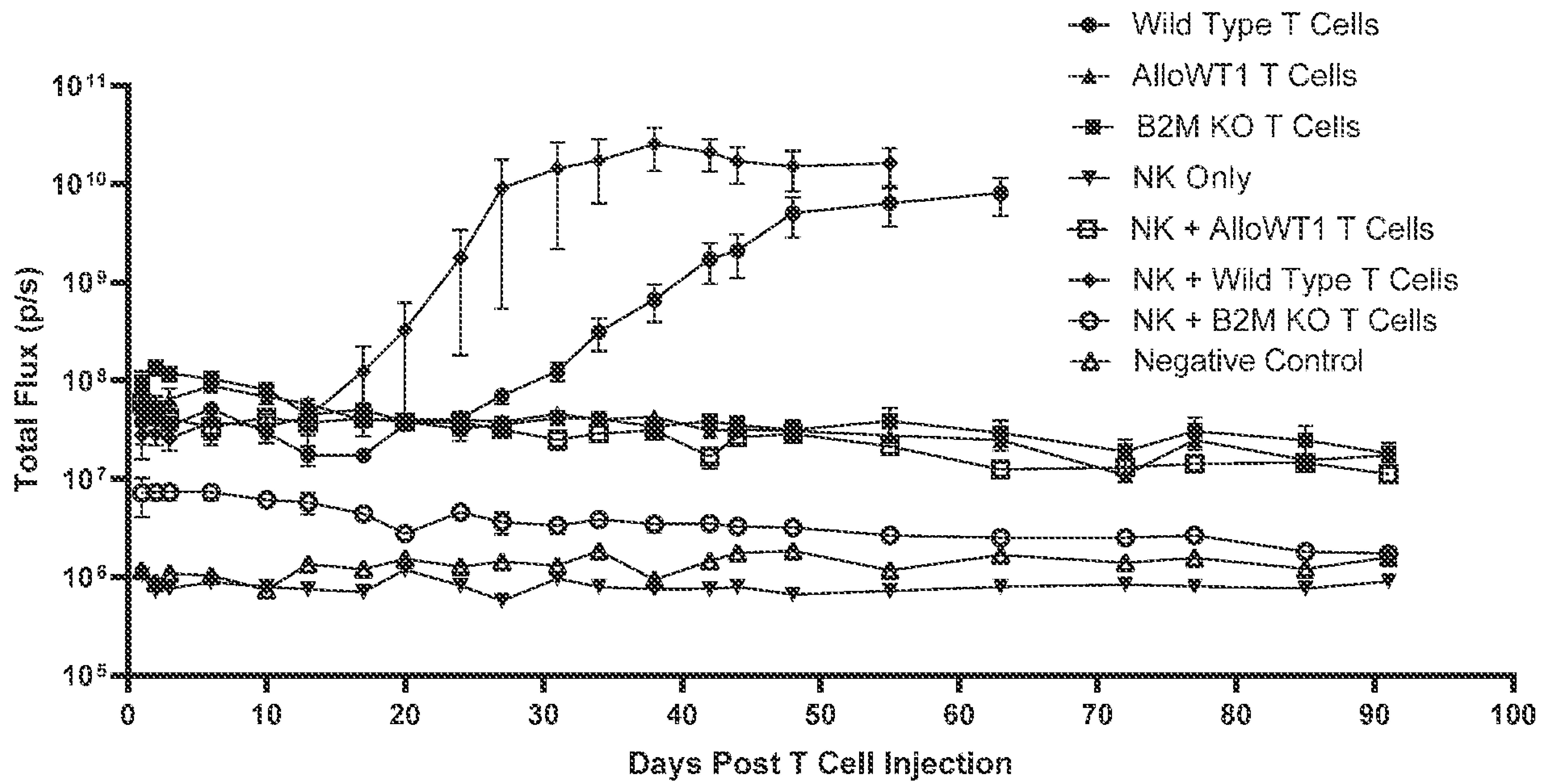


FIG. 7A

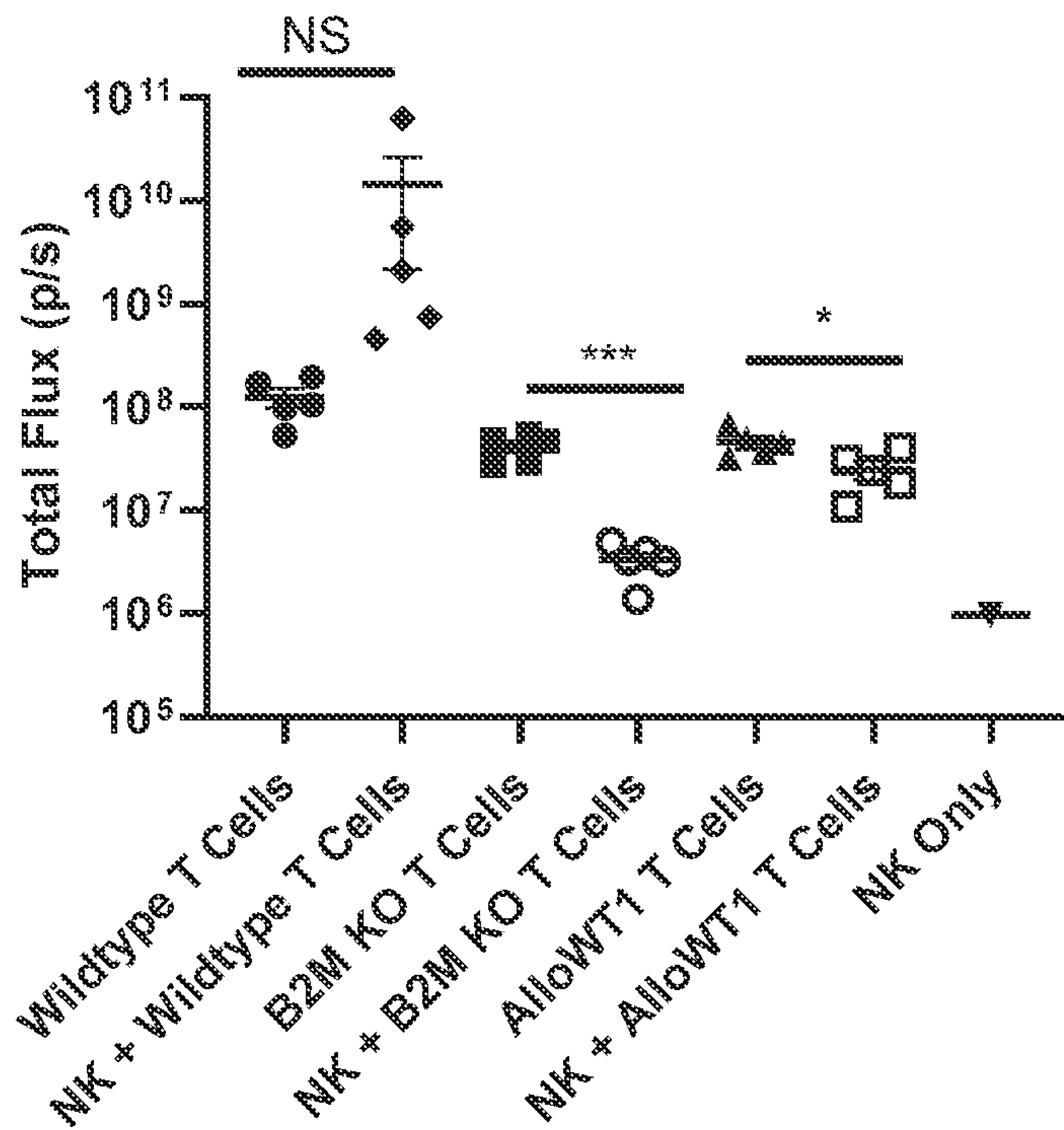


FIG. 7B

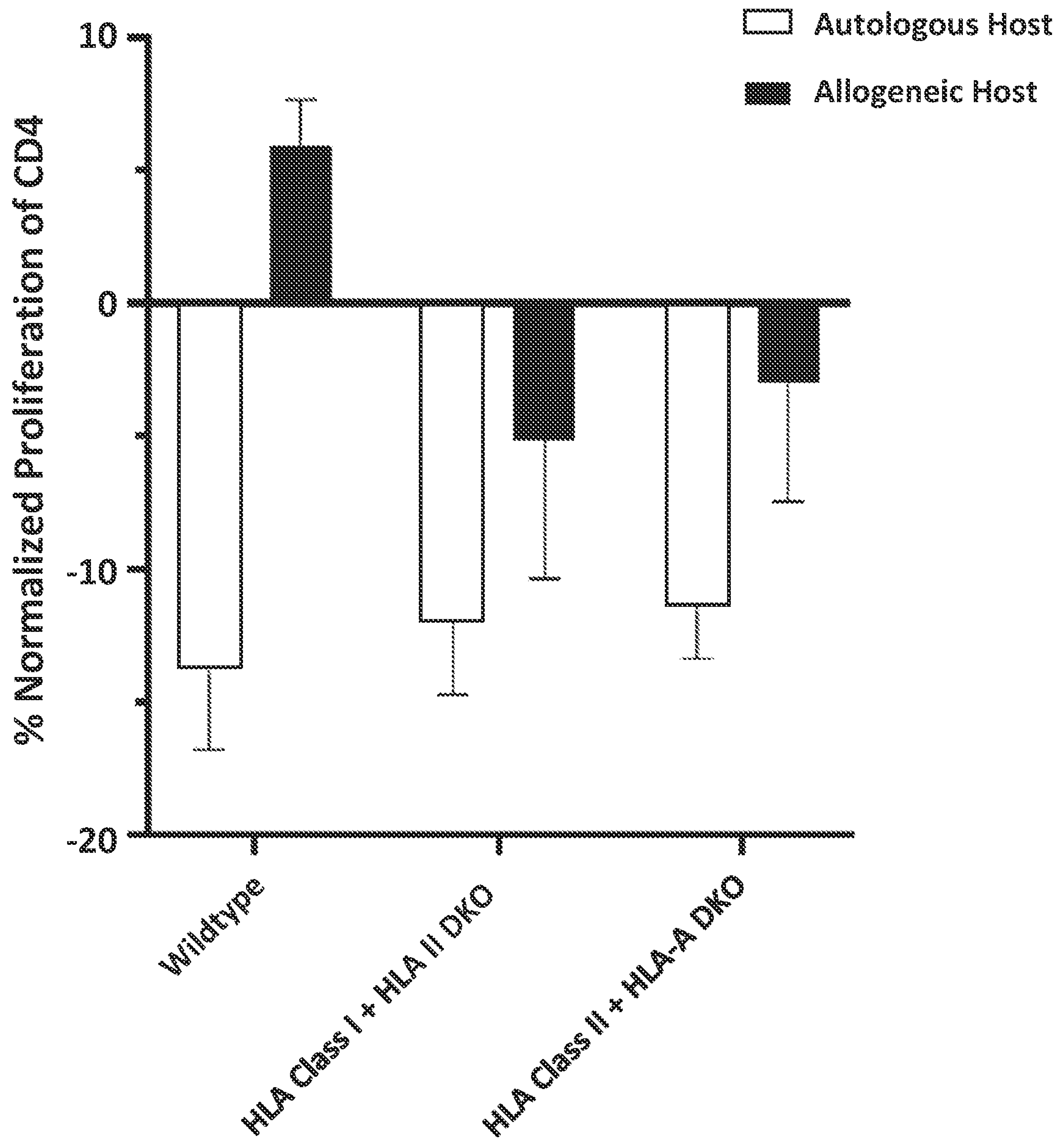


FIG. 8A

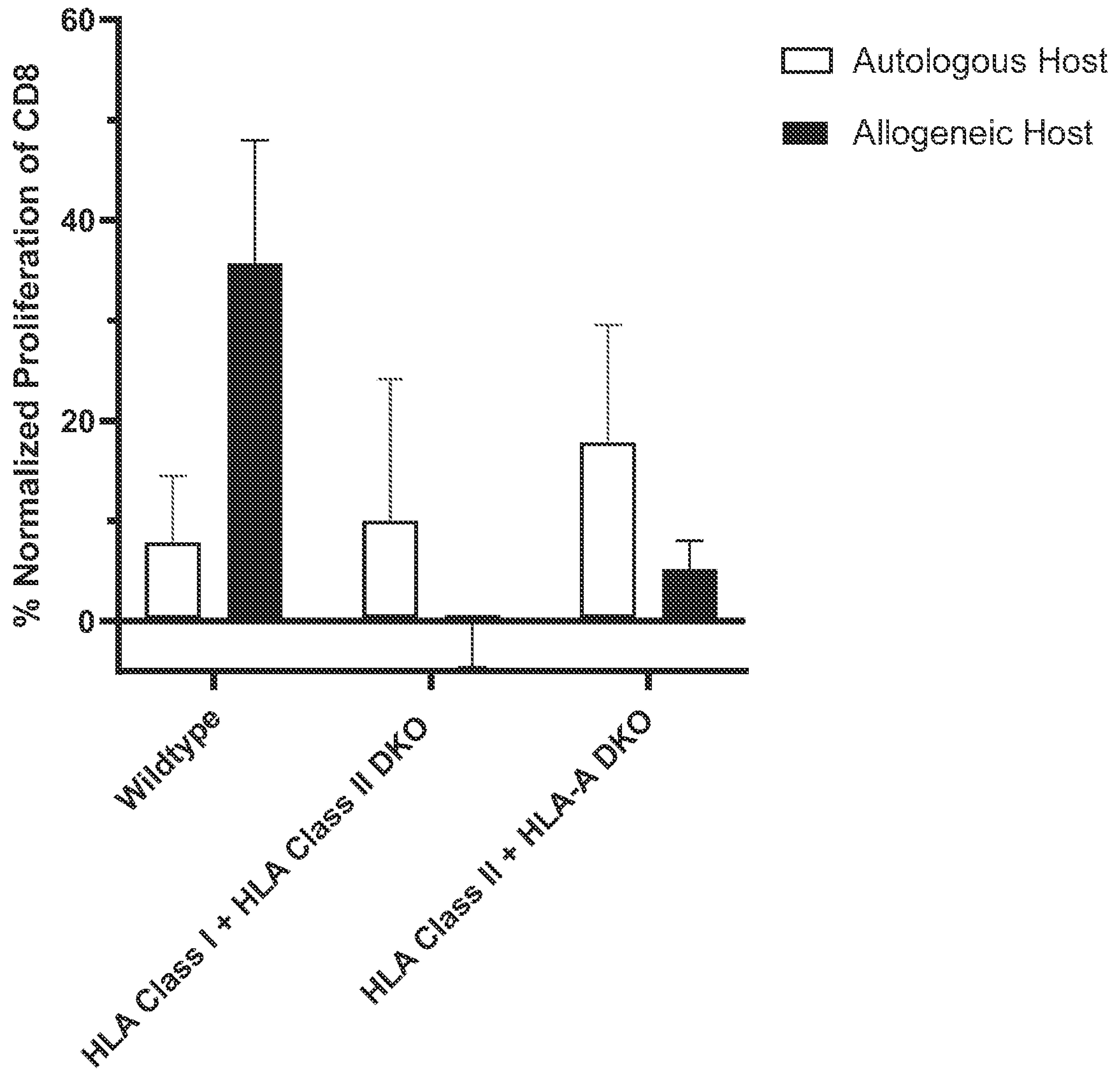


FIG. 8B

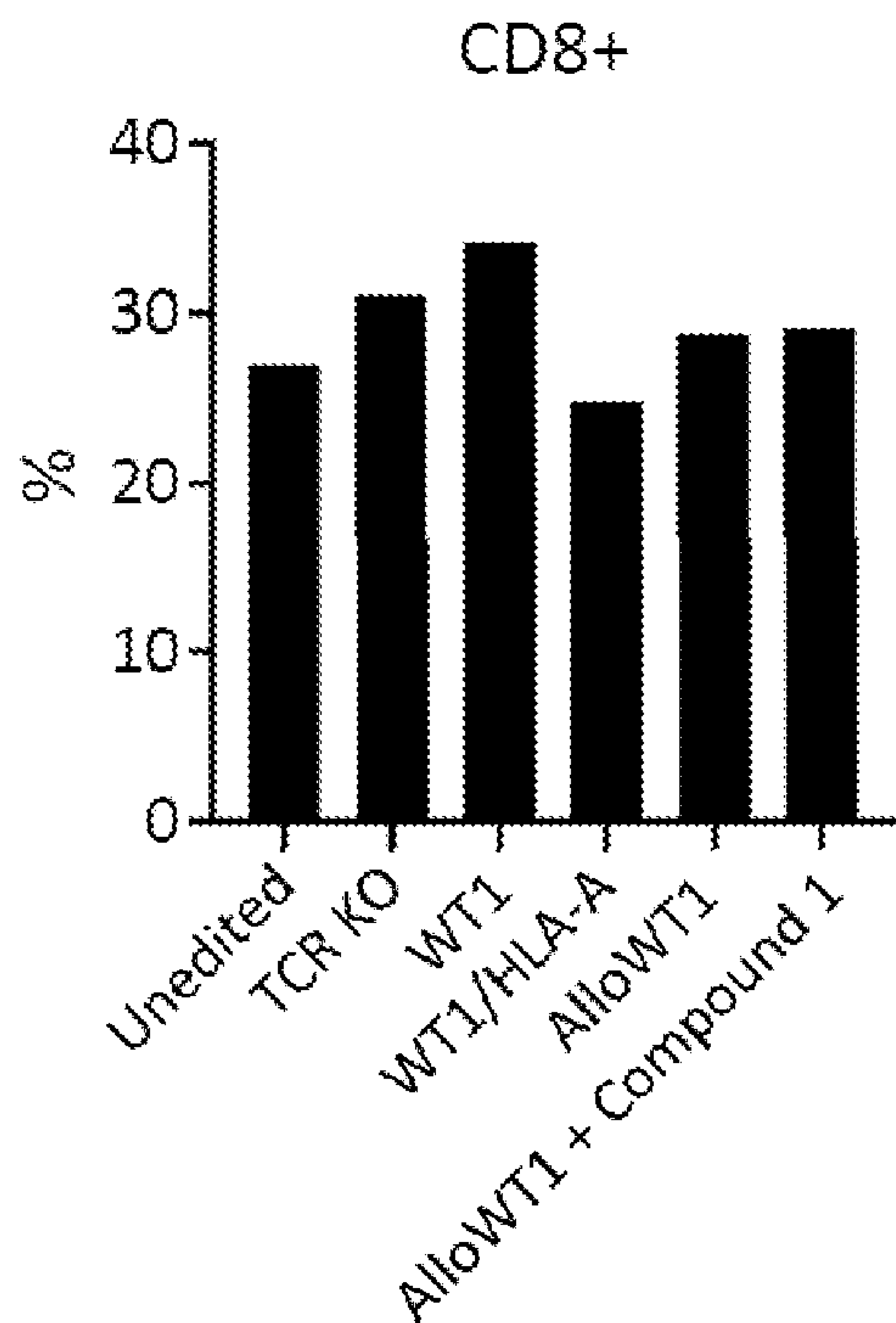


FIG. 9A

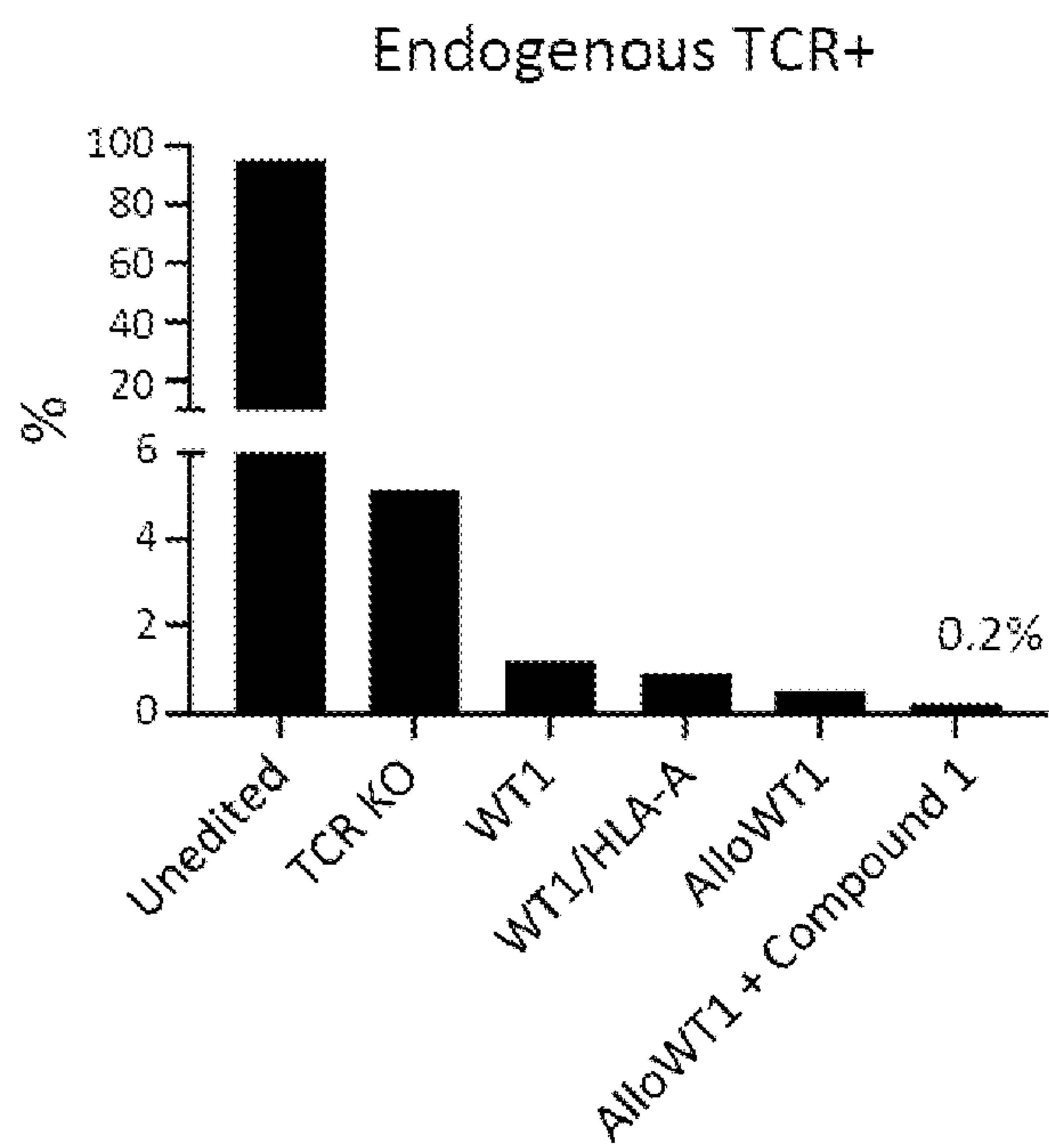


FIG. 9B

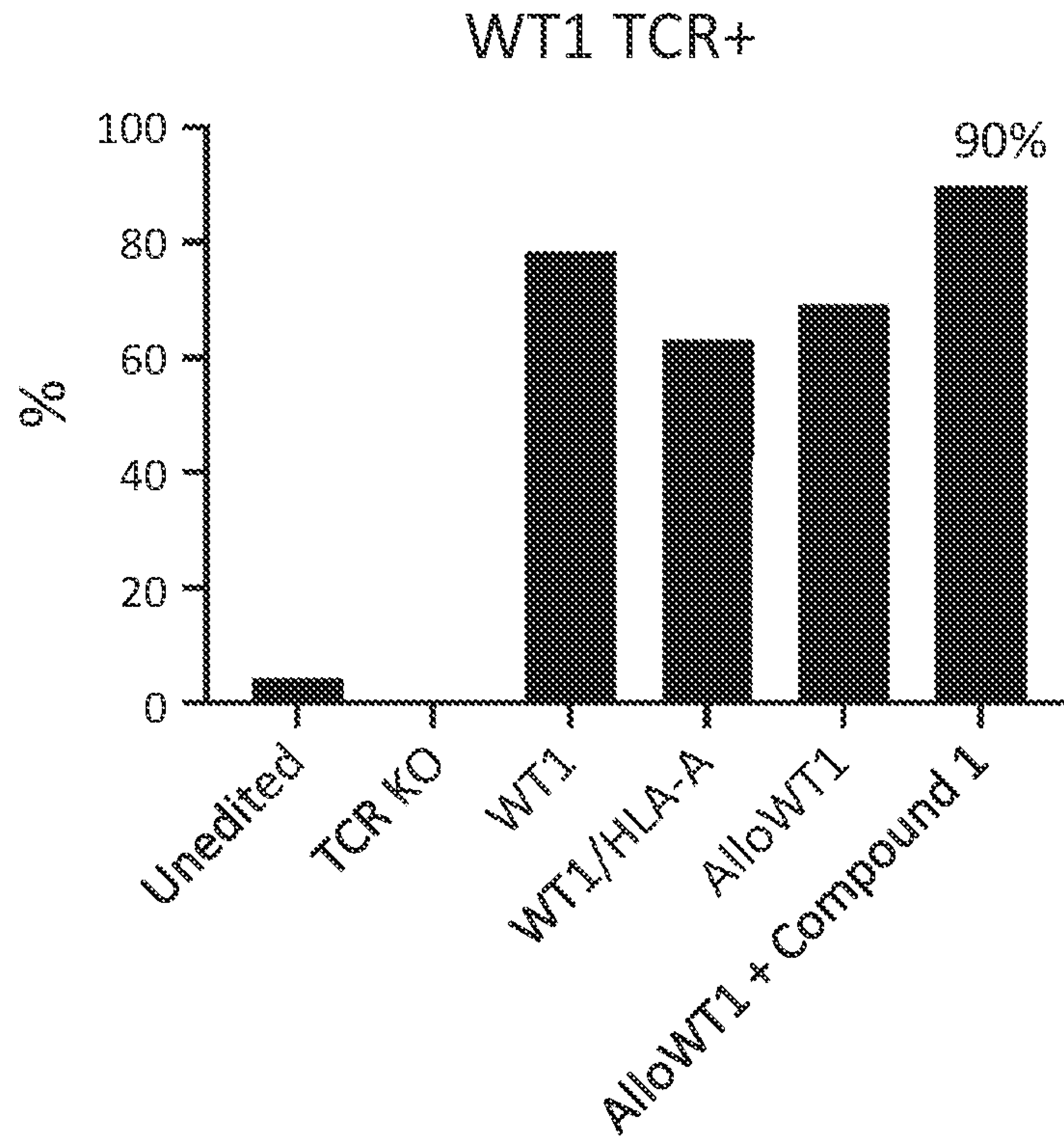


FIG. 9C

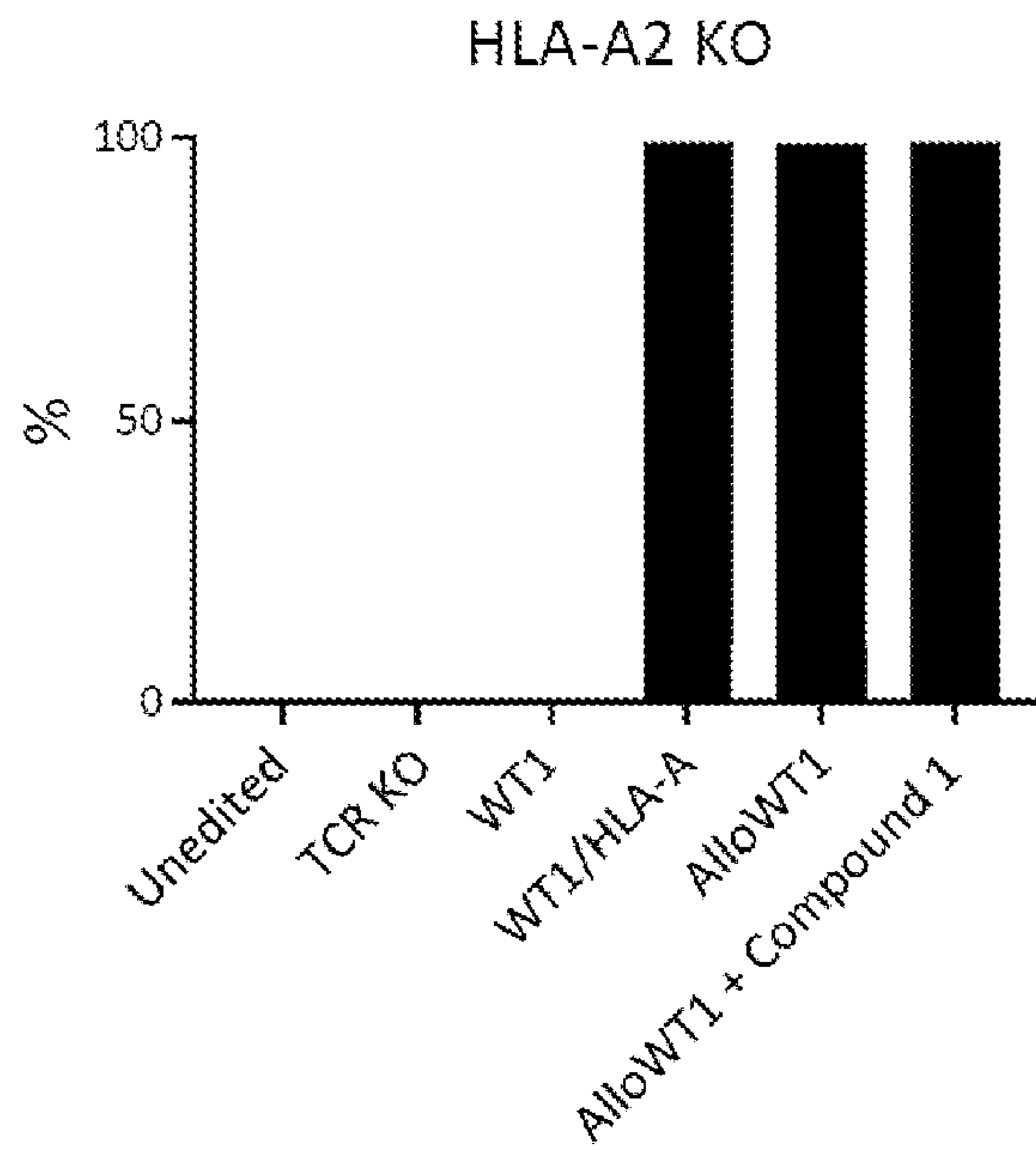


FIG. 9D

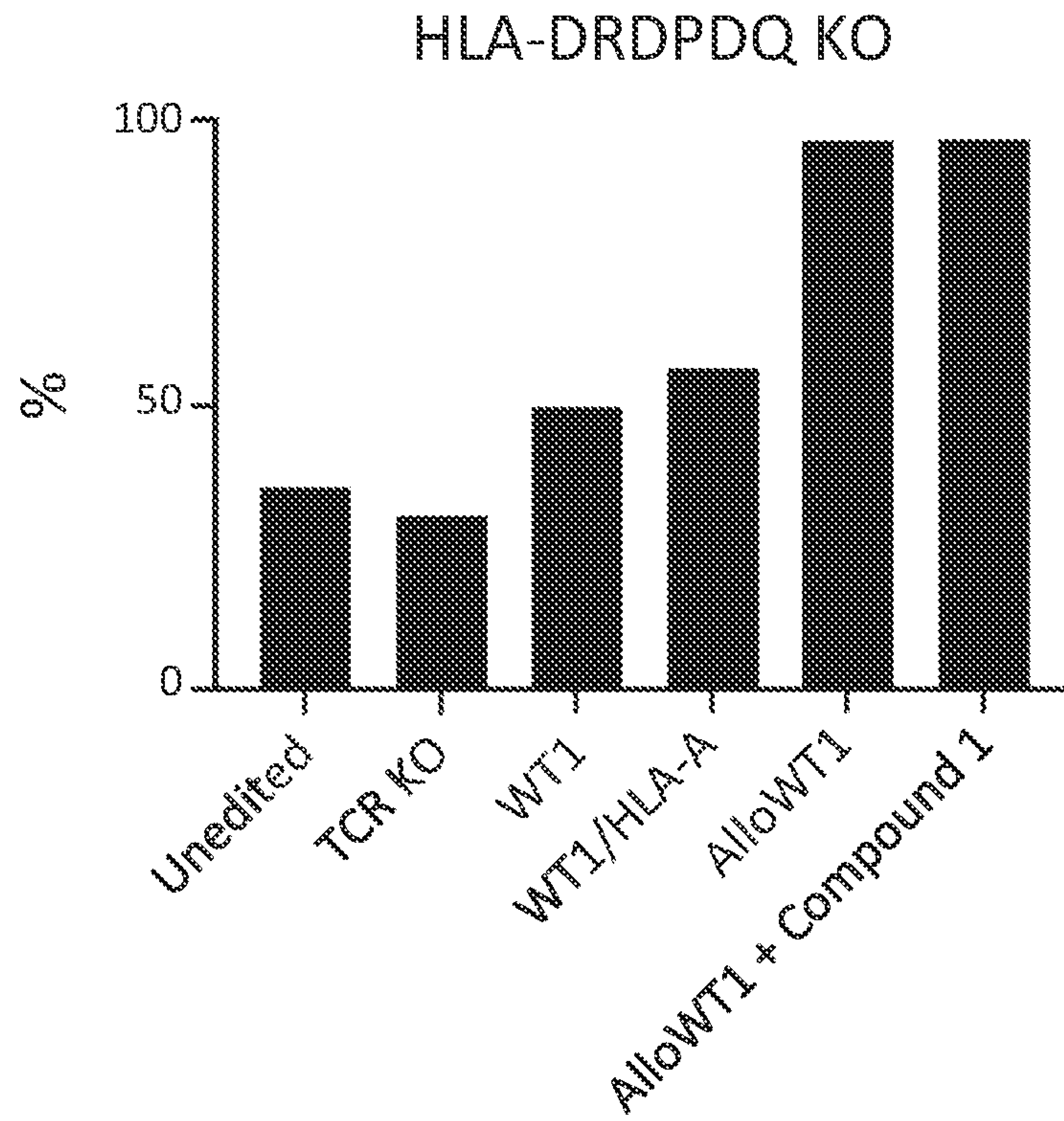


FIG. 9E

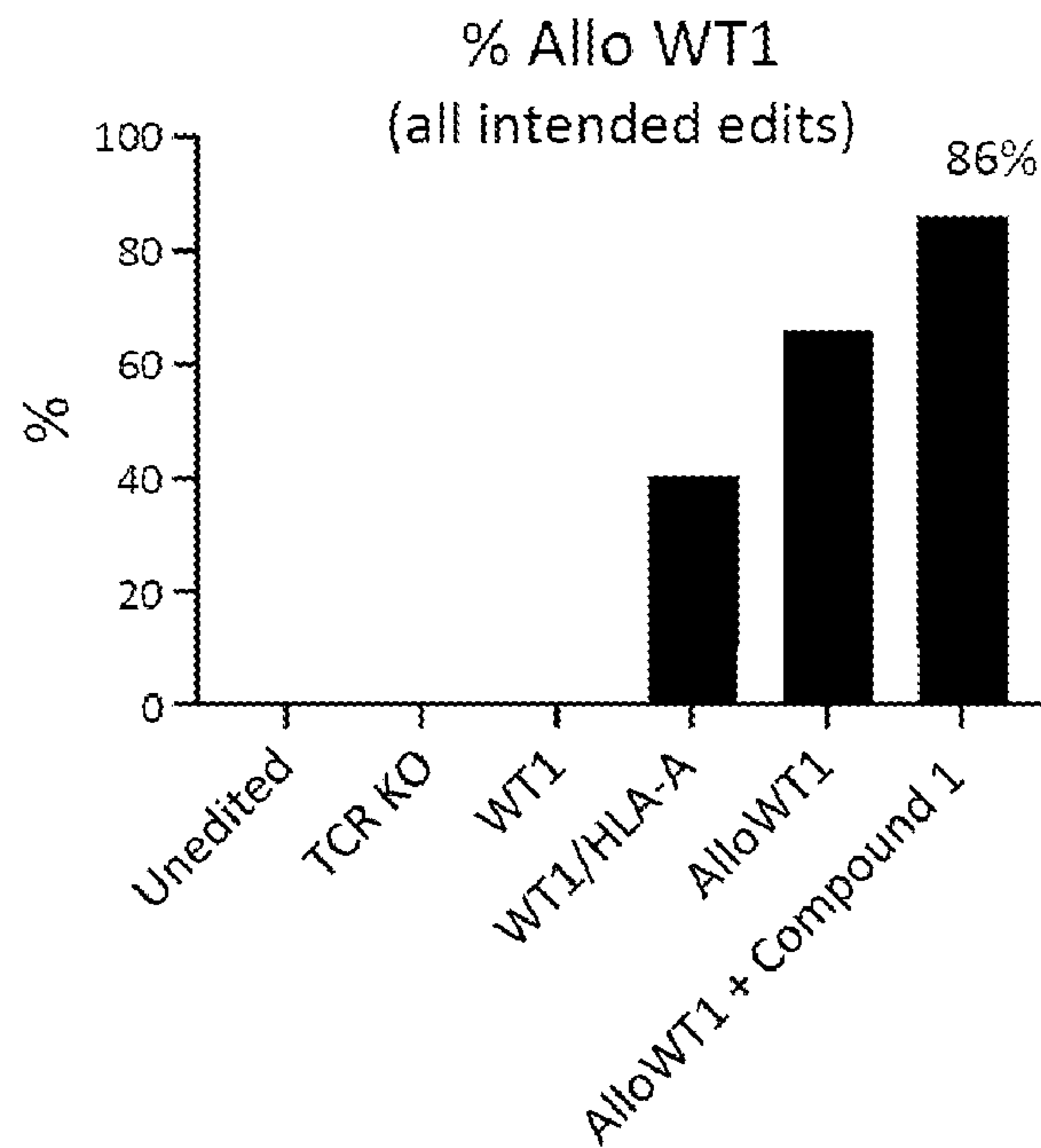


FIG. 9F

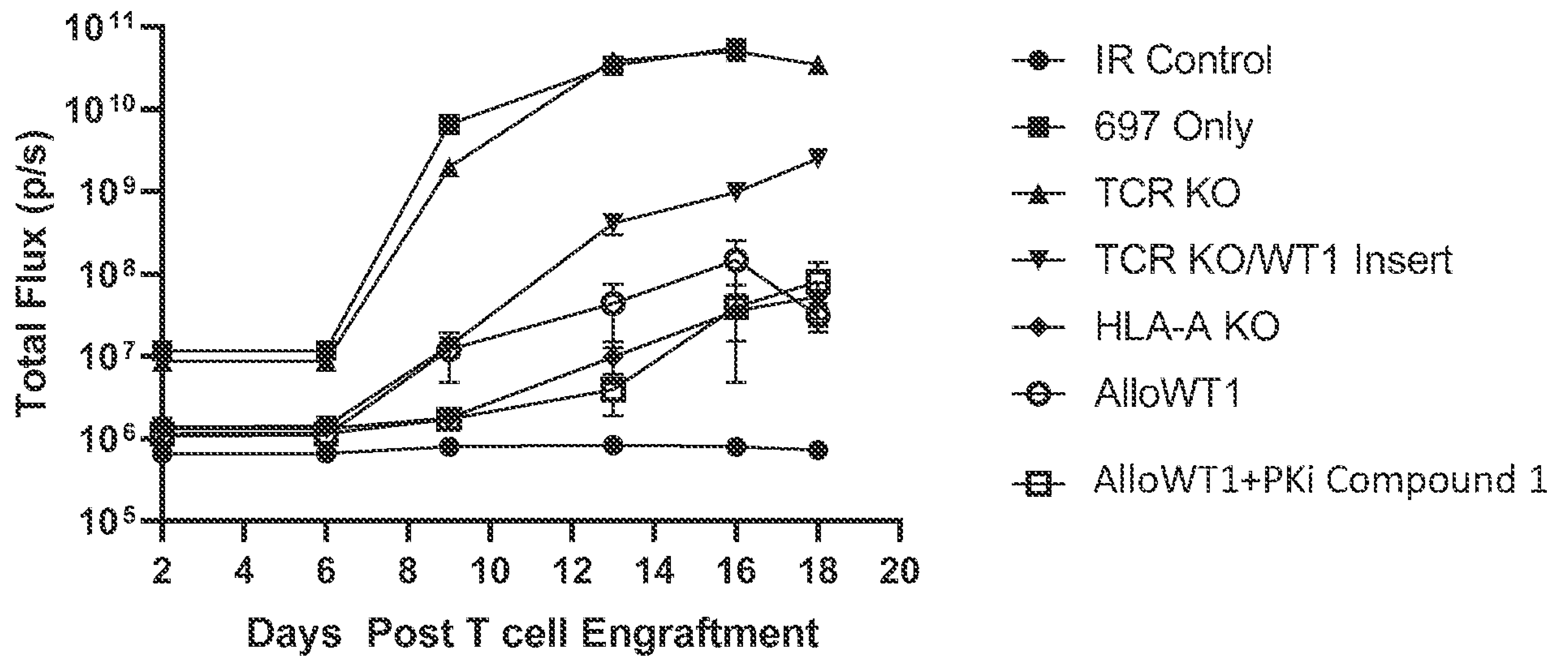


FIG. 10

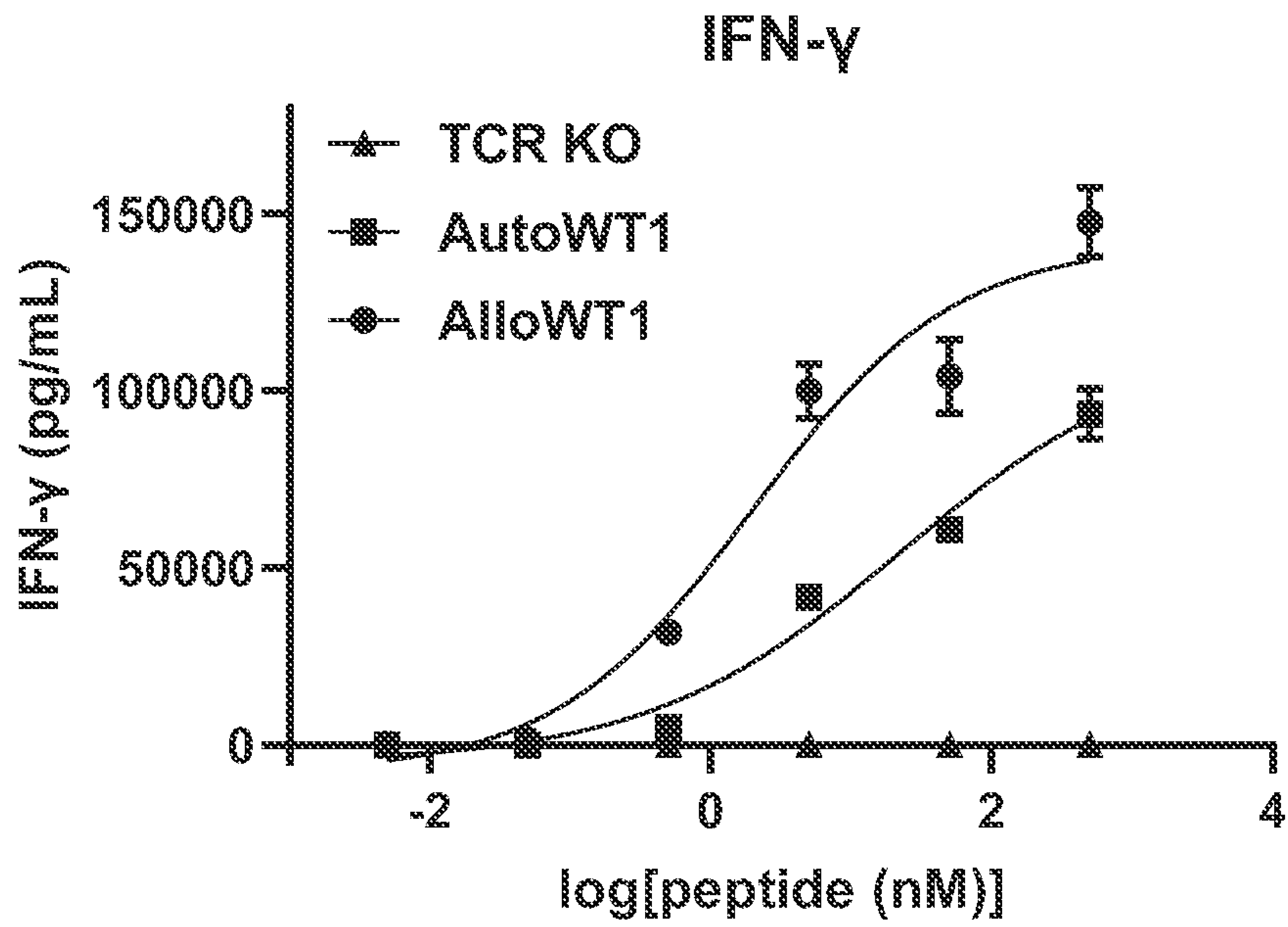


FIG. 11A

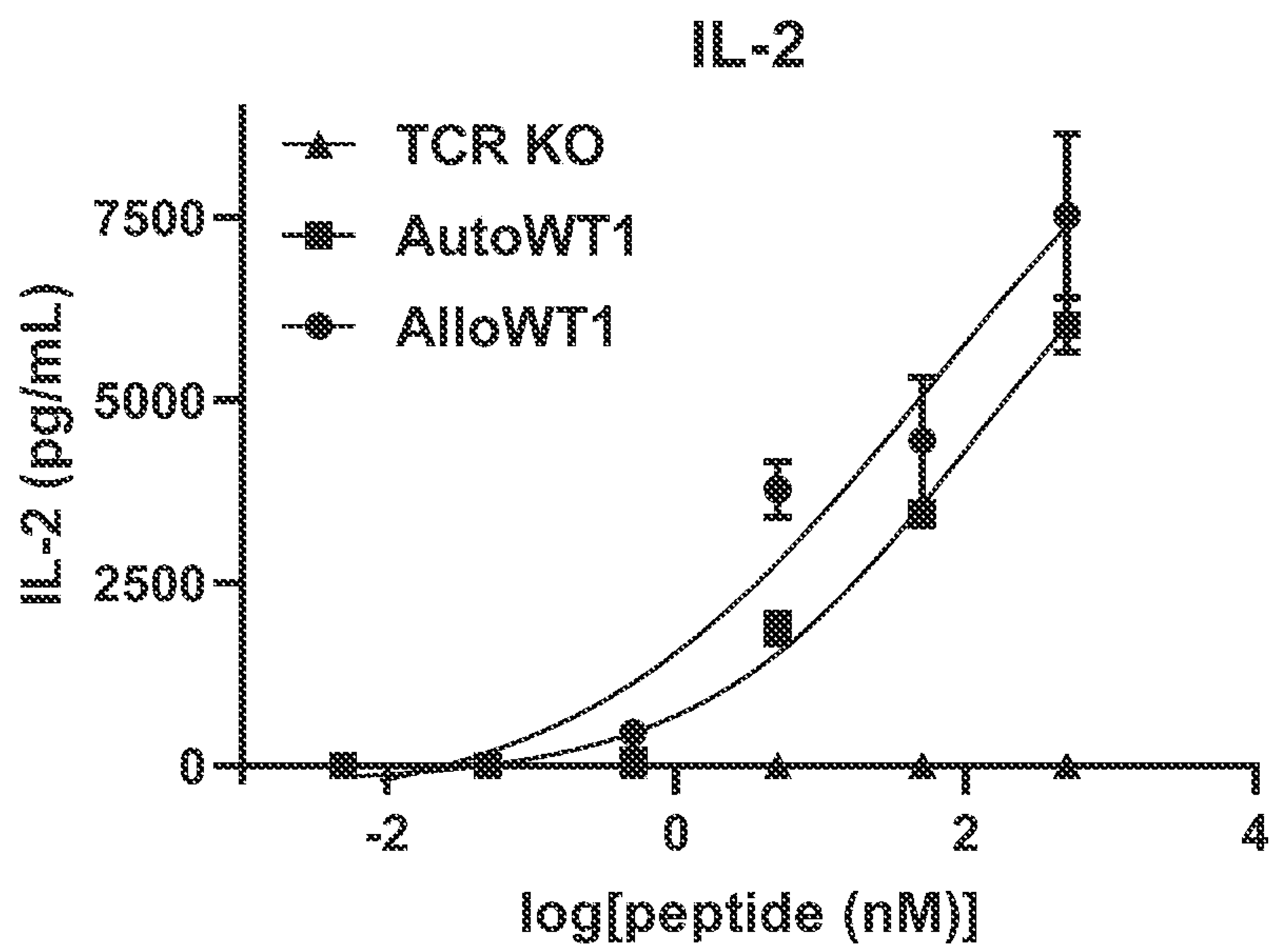


FIG. 11B

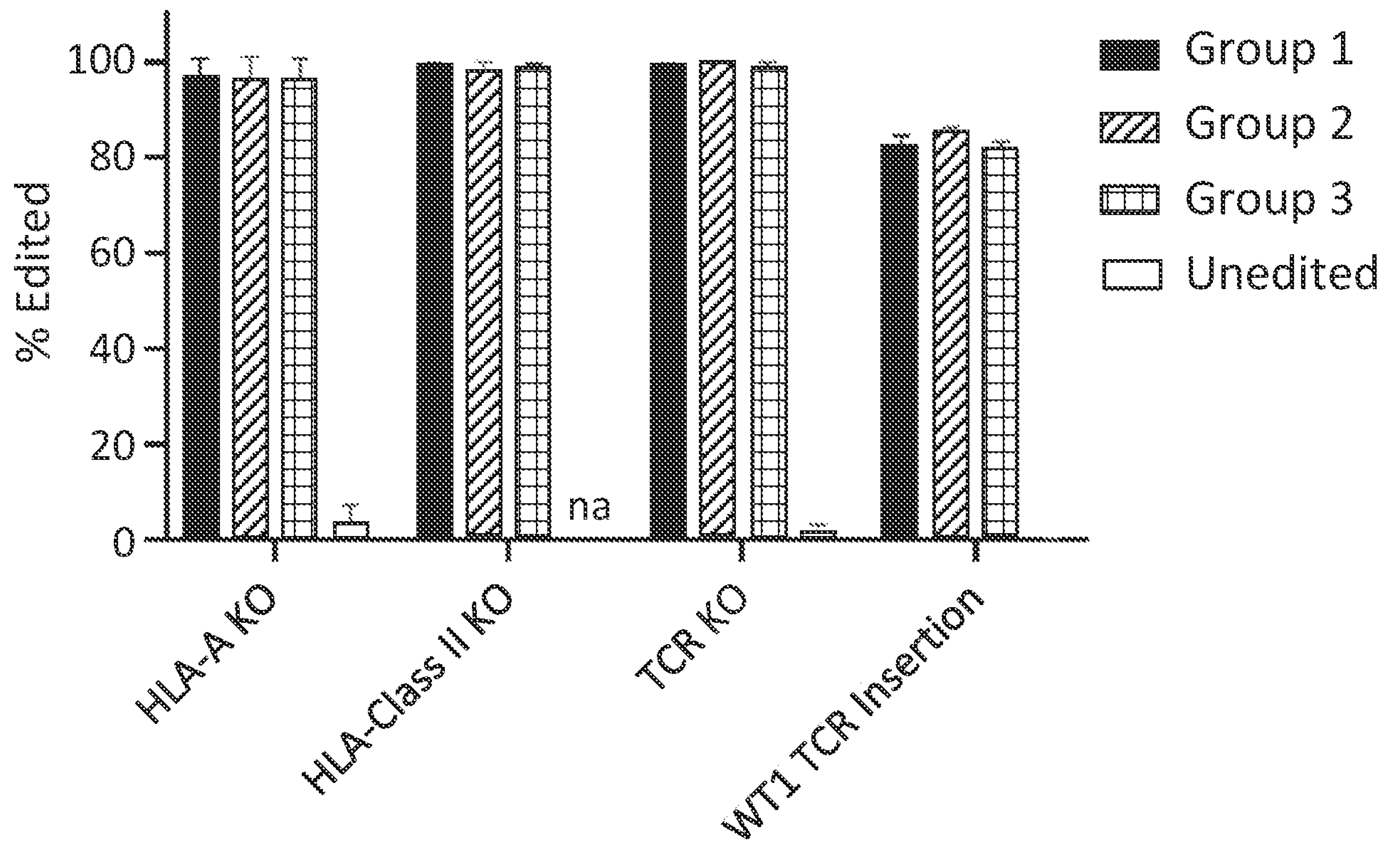


FIG. 12A

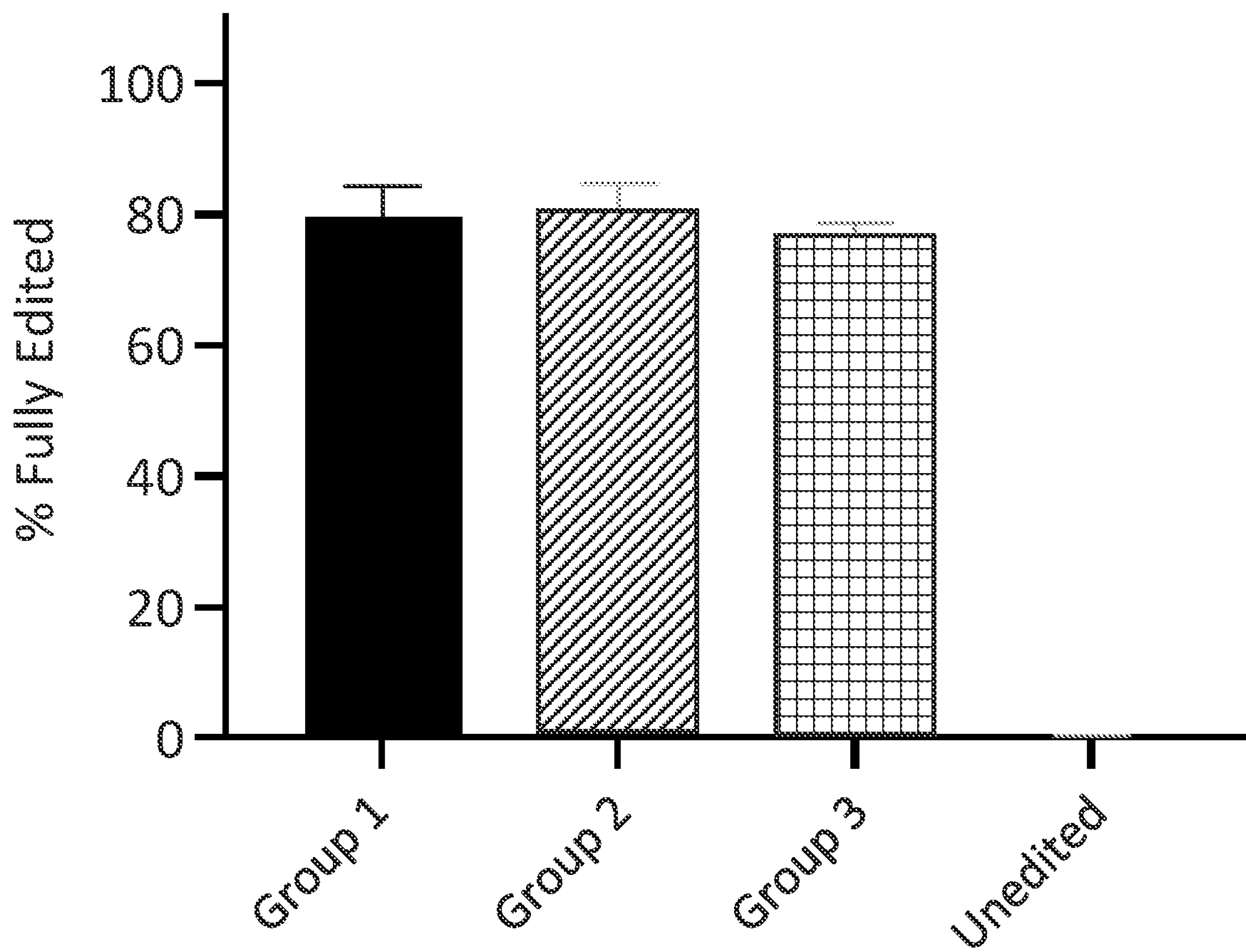


FIG. 12B

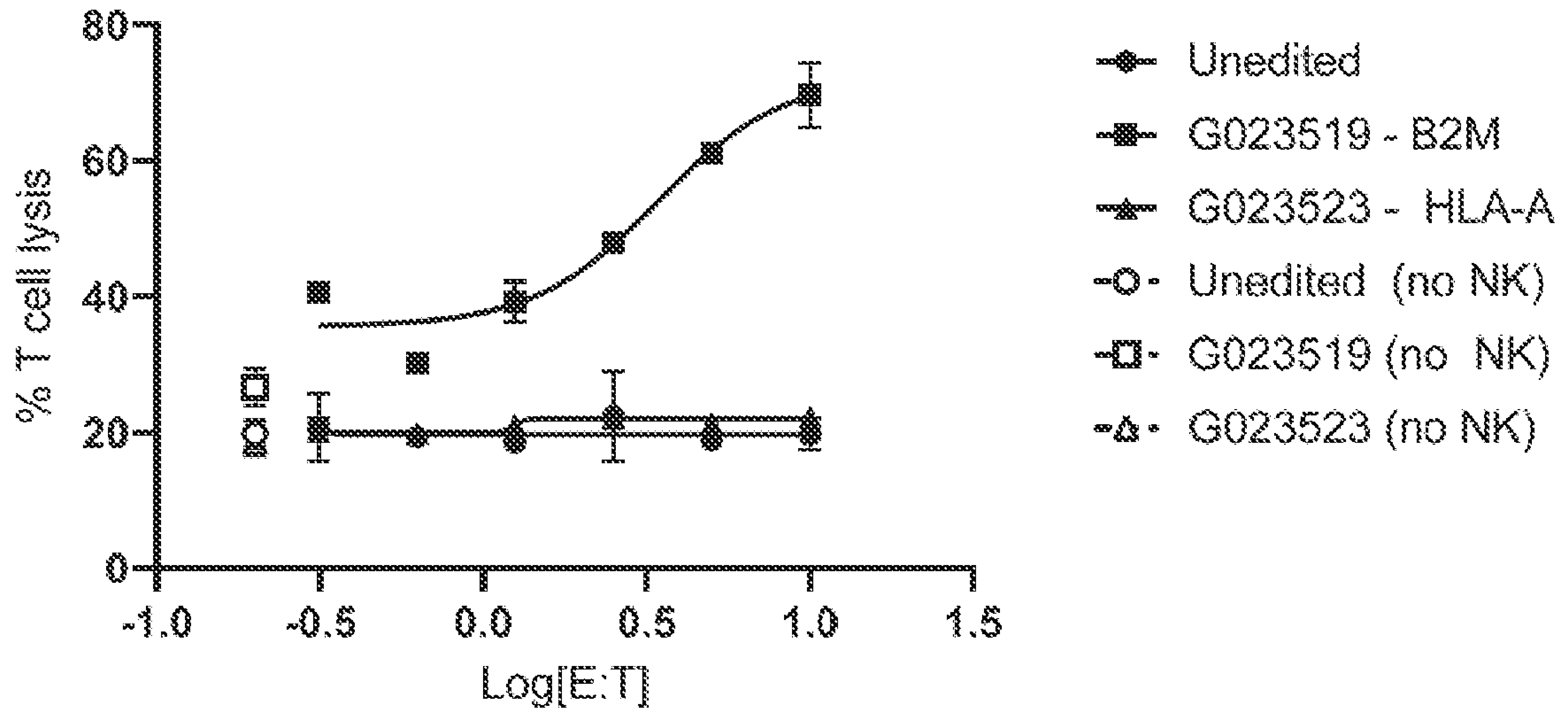


FIG. 13

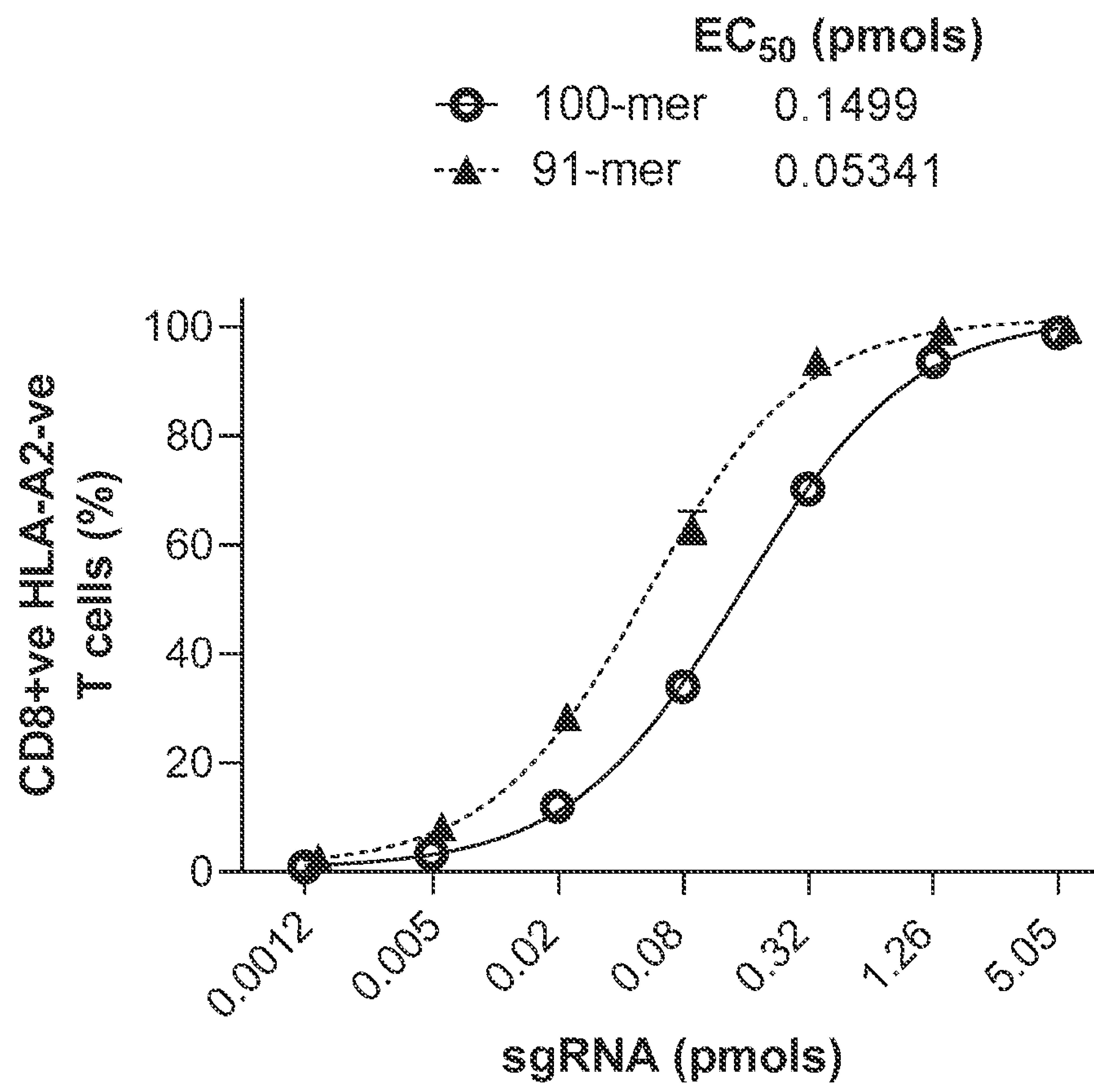


FIG. 14

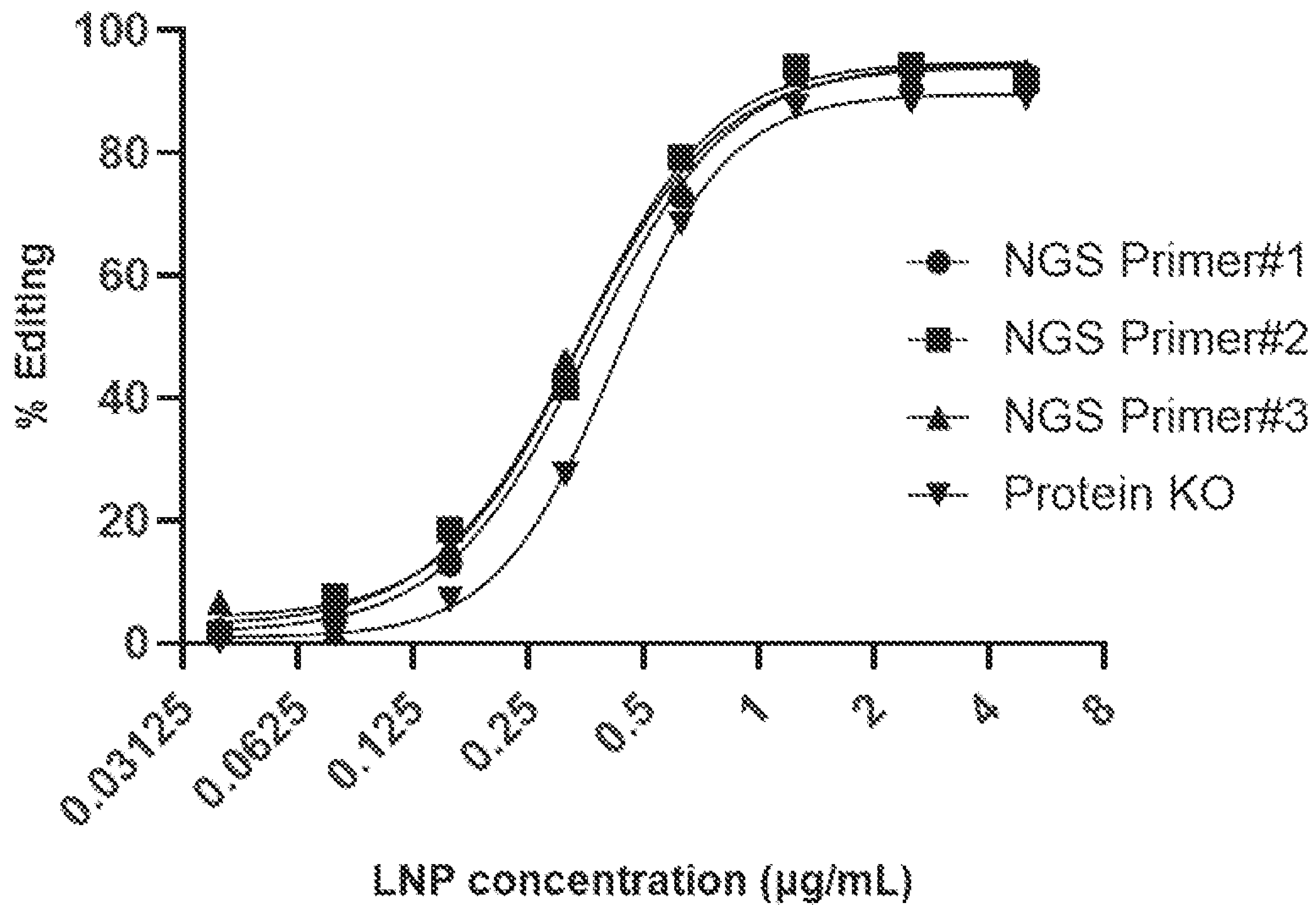


FIG. 15A

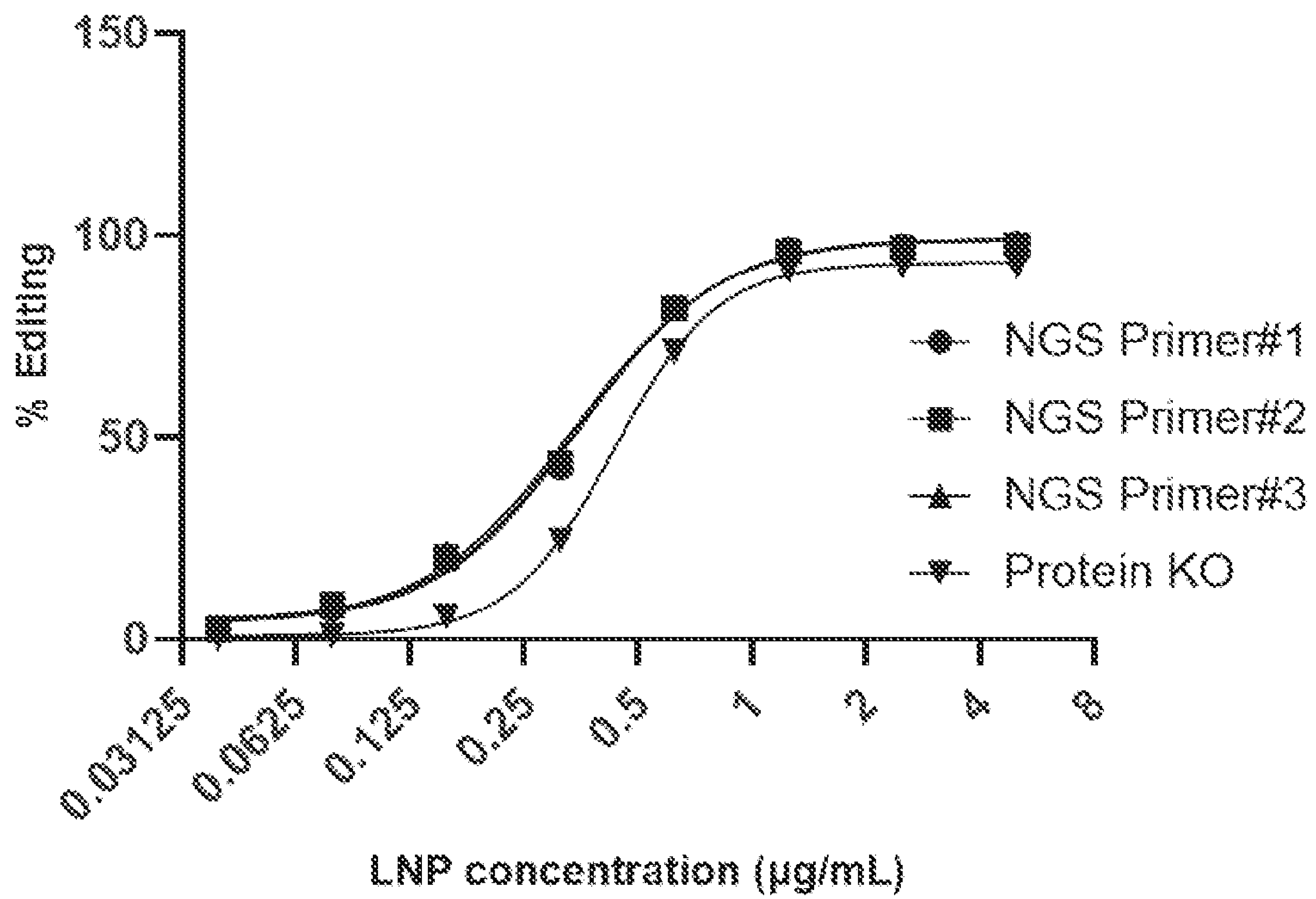


FIG. 15B

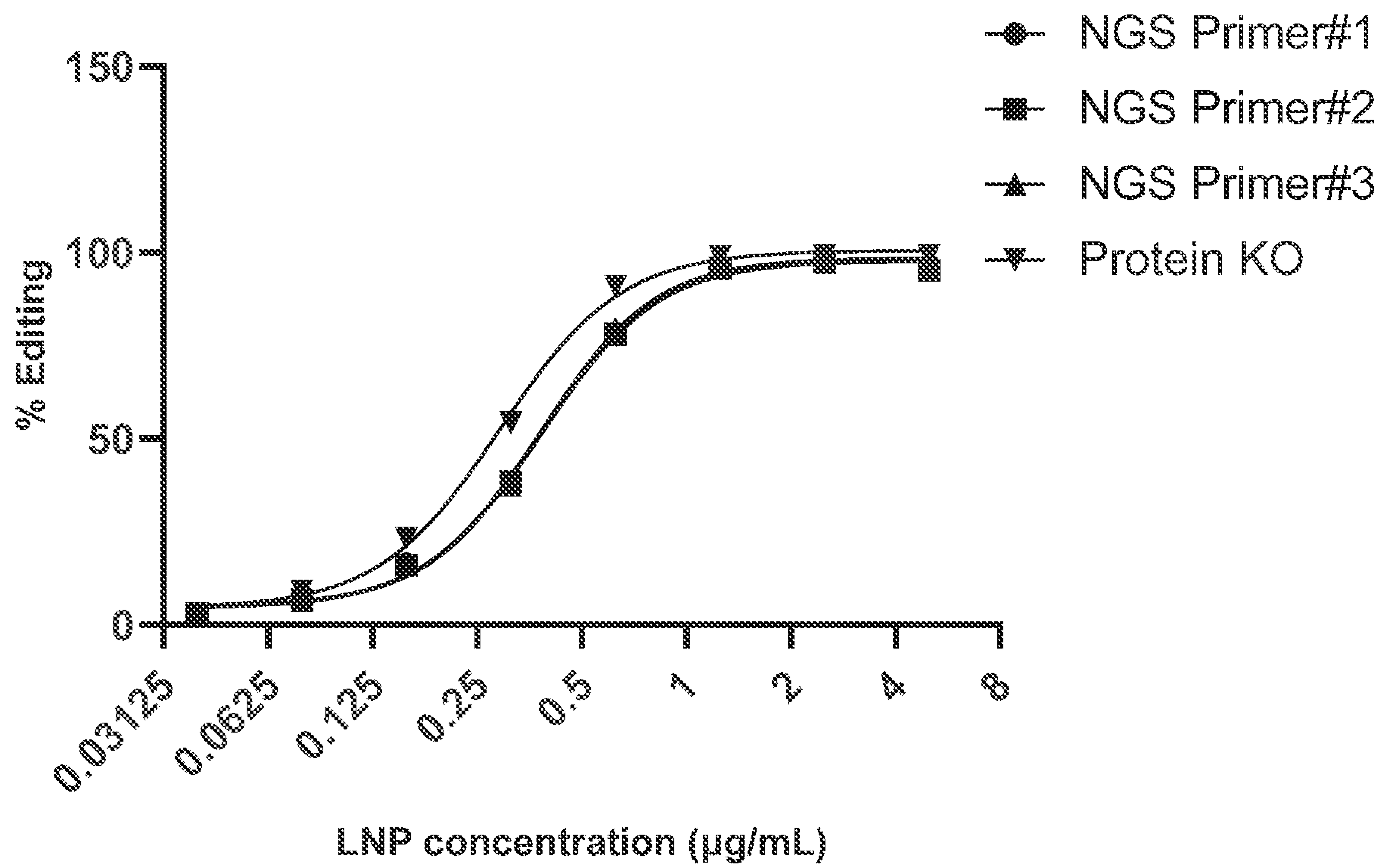


FIG. 15C

SEQUENCE LISTING

<110> INTELLIA THERAPEUTICS, INC.

<120> COMPOSITIONS AND METHODS FOR REDUCING HLA-A IN A CELL

<130> 01155-0036-00PCT

<150> US 63/130,095
<151> 2020-12-23

<150> US 63/250,996
<151> 2021-09-30

<150> US 63/254,970
<151> 2021-10-12

<150> US 63/288,492
<151> 2021-12-10

<160> 1016

<170> PatentIn version 3.5

<210> 1
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 1
uggagggccu gauguguguu   20

<210> 2
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 2
gccugaugug uguuggggugu   20

<210> 3
<211> 20

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 3
ccugaugugu guuggguguu   20

<210> 4
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 4
cccaacaccc aacacacauc   20

<210> 5
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 5
ucaggaaaca ugaagaaagc   20

<210> 6
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 6
aggcgccugg gccucucccg   20

<210> 7
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 7
cgggcuggcc ucccacaagg   20

<210> 8
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 8
acggccaucc ucggcgucug   20

<210> 9
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 9
gacggccauc cucggcgucu   20

<210> 10
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 10
gacgccgagg auggccguca   20

<210> 11
<211> 20
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 11
ugacggccau ccucggcguc   20

<210> 12
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 12
ggcgccauga cggccauccu   20

<210> 13
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 13
acagcgacgc cgcgagccag   20

<210> 14
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 14
cgacgccgcg agccagagga   20

<210> 15
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 15
cgagccagag gauggagccg   20

<210> 16
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 16
cggcuccauc cucuggcucg   20

<210> 17
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 17
gagccagagg auggagccgc   20

<210> 18
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 18
gcgcccgcgg cuccauccuc   20

<210> 19
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 19
gcccguccgu gggggaugag   20

<210> 20
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 20
ucaucccca cggacgggcc   20

<210> 21
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 21
aucucggacc cggagacugu   20

<210> 22
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 22
ggggucccgc ggcuucgggg   20

<210> 23
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 23
cucgggggucc cgcggcuucg   20

<210> 24
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 24
ucucggguc ccgcggcuuc   20

<210> 25
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 25
gucucggggu cccgcggcuu   20

<210> 26
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 26
gcaagggucu cggggucccg   20

<210> 27
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 27
ggaccccgag acccuugccc   20

<210> 28
<211> 20

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 28
gaccccgaga cccuugcccc   20

<210> 29
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 29
cgagacccuu gccccgggag   20

<210> 30
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 30
cucccggggc aagggucucg   20

<210> 31
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 31
ucucccgggg caagggucuc   20

<210> 32
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 32
cucucccggg gcaaggggucu   20

<210> 33
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 33
ccuugccccg ggagaggccc   20

<210> 34
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 34
cugggccucu cccggggcaa   20

<210> 35
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 35
ccugggccuc ucccggggca   20

<210> 36
<211> 20
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 36
uuuaggccaa aaaucccccc   20

<210> 37
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 37
cgcugcagcg cacggguacc   20

<210> 38
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 38
gcugcagcgc acggguacca   20

<210> 39
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 39
cugcagcgca cggguaccag   20

<210> 40
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 40
cgcacgggua ccaggggcca   20

<210> 41
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 41
gcacggguac caggggccac   20

<210> 42
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 42
cacggguacc aggggccacg   20

<210> 43
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 43
gggaggcgcc ccguggcccc   20

<210> 44
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 44
gcgaucaggg aggcgccccg   20

<210> 45
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 45
uccuuguggg aggccagccc   20

<210> 46
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 46
cuccuugugg gaggccagcc   20

<210> 47
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 47
ggcuggccuc ccacaaggag   20

<210> 48
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 48
uugucucccc uccuuguggg   20

<210> 49
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 49
ccacaaggag gggagacaau   20

<210> 50
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 50
cacaaggagg ggagacaauu   20

<210> 51
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 51
caauugucuc cccuccuugu   20

<210> 52
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 52
ccaauugucu ccccuccuug   20

<210> 53
<211> 20

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 53
aucccucgaa uacugaugag   20

<210> 54
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 54
aaccacucau caguauucga   20

<210> 55
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 55
gaaccacuca ucaguauucg   20

<210> 56
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 56
gaggaaaagu cacgggccca   20

<210> 57
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 57
ggcccgugac uuuuccucuc   20

<210> 58
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 58
ugcuucacac ucaaugugug   20

<210> 59
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 59
gcuucacacu caaugugugu   20

<210> 60
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 60
cuucacacuc aaugugugug   20

<210> 61
<211> 20
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 61
uucacacuca augugugugg   20

<210> 62
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 62
uugagaaugg acaggacacc   20

<210> 63
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 63
aggcauuuug caucugucau   20

<210> 64
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 64
caggcauuuu gcaucuguca   20

<210> 65
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 65
aggggcccug acccugcuaa   20

<210> 66
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 66
ugggaaaaga ggggaaggug   20

<210> 67
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 67
uggaggagga agagcucagg   20

<210> 68
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 68
ugagauuucu ugucucacug   20

<210> 69
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 69
gagauuucuu gucucacuga   20

<210> 70
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 70
uaaagcaccu guuaaaauga   20

<210> 71
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 71
aaucuguccu ucauuuuaac   20

<210> 72
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 72
gucacagggg aaggucccug   20

<210> 73
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 73
aaacaugaag aaagcaggug   20

<210> 74
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 74
uguccuguga gauaccagaa   20

<210> 75
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 75
augaaggagg cugaugccug   20

<210> 76
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 76
aggcugaugc cugagguccu   20

<210> 77
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 77
ggcugaugcc ugagguccuu   20

<210> 78
<211> 20

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 78
cacaauaucc caaggaccuc   20

<210> 79
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 79
gguccuuggg auauuguguu   20

<210> 80
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 80
guccuuggga uauuguguuu   20

<210> 81
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 81
cucccaaaca caauauccca   20

<210> 82
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 82
uccucuagcc acaucuucug   20

<210> 83
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 83
acagaagaug uggcuagagg   20

<210> 84
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 84
ccucuagcca caucuucugu   20

<210> 85
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 85
cccacagaag auguggcuag   20

<210> 86
<211> 20
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 86
gucagauccc acagaagaug   20

<210> 87
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 87
aucuucugug ggaucugacc   20

<210> 88
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 88
cccaggcagu gacagugccc   20

<210> 89
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 89
cugggcacug ucacugccug   20

<210> 90
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 90
ccugggcacu gucacugccu   20

<210> 91
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 91
cccugggcac ugucacugcc   20

<210> 92
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 92
uuggguguug ggcggaacag   20

<210> 93
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 93
uggauguauu gagcaugcga   20

<210> 94
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 94
ggauguauug agcaugcgau   20

<210> 95
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 95
aacaugaaga aagcaggugu   20

<210> 96
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 96
uagcccacgg cgaugaagcg   20

<210> 97
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 97
guagcccacg gcgaugaagc   20

<210> 98
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 98
cguagcccac ggcgaugaag   20

<210> 99
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 99
cuucaucgcc gugggcuacg   20

<210> 100
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 100
cgugucgucc acguagccca   20

<210> 101
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 101
uggacgacac gcaguucgug   20

<210> 102
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 102
ggauggagcc gcgggcgccg   20

<210> 103
<211> 20

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 103
gcgggcgccg uggauagagc   20

<210> 104
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 104
ugcucuaucc acggcgcccg   20

<210> 105
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 105
ggcgccgugg auagagcagg   20

<210> 106
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 106
gcgccgugga uagagcagga   20

<210> 107
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 107
cgccguggau agagcaggag   20

<210> 108
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 108
guggauagag caggaggggc   20

<210> 109
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 109
ggccccuccu gcucuaucca   20

<210> 110
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 110
agcaggaggg gccggaguau   20

<210> 111
<211> 20
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 111
gcaggagggg ccggaguauu   20

<210> 112
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 112
ggaguggcuc cgcagauacc   20

<210> 113
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 113
cuccgcagau accuggagaa   20

<210> 114
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 114
uccgcagaua ccuggagaac   20

<210> 115
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 115
cagauaccug gagaacggga   20

<210> 116
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 116
ucccguucuc cagguaucug   20

<210> 117
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 117
gcgucuccuu cccguucucc   20

<210> 118
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 118
gaaggagacg cugcagcgca   20

<210> 119
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 119
aaggagacgc ugcagcgcac   20

<210> 120
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 120
agaucuacag gcgaucaggg   20

<210> 121
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 121
ugaucgccug uagaucuccc   20

<210> 122
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 122
gggagaucua caggcgauca   20

<210> 123
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 123
cgggagaucu acaggcgauc   20

<210> 124
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 124
cgccuguaga ucucccgggc   20

<210> 125
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 125
ggccagcccg ggagaucuac   20

<210> 126
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 126
ucccgggcug gccucccaca   20

<210> 127
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 127
gggcuggccu cccacaagga   20

<210> 128
<211> 20

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 128
cugaucgccu guagaucucc   20

<210> 129
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 129
aggauggagc cgcgggcgcc   20

<210> 130
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 130
ggaaggagac gcugcagcgc   20

<210> 131
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 131
gacagcgacg ccgcgagcca   20

<210> 132
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 132
cgggaaggag acgcugcagc   20

<210> 133
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 133
ccgugcgcug cagcgucucc   20

<210> 134
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 134
acgcaguucg ugcgguucga cagc   24

<210> 135
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 135
ucgugcgguu cgacagcgac gccg   24

<210> 136
<211> 24
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 136
cagcgacgcc gcgagccaga ggau   24

<210> 137
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 137
gcucuaucca cggcgcccgc ggcu   24

<210> 138
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 138
uccugcucua uccacggcgc ccgc   24

<210> 139
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 139
ccggccccuc cugcucuauc cacg   24

<210> 140
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 140
uccggccccu ccugcucuau ccac   24

<210> 141
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 141
gggaaggaga cgcugcagcg cacg   24

<210> 142
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 142
agacgcugca gcgcacgggu acca   24

<210> 143
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 143
gcgcacgggu accaggggcc acgg   24

<210> 144
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 144
cacggguacc aggggccacg gggc   24

<210> 145
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 145
acggguacca ggggccacgg ggcg   24

<210> 146
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 146
caggggccac ggggcgccuc ccug   24

<210> 147
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 147
cagggaggcg ccccguggcc ccug   24

<210> 148
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 148
ucagggaggc gccccguggc cccu   24

<210> 149
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 149
caggcgauca gggaggcgcc ccgu   24

<210> 150
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 150
acaggcgauc agggaggcgc cccg   24

<210> 151
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 151
uacaggcgau cagggaggcg cccc   24

<210> 152
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 152
gggcgccucc cugaucgccu guag   24

<210> 153
<211> 24

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 153
ggcgccuccc ugaucgccug uaga   24

<210> 154
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 154
gagaucuaca ggcgaucagg gagg   24

<210> 155
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 155
ggagaucuac aggcgaucag ggag   24

<210> 156
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 156
gggagaucua caggcgauca ggga   24

<210> 157
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 157
cugaucgccu guagaucucc cggg   24

<210> 158
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 158
aucgccugua gaucucccgg gcug   24

<210> 159
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 159
ucgccuguag aucucccggg cugg   24

<210> 160
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 160
uugucucccc uccuuguggg aggc   24

<210> 161
<211> 24
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 161
auugucuccc cuccuugugg gagg   24

<210> 162
<211> 24
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 162
cccaauuguc uccccuccuu gugg   24

<210> 163
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 163
ggauggagcc gcgggcgccg   20

<210> 164
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 164
gcgggcgccg uggauagagc   20

<210> 165
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 165
ugcucuaucc acggcgcccg   20

<210> 166
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 166
ggcgccgugg auagagcagg   20

<210> 167
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 167
gcgccgugga uagagcagga   20

<210> 168
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 168
cgccguggau agagcaggag   20

<210> 169
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 169
guggauagag caggaggggc   20

<210> 170
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 170
gcgucuccuu cccguucucc   20

<210> 171
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 171
gaaggagacg cugcagcgca   20

<210> 172
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 172
aaggagacgc ugcagcgcac   20

<210> 173
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 173
gcugcagcgc acggguacca   20

<210> 174
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 174
agaucuacag gcgaucaggg   20

<210> 175
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 175
cugaucgccu guagaucucc   20

<210> 176
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 176
ugaucgccug uagaucuccc   20

<210> 177
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 177
gggagaucua caggcgauca   20

<210> 178
<211> 20

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 178
cgggagaucu acaggcgauc   20

<210> 179
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 179
cgccuguaga ucucccgggc   20

<210> 180
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 180
ggccagcccg ggagaucuac   20

<210> 181
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 181
ucccgggcug gccucccaca   20

<210> 182
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 182
gggcuggccu cccacaagga   20

<210> 183
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 183
acgacacuga uuggcuucuc   20

<210> 184
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 184
accccucauc ccccacggac   20

<210> 185
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 185
ggcccguccg ugggggauga   20

<210> 186
<211> 20
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 186
gccaggucgc ccacagucuc   20

<210> 187
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 187
guuuaggcca aaaauccccc   20

<210> 188
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 188
ggccaaaaau ccccccgggu   20

<210> 189
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 189
gaccaacccg gggggauuuu   20

<210> 190
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 190
cacgggccca aggcugcugc   20

<210> 191
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 191
acccucaugc ugcacauggc   20

<210> 192
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 192
ccucuaggac cuuaaggccc   20

<210> 193
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 193
gcuccuuucu gguaucucac   20

<210> 194
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 194
gcuaugggu uucuuugcau   20

<210> 195
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 195
gccuuugcag aaacaaaguc   20

<210> 196
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 196
uggaccaacc gcccuccuga   20

<210> 197
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 197
agccucucug accuuuagca   20

<210> 198
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 198
cgcccuccug aagguccuca   20

<210> 199

<400> 199
000

<210> 200
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 200
ccgcccuccu gaagguccuc   20

<210> 201
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 201
ugguucccuu ugacacacac   20

<210> 202
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 202
gacccugcua aaggucagag   20

<210> 203
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 203

aggaccuuca ggagggcggu 20

<210> 204
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 204
gcacacuucu accugggucu 20

<210> 205
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 205
gagccucucu gaccuuuagc 20

<210> 206
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 206
acacuccucc agcacacaug 20

<210> 207
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 207
cucugaccuu uagcaggguc 20

<210> 208
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 208
caagauagcc acaugugugc   20

<210> 209
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 209
ucugaccuuu agcaggguca   20

<210> 210
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 210
uguaaaggug agagccugga   20

<210> 211
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 211
gaaggucccu gaggaccuuc   20

<210> 212

<400> 212
000

<210> 213
<211> 22
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 213
guuuuagagc uaugcuguuu ug   22

<210> 214
<211> 80
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 214
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaac uugaaaaagu   60

ggcaccgagu cggugcuuuu   80

<210> 215
<211> 76
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 215
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaac uugaaaaagu   60

ggcaccgagu cggugc   76

<210> 216
<211> 68
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 216
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaac uuggcaccga   60

gucggugc   68

<210> 217

<400> 217
000

<210> 218

<400> 218
000

<210> 219

<400> 219
000

<210> 220

<400> 220
000

<210> 221

<400> 221
000

<210> 222

<400> 222
000

<210> 223

<400> 223
000

<210> 224

<400> 224
000

<210> 225

<400> 225
000

<210> 226

<400> 226
000

<210> 227

<400> 227
000

<210> 228

<400> 228
000

<210> 229

<400> 229
000

<210> 230
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 230
gaguccgagc agaagaagaa   20

<210> 231
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 231
gacccccucc accccgccuc   20

<210> 232
<211> 20
<212> RNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 232
gacuuguuuu cauuguucuc   20

<210> 233
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 233
cucucagcug guacacggca   20

<210> 234
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 234
ugugcagacu cagaggugag   20

<210> 235
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 235
ggccacggag cgagacaucu   20

<210> 236
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 236
cccccggacg guucaagcaa   20

<210> 237

<400> 237
000

<210> 238

<400> 238
000

<210> 239

<400> 239
000

<210> 240
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 240
gaguccgagc agaagaagaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 241
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 241
gacccccucc accccgccuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 242
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 242
gacuuguuuu cauuguucuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 243
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 243
cucucagcug guacacggca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 244
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 244
ugugcagacu cagaggugag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 245
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 245
ggccacggag cgagacaucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 246
<211> 100

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 246
cccccggacg guucaagcaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 247
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 247
ggccucggcg cugacgaucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 248
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>

<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 248
uggucagggc aagagcuauu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 249
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 249
uggagggccu gaugugugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 250
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 250
gccugaugug uguugggugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 251
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 251
ccugaugugu guuggguguu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 252
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 252
cccaacaccc aacacacauc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 253
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 253
ucaggaaaca ugaagaaagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 254
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 254
aggcgccugg gccucucccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 255
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 255
cgggcuggcc ucccacaagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 256
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 256
acggccaucc ucggcgucug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 257
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 257
gacggccauc cucggcgucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 258
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 258
gacgccgagg auggccguca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 259
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 259
ugacggccau ccucggcguc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 260
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 260
ggcgccauga cggccauccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 261
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 261
acagcgacgc cgcgagccag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 262
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 262
cgacgccgcg agccagagga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 263
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 263
cgagccagag gauggagccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 264
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 264
cggcuccauc cucuggcucg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 265
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 265
gagccagagg auggagccgc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 266

<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 266
gcgcccgcgg cuccauccuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 267
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 267
gcccguccgu gggggaugag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 268
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 268
ucaucccccca cggacgggcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 269
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 269

aucucggacc cggagacugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 270
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 270
ggggucccgc ggcuucgggg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 271
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 271
cucgggguce cgcggcuucg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 272
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 272
ucucgggguc ccgcggcuuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 273
<211> 100
<212> RNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 273
gucucggggu cccgcggcuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 274
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 274
gcaaggg ucu cggggucccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 275
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 275
ggaccccgag acccuugccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 276
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 276
gaccccgaga cccuugcccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 277
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 277
cgagacccuu gccccgggag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 278
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 278
cucccggggc aagggucucg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 279
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 279
ucucccgggg caagggucuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 280
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 280
cucucccggg gcaagggucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 281
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 281
ccuugccccg ggagaggccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 282
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 282
cugggccucu cccggggcaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 283
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 283
ccugggccuc ucccggggca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 284
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 284
uuuaggccaa aaaucccccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 285
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 285
cgcugcagcg cacggguacc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 286
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 286
gcugcagcgc acggguacca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 287
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 287
cugcagcgca cggguaccag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 288
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 288
cgcacgggua ccaggggcca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 289
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 289
gcacggguac caggggccac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 290
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 290
cacggguacc aggggccacg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 291

<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 291
gggaggcgcc ccguggcccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 292
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 292
gcgaucaggg aggcgccccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 293
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 293
uccuuguggg aggccagccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 294
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 294

cuccuugugg gaggccagcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 295
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 295
ggcuggccuc ccacaaggag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 296
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 296
uugucucccc uccuuguggg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 297
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 297
ccacaaggag gggagacaau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 298
<211> 100
<212> RNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 298
cacaaggagg ggagacaauu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 299
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 299
caauugucuc cccuccuugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 300
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 300
ccaauugucu ccccuccuug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 301
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 301
aucccucgaa uacugaugag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 302
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 302
aaccacucau caguauucga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 303
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 303
gaaccacuca ucaguauucg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 304
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 304
gaggaaaagu cacgggccca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 305
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 305
ggcccgugac uuuuccucuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 306
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 306
ugcuucacac ucaaugugug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 307
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 307
gcuucacacu caaugugugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 308
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 308
cuucacacuc aaugugugug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 309
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 309
uucacacuca augugugugg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 310
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 310
uugagaaugg acaggacacc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 311
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 311
aggcauuuug caucugucau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 312
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 312
caggcauuuu gcaucuguca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 313
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 313
aggggcccug acccugcuaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 314
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 314
ugggaaaaga ggggaaggug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 315
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 315
uggaggagga agagcucagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 316

<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 316
ugagauuucu ugucucacug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 317
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 317
gagauuucuu gucucacuga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 318
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 318
uaaagcaccu guuaaaauga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 319
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 319

aaucuguccu ucauuuuaac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 320
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 320
gucacagggg aaggucccug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 321
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 321
aaacaugaag aaagcaggug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 322
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 322
uguccuguga gauaccagaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 323
<211> 100
<212> RNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 323
augaaggagg cugaugccug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 324
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 324
aggcugaugc cugagguccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 325
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 325
ggcugaugcc ugagguccuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 326
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 326
cacaauaucc caaggaccuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 327
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 327
gguccuuggg auauuguguu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 328
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 328
guccuuggga uauuguguuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 329
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 329
cucccaaaca caauauccca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 330
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 330
uccucuagcc acaucuucug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 331
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 331
acagaagaug uggcuagagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 332
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 332
ccucuagcca caucuucugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 333
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 333
cccacagaag auguggcuag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 334
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 334
gucagauccc acagaagaug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 335
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 335
aucuucugug ggaucugacc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 336
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 336
cccaggcagu gacagugccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 337
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 337
cugggcacug ucacugccug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 338
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 338
ccugggcacu gucacugccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 339
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 339
cccugggcac ugucacugcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 340
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 340
uuggguguug ggcggaacag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 341

<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 341
uggauguauu gagcaugcga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 342
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 342
ggauguauug agcaugcgau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 343
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 343
aacaugaaga aagcaggugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 344
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 344
uggagggccu gaugugugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 345
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 345
gccugaugug uguugggugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 346
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 346
ccugaugugu guuggguguu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 347
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 347
cccaacaccc aacacacauc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 348
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 348
ucaggaaaca ugaagaaagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 349
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 349
aggcgccugg gccucucccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 350
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 350
cgggcuggcc ucccacaagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 351
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed

for detailed description of substitutions and preferred
embodiments

<400> 351
acggccaucc ucggcgucug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 352
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 352
gacggccauc cucggcgucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 353
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 353
gacgccgagg auggccguca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 354
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 354
ugacggccau ccucggcguc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 355
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 355
ggcgccauga cggccauccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 356
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 356
acagcgacgc cgcgagccag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 357
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 357
cgacgccgcg agccagagga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 358
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 358
cgagccagag gauggagccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 359
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 359
cggcuccauc cucuggcucg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 360
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 360
gagccagagg auggagccgc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 361
<211> 100

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 361
gcgcccgcgg cuccauccuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 362
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 362
gcccguccgu gggggaugag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 363
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>

<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 363
ucaucccccca cggacgggcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 364
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 364
aucucggacc cggagacugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 365
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 365
ggggucccgc ggcuucgggg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 366
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 366
cucggggucc cgcggcuucg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 367
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 367
ucucgggguc ccgcggcuuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 368
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 368
gucucggggu cccgcggcuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 369
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 369
gcaagggucu cggggucccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 370
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred

embodiments

<400> 370
ggaccccgag acccuugccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 371
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 371
gaccccgaga cccuugcccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 372
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 372
cgagacccuu gccccgggag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 373
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 373
cucccggggc aagggucucg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 374
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 374
ucucccgggg caagggucuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 375
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 375
cucucccggg gcaagggucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 376
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 376
ccuugccccg ggagaggccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 377
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 377

cugggccucu cccggggcaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 378
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 378
ccugggccuc ucccggggca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 379
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 379
uuuaggccaa aaaucccccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 380
<211> 100
<212> RNA

<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 380
cgcugcagcg cacggguacc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 381
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 381
gcugcagcgc acggguacca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 382
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature

<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 382
cugcagcgca cggguaccag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 383
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 383
cgcacgggua ccaggggcca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 384
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 384
gcacggguac caggggccac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 385
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 385
cacggguacc aggggccacg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 386
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 386
gggaggcgcc ccguggcccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 387
<211> 100
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 387
gcgaucaggg aggcgccccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 388
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 388
uccuuguggg aggccagccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 389
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 389
cuccuugugg gaggccagcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 390
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 390
ggcuggccuc ccacaaggag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 391
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 391
uugucucccc uccuuguggg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 392

<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 392
ccacaaggag gggagacaau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 393
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 393
cacaaggagg ggagacaauu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 394
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 394
caauugucuc cccuccuugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 395
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 395
ccaauugucu ccccuccuug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 396
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 396
aucccucgaa uacugaugag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 397
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 397
aaccacucau caguauucga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 398
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 398
gaaccacuca ucaguauucg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 399
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 399
gaggaaaagu cacgggccca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 400
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 400
ggcccgugac uuuuccucuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 401
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed

for detailed description of substitutions and preferred
embodiments

<400> 401
ugcuucacac ucaaugugug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 402
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 402
gcuucacacu caaugugugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 403
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 403
cuucacacuc aaugugugug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 404
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 404
uucacacuca augugugugg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 405
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 405
uugagaaugg acaggacacc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 406
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 406
aggcauuuug caucugucau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 407
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 407
caggcauuuu gcaucuguca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 408
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 408
aggggcccug acccugcuaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 409
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 409
ugggaaaaga ggggaaggug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 410
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 410
uggaggagga agagcucagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 411
<211> 100

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 411
ugagauuucu ugucucacug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 412
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 412
gagauuucuu gucucacuga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 413
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>

<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 413
uaaagcaccu guuaaaauga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 414
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 414
aaucuguccu ucauuuuaac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 415
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 415
gucacagggg aagguccug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 416
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 416
aaacaugaag aaagcaggug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 417
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 417
uguccuguga gauaccagaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 418
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 418
augaaggagg cugaugccug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 419
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 419
aggcugaugc cugagguccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 420
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred

embodiments

<400> 420
ggcugaugcc ugagguccuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 421
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 421
cacaauaucc caaggaccuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 422
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 422
gguccuuggg auauuguguu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 423
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 423
guccuuggga uauuguguuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 424
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 424
cucccaaaca caauauccca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 425
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 425
uccucuagcc acaucuucug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 426
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 426
acagaagaug uggcuagagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 427
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 427

ccucuagcca caucuucugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 428
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 428
cccacagaag auguggcuag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 429
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 429
gucagauccc acagaagaug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 430
<211> 100
<212> RNA

<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 430
aucuucugug ggaucugacc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 431
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 431
cccaggcagu gacagugccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 432
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature

<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 432
cugggcacug ucacugccug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 433
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 433
ccugggcacu gucacugccu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 434
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 434
cccugggcac ugucacugcc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 435
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 435
uuggguguug ggcggaacag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 436
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 436
uggauguauu gagcaugcga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 437
<211> 100
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 437
ggauguauug agcaugcgau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 438
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 438
aacaugaaga aagcaggugu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 439
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 439
uagcccacgg cgaugaagcg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 440
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 440
guagcccacg gcgaugaagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 441
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 441
cguagcccac ggcgaugaag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 442
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 442
cuucaucgcc gugggcuacg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 443
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 443
cgugucgucc acguagccca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 444
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 444
uggacgacac gcaguucgug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 445
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 445
ggauggagcc gcgggcgccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 446
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 446
gcgggcgccg uggauagagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 447
<211> 100

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 447
ugcucuaucc acggcgcccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 448
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 448
ggcgccgugg auagagcagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 449
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 449
gcgccgugga uagagcagga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 450
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 450
cgccguggau agagcaggag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 451
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 451
guggauagag caggaggggc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 452
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 452
ggccccuccu gcucuaucca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 453
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 453
agcaggaggg gccggaguau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 454
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 454
gcaggagggg ccggaguauu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 455
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 455
ggaguggcuc cgcagauacc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 456
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 456
cuccgcagau accuggagaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 457
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 457
uccgcagaua ccuggagaac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 458
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 458
cagauaccug gagaacggga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 459
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 459
ucccguucuc cagguaucug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 460
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 460
gcgucuccuu cccguucucc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 461
<211> 100
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 461
gaaggagacg cugcagcgca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 462
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 462
aaggagacgc ugcagcgcac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 463
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 463
agaucuacag gcgaucaggg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 464
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 464
ugaucgccug uagaucuccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 465
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 465
gggagaucua caggcgauca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 466
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 466
cgggagaucu acaggcgauc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 467
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 467
cgccuguaga ucucccgggc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 468
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 468
ggccagcccg ggagaucuac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 469
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 469
ucccgggcug gccucccaca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 470
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 470
gggcuggccu cccacaagga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 471
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 471
cugaucgccu guagaucucc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 472
<211> 100

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 472
uagcccacgg cgaugaagcg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 473
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 473
guagcccacg gcgaugaagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 474
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>

<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 474
cguagcccac ggcgaugaag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 475
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 475
cuucaucgcc gugggcuacg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 476
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 476
cgugucgucc acguagccca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 477
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 477
uggacgacac gcaguucgug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 478
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 478
ggauggagcc gcgggcgccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 479
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 479
gcgggcgccg uggauagagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 480
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 480
ugcucuaucc acggcgcccg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 481
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred

embodiments

<400> 481
ggcgccgugg auagagcagg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 482
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 482
gcgccgugga uagagcagga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 483
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 483
cgccguggau agagcaggag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 484
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 484
guggauagag caggaggggc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 485
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 485
ggccccuccu gcucuaucca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 486
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 486
agcaggaggg gccggaguau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 487
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 487
gcaggagggg ccggaguauu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 488
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 488

ggaguggcuc cgcagauacc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 489
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed for detailed description of substitutions and preferred embodiments

<400> 489
cuccgcagau accuggagaa guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 490
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed for detailed description of substitutions and preferred embodiments

<400> 490
uccgcagaua ccuggagaac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 491
<211> 100
<212> RNA

<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 491
cagauaccug gagaacggga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 492
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 492
ucccguucuc cagguaucug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 493
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature

<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 493
gcgucuccuu cccguucucc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 494
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 494
gaaggagacg cugcagcgca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 495
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 495
aaggagacgc ugcagcgcac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 496
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 496
agaucuacag gcgaucaggg guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 497
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 497
ugaucgccug uagaucuccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 498
<211> 100
<212> RNA
<213> Artificial Sequence

<220>

<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 498
gggagaucua caggcgauca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 499
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 499
cgggagaucu acaggcgauc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 500
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 500
cgccuguaga ucucccgggc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 501
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 501
ggccagcccg ggagaucuac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 502
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 502
ucccgggcug gccucccaca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 503

<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 503
gggcuggccu cccacaagga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 504
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 504
cugaucgccu guagaucucc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 505
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 505

acgacacuga uuggcuucuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 506
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 506
accccucauc ccccacggac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 507
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 507
ggcccguccg ugggggauga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 508
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 508
gccaggucgc ccacagucuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 509
<211> 100
<212> RNA

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 509
guuuaggcca aaaauccccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 510
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 510
ggccaaaaau ccccccgggu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 511
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 511
gaccaacccg gggggauuuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 512
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 512
cacgggccca aggcugcugc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 513
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 513
acccucaugc ugcacauggc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 514
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 514
ccucuaggac cuuaaggccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 515
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 515
gcuccuuucu gguaucucac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 516
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 516
gcuaugggu uucuuugcau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 517
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 517
gccuuugcag aaacaaaguc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 518
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 518
uggaccaacc gcccuccuga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 519
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 519
agccucucug accuuuagca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 520
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 520
cgcccuccug aagguccuca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 521
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 521
ccgcccuccu gaagguccuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 522
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 522
ugguucccuu ugacacacac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 523
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 523
gacccugcua aaggucagag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 524
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 524
aggaccuuca ggagggcggu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 525
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 525
gcacacuucu accugggucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 526
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 526
gagccucucu gaccuuuagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 527

<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 527
acacuccucc agcacacaug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 528
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 528
cucugaccuu uagcaggguc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 529
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 529
caagauagcc acaugugugc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 530
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 530

ucugaccuuu agcaggguca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 531
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 531
uguaaaggug agagccugga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 532
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 532
gaaggucccu gaggaccuuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 533
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed for detailed description of substitutions and preferred embodiments

<400> 533
acgacacuga uuggcuucuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 534
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 534
accccucauc ccccacggac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 535
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 535
ggcccguccg ugggggauga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 536
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 536
gccaggucgc ccacagucuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 537
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 537
guuuaggcca aaaauccccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 538
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed

for detailed description of substitutions and preferred
embodiments

<400> 538
ggccaaaaau ccccccgggu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 539
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 539
gaccaacccg gggggauuuu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 540
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 540
cacgggccca aggcugcugc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 541
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 541
acccucaugc ugcacauggc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 542
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 542
ccucuaggac cuuaaggccc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 543
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 543
gcuccuuucu gguaucucac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 544
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 544
gcuaugggu uucuuugcau guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 545
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 545
gccuuugcag aaacaaaguc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 546
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 546
uggaccaacc gcccuccuga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 547
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 547
agccucucug accuuuagca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 548
<211> 100

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 548
cgcccuccug aagguccuca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 549
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 549
ccgcccuccu gaagguccuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 550
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>

<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 550
ugguucccuu ugacacacac guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 551
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 551
gacccugcua aaggucagag guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 552
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 552
aggaccuuca ggagggcggu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 553
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 553
gcacacuucu accugggucu guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 554
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 554
gagccucucu gaccuuuagc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu 100

<210> 555
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 555
acacuccucc agcacacaug guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 556
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 556
cucugaccuu uagcaggguc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 557
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred

embodiments

<400> 557
caagauagcc acaugugugc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 558
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 558
ucugaccuuu agcaggguca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 559
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 559
uguaaaggug agagccugga guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 560
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
for detailed description of substitutions and preferred
embodiments

<400> 560
gaaggucccu gaggaccuuc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 561

<400> 561
000

<210> 562

<400> 562
000

<210> 563

<400> 563
000

<210> 564

<400> 564
000

<210> 565

<400> 565
000

<210> 566

<400> 566
000

<210> 567

<400> 567
000

<210> 568

<400> 568
000

<210> 569

<400> 569
000

<210> 570

<400> 570
000

<210> 571

<400> 571
000

<210> 572

<400> 572
000

<210> 573

<400> 573
000

<210> 574

<400> 574
000

<210> 575

<400> 575
000

<210> 576

<400> 576
000

<210> 577

<400> 577
000

<210> 578

<400> 578
000

<210> 579

<400> 579
000

<210> 580

<400> 580
000

<210> 581

<400> 581
000

<210> 582

<400> 582
000

<210> 583

<400> 583
000

<210> 584

<400> 584
000

<210> 585

<400> 585
000

<210> 586

<400> 586
000

<210> 587

<400> 587
000

<210> 588

<400> 588
000

<210> 589

<400> 589
000

<210> 590

<400> 590
000

<210> 591

<400> 591
000

<210> 592

<400> 592
000

<210> 593

<400> 593
000

<210> 594

<400> 594
000

<210> 595

<400> 595
000

<210> 596

<400> 596
000

<210> 597

<400> 597
000

<210> 598

<400> 598
000

<210> 599

<400> 599
000

<210> 600
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 600

Pro Lys Lys Lys Arg Lys Val
1   5

<210> 601
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 601

Pro Lys Lys Lys Arg Arg Val
1   5

<210> 602
<211> 16
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 602

Lys Arg Pro Ala Ala Thr Lys Lys Ala Gly Gln Ala Lys Lys Lys Lys
1   5   10   15

<210> 603

<400> 603
000

<210> 604

<400> 604
000

<210> 605

<400> 605
000

<210> 606

<400> 606
000

<210> 607

<400> 607
000

<210> 608

<400> 608
000

<210> 609

<400> 609
000

<210> 610

<400> 610
000

<210> 611

<400> 611
000

<210> 612

<400> 612
000

<210> 613

<400> 613
000

<210> 614

<400> 614
000

<210> 615

<400> 615
000

<210> 616

<400> 616
000

<210> 617

<400> 617
000

<210> 618

<400> 618
000

<210> 619

<400> 619
000

<210> 620

<400> 620
000

<210> 621

<400> 621
000

<210> 622

<400> 622
000

<210> 623

<400> 623
000

<210> 624

<400> 624
000

<210> 625

<400> 625
000

<210> 626

<400> 626
000

<210> 627

<400> 627
000

<210> 628

<400> 628
000

<210> 629

<400> 629
000

<210> 630

<400> 630
000

<210> 631

<400> 631
000

<210> 632

<400> 632
000

<210> 633

<400> 633
000

<210> 634

<400> 634
000

<210> 635

<400> 635
000

<210> 636

<400> 636
000

<210> 637

<400> 637
000

<210> 638

<400> 638
000

<210> 639

<400> 639
000

<210> 640

<400> 640
000

<210> 641

<400> 641
000

<210> 642

<400> 642
000

<210> 643

<400> 643
000

<210> 644

<400> 644
000

<210> 645

<400> 645
000

<210> 646

<400> 646
000

<210> 647

<400> 647
000

<210> 648

<400> 648
000

<210> 649

<400> 649
000

<210> 650

<400> 650
000

<210> 651

<400> 651
000

<210> 652

<400> 652
000

<210> 653

<400> 653
000

<210> 654

<400> 654
000

<210> 655

<400> 655
000

<210> 656

<400> 656
000

<210> 657

<400> 657
000

<210> 658

<400> 658
000

<210> 659

<400> 659
000

<210> 660

<400> 660
000

<210> 661

<400> 661
000

<210> 662

<400> 662
000

<210> 663

<400> 663
000

<210> 664

<400> 664
000

<210> 665

<400> 665
000

<210> 666

<400> 666
000

<210> 667

<400> 667
000

<210> 668

<400> 668
000

<210> 669

<400> 669
000

<210> 670

<400> 670
000

<210> 671

<400> 671
000

<210> 672

<400> 672
000

<210> 673

<400> 673
000

<210> 674

<400> 674
000

<210> 675

<400> 675
000

<210> 676

<400> 676
000

<210> 677

<400> 677
000

<210> 678

<400> 678
000

<210> 679

<400> 679
000

<210> 680

<400> 680
000

<210> 681

<400> 681
000

<210> 682

<400> 682
000

<210> 683

<400> 683
000

<210> 684

<400> 684
000

<210> 685

<400> 685
000

<210> 686

<400> 686
000

<210> 687

<400> 687
000

<210> 688

<400> 688
000

<210> 689

<400> 689
000

<210> 690

<400> 690
000

<210> 691

<400> 691
000

<210> 692

<400> 692
000

<210> 693

<400> 693
000

<210> 694

<400> 694
000

<210> 695

<400> 695
000

<210> 696

<400> 696
000

<210> 697

<400> 697
000

<210> 698

<400> 698
000

<210> 699

<400> 699
000

<210> 700

<400> 700
000

<210> 701

<400> 701
000

<210> 702

<400> 702
000

<210> 703

<400> 703
000

<210> 704

<400> 704
000

<210> 705

<400> 705
000

<210> 706

<400> 706
000

<210> 707

<400> 707
000

<210> 708

<400> 708
000

<210> 709

<400> 709
000

<210> 710

<400> 710
000

<210> 711

<400> 711
000

<210> 712

<400> 712
000

<210> 713

<400> 713
000

<210> 714

<400> 714
000

<210> 715

<400> 715
000

<210> 716

<400> 716
000

<210> 717

<400> 717
000

<210> 718

<400> 718
000

<210> 719

<400> 719
000

<210> 720

<400> 720
000

<210> 721

<400> 721
000

<210> 722

<400> 722
000

<210> 723

<400> 723
000

<210> 724

<400> 724
000

<210> 725

<400> 725
000

<210> 726

<400> 726
000

<210> 727

<400> 727
000

<210> 728

<400> 728
000

<210> 729

<400> 729
000

<210> 730

<400> 730
000

<210> 731

<400> 731
000

<210> 732

<400> 732
000

<210> 733

<400> 733
000

<210> 734

<400> 734
000

<210> 735

<400> 735
000

<210> 736

<400> 736
000

<210> 737

<400> 737
000

<210> 738

<400> 738
000

<210> 739

<400> 739
000

<210> 740

<400> 740
000

<210> 741

<400> 741
000

<210> 742

<400> 742
000

<210> 743

<400> 743
000

<210> 744

<400> 744
000

<210> 745

<400> 745
000

<210> 746

<400> 746
000

<210> 747

<400> 747
000

<210> 748

<400> 748
000

<210> 749

<400> 749
000

<210> 750

<400> 750
000

<210> 751

<400> 751
000

<210> 752

<400> 752
000

<210> 753

<400> 753
000

<210> 754

<400> 754
000

<210> 755

<400> 755
000

<210> 756

<400> 756
000

<210> 757

<400> 757
000

<210> 758

<400> 758
000

<210> 759

<400> 759
000

<210> 760

<400> 760
000

<210> 761

<400> 761
000

<210> 762

<400> 762
000

<210> 763

<400> 763
000

<210> 764

<400> 764
000

<210> 765

<400> 765
000

<210> 766

<400> 766
000

<210> 767

<400> 767
000

<210> 768

<400> 768
000

<210> 769

<400> 769
000

<210> 770

<400> 770
000

<210> 771

<400> 771
000

<210> 772

<400> 772
000

<210> 773

<400> 773
000

<210> 774

<400> 774
000

<210> 775

<400> 775
000

<210> 776

<400> 776
000

<210> 777

<400> 777
000

<210> 778

<400> 778
000

<210> 779

<400> 779
000

<210> 780

<400> 780
000

<210> 781

<400> 781
000

<210> 782

<400> 782
000

<210> 783

<400> 783
000

<210> 784

<400> 784
000

<210> 785

<400> 785
000

<210> 786

<400> 786
000

<210> 787

<400> 787
000

<210> 788

<400> 788
000

<210> 789

<400> 789
000

<210> 790

<400> 790
000

<210> 791

<400> 791
000

<210> 792

<400> 792
000

<210> 793

<400> 793
000

<210> 794

<400> 794
000

<210> 795

<400> 795
000

<210> 796

<400> 796
000

<210> 797

<400> 797
000

<210> 798

<400> 798
000

<210> 799

<400> 799
000

<210> 800
<211> 1379
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 800

Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly Thr Asn Ser Val
1   5   10   15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
            20   25   30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
        35   40   45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
    50   55   60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65   70   75   80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
                85   90   95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
            100   105   110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
        115   120   125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
    130   135   140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145   150   155   160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
                165   170   175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
            180   185   190

```
Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
        195                 200                 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
    210                 215                 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225                 230                 235                 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
                245                 250                 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
            260                 265                 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
        275                 280                 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
    290                 295                 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305                 310                 315                 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
                325                 330                 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
            340                 345                 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
        355                 360                 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
    370                 375                 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
```

385   390   395   400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
                405   410   415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
            420   425   430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
        435   440   445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
    450   455   460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465   470   475   480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
                485   490   495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
            500   505   510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
        515   520   525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
    530   535   540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545   550   555   560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
                565   570   575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
            580   585   590

```
Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
        595                 600                 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
    610                 615                 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625                 630                 635                 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
                645                 650                 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
            660                 665                 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
        675                 680                 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
    690                 695                 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705                 710                 715                 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
                725                 730                 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
            740                 745                 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
        755                 760                 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
    770                 775                 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
```

785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
805 810 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
820 825 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
835 840 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
850 855 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865 870 875 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
885 890 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
900 905 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
915 920 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
930 935 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945 950 955 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
965 970 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
980 985 990

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu Phe
        995   1000   1005

Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile Ala
    1010   1015   1020

Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala Lys Tyr Phe Phe
    1025   1030   1035

Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu Ala
    1040   1045   1050

Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly Glu
    1055   1060   1065

Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr Val
    1070   1075   1080

Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys Thr
    1085   1090   1095

Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro Lys
    1100   1105   1110

Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp Pro
    1115   1120   1125

Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser Val
    1130   1135   1140

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
    1145   1150   1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
    1160   1165   1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys

1175 1180 1185

Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
1190 1195 1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
1205 1210 1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
1220 1225 1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
1355 1360 1365

Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
1370 1375

<210> 801
<211> 4140
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 801
atggacaaga agtacagcat cggactggac atcggaacaa acagcgtcgg atgggcagtc 60

atcacagacg aatacaaggt cccgagcaag aagttcaagg tcctgggaaa cacagacaga 120

cacagcatca agaagaacct gatcggagca ctgctgttcg acagcggaga aacagcagaa 180

gcaacaagac tgaagagaac agcaagaaga agatacacaa gaagaaagaa cagaatctgc 240

tacctgcagg aaatcttcag caacgaaatg gcaaaggtcg acgacagctt cttccacaga 300

ctggaagaaa gcttcctggt cgaagaagac aagaagcacg aaagacaccc gatcttcgga 360

aacatcgtcg acgaagtcgc ataccacgaa aagtacccga caatctacca cctgagaaag 420

aagctggtcg acagcacaga caaggcagac ctgagactga tctacctggc actggcacac 480

atgatcaagt tcagaggaca cttcctgatc gaaggagacc tgaacccgga caacagcgac 540

gtcgacaagc tgttcatcca gctggtccag acatacaacc agctgttcga agaaaacccg 600

atcaacgcaa gcggagtcga cgcaaaggca atcctgagcg caagactgag caagagcaga 660

agactggaaa acctgatcgc acagctgccg ggagaaaaga agaacggact gttcggaaac 720

ctgatcgcac tgagcctggg actgacaccg aacttcaaga gcaacttcga cctggcagaa 780

gacgcaaagc tgcagctgag caaggacaca tacgacgacg acctggacaa cctgctggca 840

cagatcggag accagtacgc agacctgttc ctggcagcaa agaacctgag cgacgcaatc 900

ctgctgagcg acatcctgag agtcaacaca gaaatcacaa aggcaccgct gagcgcaagc 960

atgatcaaga gatacgacga acaccaccag gacctgacac tgctgaaggc actggtcaga 1020

cagcagctgc cggaaaagta caaggaaatc ttcttcgacc agagcaagaa cggatacgca 1080

ggatacatcg acggaggagc aagccaggaa gaattctaca agttcatcaa gccgatcctg 1140

gaaaagatgg acggaacaga agaactgctg gtcaagctga acagagaaga cctgctgaga 1200

aagcagagaa cattcgacaa cggaagcatc ccgcaccaga tccacctggg agaactgcac 1260

gcaatcctga gaagacagga agacttctac ccgttcctga aggacaacag agaaaagatc 1320

gaaaagatcc tgacattcag aatcccgtac tacgtcggac cgctggcaag aggaaacagc 1380

agattcgcat ggatgacaag aaagagcgaa gaaacaatca caccgtggaa cttcgaagaa 1440

gtcgtcgaca agggagcaag cgcacagagc ttcatcgaaa gaatgacaaa cttcgacaag 1500

aacctgccga acgaaaaggt cctgccgaag cacagcctgc tgtacgaata cttcacagtc 1560

tacaacgaac tgacaaaggt caagtacgtc acagaaggaa tgagaaagcc ggcattcctg 1620

agcggagaac agaagaaggc aatcgtcgac ctgctgttca agacaaacag aaaggtcaca 1680

gtcaagcagc tgaaggaaga ctacttcaag aagatcgaat gcttcgacag cgtcgaaatc 1740

agcggagtcg aagacagatt caacgcaagc ctgggaacat accacgacct gctgaagatc 1800

atcaaggaca aggacttcct ggacaacgaa gaaaacgaag acatcctgga agacatcgtc 1860

ctgacactga cactgttcga agacagagaa atgatcgaag aaagactgaa gacatacgca 1920

cacctgttcg acgacaaggt catgaagcag ctgaagagaa gaagatacac aggatgggga 1980

agactgagca gaaagctgat caacggaatc agagacaagc agagcggaaa gacaatcctg 2040

gacttcctga agagcgacgg attcgcaaac agaaacttca tgcagctgat ccacgacgac 2100

agcctgacat tcaaggaaga catccagaag gcacaggtca gcggacaggg agacagcctg 2160

cacgaacaca tcgcaaacct ggcaggaagc ccggcaatca agaagggaat cctgcagaca 2220

gtcaaggtcg tcgacgaact ggtcaaggtc atgggaagac acaagccgga aaacatcgtc 2280

atcgaaatgg caagagaaaa ccagacaaca cagaagggac agaagaacag cagagaaaga 2340

atgaagagaa tcgaagaagg aatcaaggaa ctgggaagcc agatcctgaa ggaacacccg 2400

gtcgaaaaca cacagctgca gaacgaaaag ctgtacctgt actacctgca gaacggaaga 2460

gacatgtacg tcgaccagga actggacatc aacagactga gcgactacga cgtcgaccac 2520

atcgtcccgc agagcttcct gaaggacgac agcatcgaca acaaggtcct gacaagaagc 2580

gacaagaaca gaggaaagag cgacaacgtc ccgagcgaag aagtcgtcaa gaagatgaag 2640

aactactgga gacagctgct gaacgcaaag ctgatcacac agagaaagtt cgacaacctg 2700

acaaaggcag agagaggagg actgagcgaa ctggacaagg caggattcat caagagacag 2760

ctggtcgaaa caagacagat cacaaagcac gtcgcacaga tcctggacag cagaatgaac 2820

acaaagtacg acgaaaacga caagctgatc agagaagtca aggtcatcac actgaagagc 2880

aagctggtca gcgacttcag aaaggacttc cagttctaca aggtcagaga aatcaacaac 2940

taccaccacg cacacgacgc atacctgaac gcagtcgtcg gaacagcact gatcaagaag 3000

tacccgaagc tggaaagcga attcgtctac ggagactaca aggtctacga cgtcagaaag 3060

atgatcgcaa agagcgaaca ggaaatcgga aaggcaacag caaagtactt cttctacagc 3120

aacatcatga acttcttcaa gacagaaatc acactggcaa acggagaaat cagaaagaga 3180

ccgctgatcg aaacaaacgg agaaacagga gaaatcgtct gggacaaggg aagagacttc 3240

gcaacagtca gaaaggtcct gagcatgccg caggtcaaca tcgtcaagaa gacagaagtc 3300

cagacaggag gattcagcaa ggaaagcatc ctgccgaaga gaaacagcga caagctgatc 3360

gcaagaaaga aggactggga cccgaagaag tacggaggat tcgacagccc gacagtcgca 3420

tacagcgtcc tggtcgtcgc aaaggtcgaa aagggaaaga gcaagaagct gaagagcgtc 3480

aaggaactgc tgggaatcac aatcatggaa agaagcagct tcgaaaagaa cccgatcgac 3540

ttcctggaag caaagggata caaggaagtc aagaaggacc tgatcatcaa gctgccgaag 3600

tacagcctgt tcgaactgga aaacggaaga aagagaatgc tggcaagcgc aggagaactg 3660

cagaagggaa acgaactggc actgccgagc aagtacgtca acttcctgta cctggcaagc 3720

cactacgaaa agctgaaggg aagcccggaa gacaacgaac agaagcagct gttcgtcgaa 3780

cagcacaagc actacctgga cgaaatcatc gaacagatca gcgaattcag caagagagtc 3840

atcctggcag acgcaaacct ggacaaggtc ctgagcgcat acaacaagca cagagacaag 3900

ccgatcagag aacaggcaga aaacatcatc cacctgttca cactgacaaa cctgggagca 3960

ccggcagcat tcaagtactt cgacacaaca atcgacagaa agagatacac aagcacaaag 4020

gaagtcctgg acgcaacact gatccaccag agcatcacag gactgtacga aacaagaatc 4080

gacctgagcc agctgggagg agacggagga ggaagcccga agaagaagag aaaggtctag   4140

<210> 802
<211> 4140
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 802
atggacaaga agtactccat cggcctggac atcggcacca actccgtggg ctgggccgtg   60

atcaccgacg agtacaaggt gccctccaag aagttcaagg tgctgggcaa caccgaccgg   120

cactccatca agaagaacct gatcggcgcc ctgctgttcg actccggcga gaccgccgag   180

gccacccggc tgaagcggac cgcccggcgg cggtacaccc ggcggaagaa ccggatctgc   240

tacctgcagg agatcttctc caacgagatg gccaaggtgg acgactcctt cttccaccgg   300

ctggaggagt ccttcctggt ggaggaggac aagaagcacg agcggcaccc catcttcggc   360

aacatcgtgg acgaggtggc ctaccacgag aagtacccca ccatctacca cctgcggaag   420

aagctggtgg actccaccga caaggccgac ctgcggctga tctacctggc cctggcccac   480

atgatcaagt tccggggcca cttcctgatc gagggcgacc tgaaccccga caactccgac   540

gtggacaagc tgttcatcca gctggtgcag acctacaacc agctgttcga ggagaacccc   600

atcaacgcct ccggcgtgga cgccaaggcc atcctgtccg cccggctgtc caagtcccgg   660

cggctggaga acctgatcgc ccagctgccc ggcgagaaga agaacggcct gttcggcaac   720

ctgatcgccc tgtccctggg cctgaccccc aacttcaagt ccaacttcga cctggccgag   780

gacgccaagc tgcagctgtc caaggacacc tacgacgacg acctggacaa cctgctggcc   840

cagatcggcg accagtacgc cgacctgttc ctggccgcca agaacctgtc cgacgccatc   900

ctgctgtccg acatcctgcg ggtgaacacc gagatcacca aggcccccct gtccgcctcc   960

atgatcaagc ggtacgacga gcaccaccag gacctgaccc tgctgaaggc cctggtgcgg   1020

cagcagctgc ccgagaagta caaggagatc ttcttcgacc agtccaagaa cggctacgcc   1080

ggctacatcg acggcggcgc ctcccaggag gagttctaca agttcatcaa gcccatcctg   1140

gagaagatgg acggcaccga ggagctgctg gtgaagctga accgggagga cctgctgcgg 1200

aagcagcgga ccttcgacaa cggctccatc ccccaccaga tccacctggg cgagctgcac 1260

gccatcctgc ggcggcagga ggacttctac cccttcctga aggacaaccg ggagaagatc 1320

gagaagatcc tgaccttccg gatcccctac tacgtgggcc ccctggcccg gggcaactcc 1380

cggttcgcct ggatgacccg gaagtccgag gagaccatca ccccctggaa cttcgaggag 1440

gtggtggaca agggcgcctc cgcccagtcc ttcatcgagc ggatgaccaa cttcgacaag 1500

aacctgccca acgagaaggt gctgcccaag cactccctgc tgtacgagta cttcaccgtg 1560

tacaacgagc tgaccaaggt gaagtacgtg accgagggca tgcggaagcc cgccttcctg 1620

tccggcgagc agaagaaggc catcgtggac ctgctgttca agaccaaccg gaaggtgacc 1680

gtgaagcagc tgaaggagga ctacttcaag aagatcgagt gcttcgactc cgtggagatc 1740

tccggcgtgg aggaccggtt caacgcctcc ctgggcacct accacgacct gctgaagatc 1800

atcaaggaca aggacttcct ggacaacgag gagaacgagg acatcctgga ggacatcgtg 1860

ctgaccctga ccctgttcga ggaccgggag atgatcgagg agcggctgaa gacctacgcc 1920

cacctgttcg acgacaaggt gatgaagcag ctgaagcggc ggcggtacac cggctggggc 1980

cggctgtccc ggaagctgat caacggcatc cgggacaagc agtccggcaa gaccatcctg 2040

gacttcctga agtccgacgg cttcgccaac cggaacttca tgcagctgat ccacgacgac 2100

tccctgacct tcaaggagga catccagaag gcccaggtgt ccggccaggg cgactccctg 2160

cacgagcaca tcgccaacct ggccggctcc cccgccatca agaagggcat cctgcagacc 2220

gtgaaggtgg tggacgagct ggtgaaggtg atgggccggc acaagcccga gaacatcgtg 2280

atcgagatgg cccgggagaa ccagaccacc cagaagggcc agaagaactc ccgggagcgg 2340

atgaagcgga tcgaggaggg catcaaggag ctgggctccc agatcctgaa ggagcacccc 2400

gtggagaaca cccagctgca gaacgagaag ctgtacctgt actacctgca gaacggccgg 2460

gacatgtacg tggaccagga gctggacatc aaccggctgt ccgactacga cgtggaccac 2520

atcgtgcccc agtccttcct gaaggacgac tccatcgaca acaaggtgct gacccggtcc 2580

gacaagaacc ggggcaagtc cgacaacgtg ccctccgagg aggtggtgaa gaagatgaag 2640

aactactggc ggcagctgct gaacgccaag ctgatcaccc agcggaagtt cgacaacctg 2700

accaaggccg agcggggcgg cctgtccgag ctggacaagg ccggcttcat caagcggcag 2760

ctggtggaga cccggcagat caccaagcac gtggcccaga tcctggactc ccggatgaac 2820

accaagtacg acgagaacga caagctgatc cgggaggtga aggtgatcac cctgaagtcc 2880

aagctggtgt ccgacttccg gaaggacttc cagttctaca aggtgcggga gatcaacaac 2940

taccaccacg cccacgacgc ctacctgaac gccgtggtgg gcaccgccct gatcaagaag 3000

taccccaagc tggagtccga gttcgtgtac ggcgactaca aggtgtacga cgtgcggaag 3060

atgatcgcca agtccgagca ggagatcggc aaggccaccg ccaagtactt cttctactcc 3120

aacatcatga acttcttcaa gaccgagatc accctggcca acggcgagat ccggaagcgg 3180

cccctgatcg agaccaacgg cgagaccggc gagatcgtgt gggacaaggg ccgggacttc 3240

gccaccgtgc ggaaggtgct gtccatgccc caggtgaaca tcgtgaagaa gaccgaggtg 3300

cagaccggcg gcttctccaa ggagtccatc ctgcccaagc ggaactccga caagctgatc 3360

gcccggaaga aggactggga ccccaagaag tacggcggct tcgactcccc caccgtggcc 3420

tactccgtgc tggtggtggc caaggtggag aagggcaagt ccaagaagct gaagtccgtg 3480

aaggagctgc tgggcatcac catcatggag cggtcctcct tcgagaagaa ccccatcgac 3540

ttcctggagg ccaagggcta caaggaggtg aagaaggacc tgatcatcaa gctgcccaag 3600

tactccctgt tcgagctgga gaacggccgg aagcggatgc tggcctccgc cggcgagctg 3660

cagaagggca acgagctggc cctgccctcc aagtacgtga acttcctgta cctggcctcc 3720

cactacgaga agctgaaggg ctcccccgag gacaacgagc agaagcagct gttcgtggag 3780

cagcacaagc actacctgga cgagatcatc gagcagatct ccgagttctc caagcgggtg 3840

atcctggccg acgccaacct ggacaaggtg ctgtccgcct acaacaagca ccgggacaag 3900

cccatccggg agcaggccga gaacatcatc cacctgttca ccctgaccaa cctgggcgcc 3960

cccgccgcct tcaagtactt cgacaccacc atcgaccgga agcggtacac ctccaccaag 4020

gaggtgctgg acgccaccct gatccaccag tccatcaccg gcctgtacga gacccggatc 4080

gacctgtccc agctgggcgg cgacggcggc ggctccccca agaagaagcg gaaggtgtga 4140

<210> 803
<211> 4197
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 803
auggacaaga aguacuccau cggccuggac aucggcacca acuccguggg cugggccgug   60

aucaccgacg aguacaaggu gcccuccaag aaguucaagg ugcugggcaa caccgaccgg   120

cacuccauca agaagaaccu gaucggcgcc cugcuguucg acuccggcga gaccgccgag   180

gccacccggc ugaagcggac cgcccggcgg cgguacaccc ggcggaagaa ccggaucugc   240

uaccugcagg agaucuucuc caacgagaug gccaaggugg acgacuccuu cuuccaccgg   300

cuggaggagu ccuuccuggu ggaggaggac aagaagcacg agcggcaccc caucuucggc   360

aacaucgugg acgagguggc cuaccacgag aaguacccca ccaucuacca ccugcggaag   420

aagcuggugg acuccaccga caaggccgac cugcggcuga ucuaccuggc ccuggcccac   480

augaucaagu uccggggcca cuuccugauc gagggcgacc ugaaccccga caacuccgac   540

guggacaagc uguucaucca gcuggugcag accuacaacc agcuguucga ggagaacccc   600

aucaacgccu ccggcgugga cgccaaggcc auccuguccg cccggcuguc caagucccgg   660

cggcuggaga accugaucgc ccagcugccc ggcgagaaga agaacggccu guucggcaac   720

cugaucgccc ugucccuggg ccugaccccc aacuucaagu ccaacuucga ccuggccgag   780

gacgccaagc ugcagcuguc caaggacacc uacgacgacg accuggacaa ccugcuggcc   840

cagaucggcg accaguacgc cgaccuguuc cuggccgcca agaaccuguc cgacgccauc   900

cugcuguccg acauccugcg ggugaacacc gagaucacca aggccccccu guccgccucc   960

augaucaagc gguacgacga gcaccaccag gaccugaccc ugcugaaggc ccuggugcgg   1020

cagcagcugc ccgagaagua caaggagauc uucuucgacc aguccaagaa cggcuacgcc   1080

ggcuacaucg acggcggcgc cucccaggag gaguucuaca aguucaucaa gcccauccug   1140

gagaagaugg acggcaccga ggagcugcug gugaagcuga accgggagga ccugcugcgg   1200

aagcagcgga ccuucgacaa cggcuccauc ccccaccaga uccaccuggg cgagcugcac 1260

gccauccugc ggcggcagga ggacuucuac cccuuccuga aggacaaccg ggagaagauc 1320

gagaagaucc ugaccuuccg gauccccuac uacgugggcc cccuggcccg gggcaacucc 1380

cgguucgccu ggaugacccg gaaguccgag gagaccauca cccccuggaa cuucgaggag 1440

gugguggaca agggcgccuc cgcccagucc uucaucgagc ggaugaccaa cuucgacaag 1500

aaccugccca acgagaaggu gcugcccaag cacucccugc uguacgagua cuucaccgug 1560

uacaacgagc ugaccaaggu gaaguacgug accgagggca ugcggaagcc cgccuuccug 1620

uccggcgagc agaagaaggc caucguggac cugcuguuca agaccaaccg gaaggugacc 1680

gugaagcagc ugaaggagga cuacuucaag aagaucgagu gcuucgacuc cguggagauc 1740

uccggcgugg aggaccgguu caacgccucc cugggcaccu accacgaccu gcugaagauc 1800

aucaaggaca aggacuuccu ggacaacgag gagaacgagg acauccugga ggacaucgug 1860

cugacccuga cccuguucga ggaccgggag augaucgagg agcggcugaa gaccuacgcc 1920

caccuguucg acgacaaggu gaugaagcag cugaagcggc ggcgguacac cggcuggggc 1980

cggcuguccc ggaagcugau caacggcauc cgggacaagc aguccggcaa gaccauccug 2040

gacuuccuga aguccgacgg cuucgccaac cggaacuuca ugcagcugau ccacgacgac 2100

ucccugaccu ucaaggagga cauccagaag gcccaggugu ccggccaggg cgacucccug 2160

cacgagcaca ucgccaaccu ggccggcucc cccgccauca agaagggcau ccugcagacc 2220

gugaaggugg uggacgagcu ggugaaggug augggccggc acaagcccga gaacaucgug 2280

aucgagaugg cccgggagaa ccagaccacc cagaagggcc agaagaacuc ccgggagcgg 2340

augaagcgga ucgaggaggg caucaaggag cugggcuccc agauccugaa ggagcacccc 2400

guggagaaca cccagcugca gaacgagaag cuguaccugu acuaccugca gaacggccgg 2460

gacauguacg uggaccagga gcuggacauc aaccggcugu ccgacuacga cguggaccac 2520

aucgugcccc aguccuuccu gaaggacgac uccaucgaca acaaggugcu gacccggucc 2580

gacaagaacc ggggcaaguc cgacaacgug cccuccgagg agguggugaa gaagaugaag 2640

aacuacuggc ggcagcugcu gaacgccaag cugaucaccc agcggaaguu cgacaaccug 2700

```
accaaggccg agcggggcgg ccuguccgag cuggacaagg ccggcuucau caagcggcag     2760
cugguggaga cccggcagau caccaagcac guggcccaga uccuggacuc ccggaugaac     2820
accaaguacg acgagaacga caagcugauc cgggaggaga aggugaucac ccugaagucc     2880
aagcuggugu ccgacuuccg gaaggacuuc caguucuaca aggugcggga gaucaacaac     2940
uaccaccacg cccacgacgc cuaccugaac gccguggugg gcaccgcccu gaucaagaag     3000
uaccccaagc uggaguccga guucguguac ggcgacuaca agguguacga cgugcggaag     3060
augaucgcca aguccgagca ggagaucggc aaggccaccg ccaaguacuu cuucuacucc     3120
aacaucauga acuucuucaa gaccgagauc acccuggcca acggcgagau ccggaagcgg     3180
ccccugaucg agaccaacgg cgagaccggc gagaucgugu gggacaaggg ccgggacuuc     3240
gccaccgugc ggaaggugcu guccaugccc caggugaaca ucgugaagaa gaccgaggug     3300
cagaccggcg gcuucuccaa ggaguccauc cugcccaagc ggaacuccga caagcugauc     3360
gcccggaaga aggacuggga ccccaagaag uacggcggcu ucgacucccc caccguggcc     3420
uacuccgugc ugguggugc caagguggag aagggcaagu ccaagaagcu gaaguccgug     3480
aaggagcugc ugggcaucac caucauggag cgguccuccu ucgagaagaa ccccaucgac     3540
uuccuggagg ccaagggcua caaggaggug aagaaggacc ugaucaucaa gcugcccaag     3600
uacucccugu ucgagcugga gaacggccgg aagcggaugc uggccuccgc cggcgagcug     3660
cagaagggca acgagcuggc ccugcccucc aaguacguga acuuccugua ccuggccucc     3720
cacuacgaga agcugaaggg cucccccgag gacaacgagc agaagcagcu guucguggag     3780
cagcacaagc acuaccugga cgagaucauc gagcagaucu ccgaguucuc caagcgggug     3840
auccuggccg acgccaaccu ggacaaggug cuguccgccu acaacaagca ccgggacaag     3900
cccauccggg agcaggccga gaacaucauc caccuguuca cccugaccaa ccugggcgcc     3960
cccgccgccu ucaaguacuu cgacaccacc aucgaccgga agcgguacac cuccaccaag     4020
gaggugcugg acgccacccu gauccaccag uccaucaccg gccuguacga gacccggauc     4080
gaccuguccc agcugggcgg cgacggcggc ggcuccccca agaagaagcg gaagguguccc    4140
gaguccgcca cccccgaguc cguguccggc uggcggcugu ucaagaagau cuccuga        4197
```

<210> 804
<211> 4782
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 804
auggaggccu cccccgccuc cggcccccgg caccugaugg acccccacau cuucaccucc 60

aacuucaaca acggcaucgg ccggcacaag accuaccugu gcuacgaggu ggagcggcug 120

gacaacggca ccuccgugaa gauggaccag caccggggcu uccugcacaa ccaggccaag 180

aaccugcugu gcggcuucua cggccggcac gccgagcugc gguuccugga ccuggugccc 240

ucccugcagc uggaccccgc ccagaucuac cgggugaccu gguucaucuc cugguccccc 300

ugcuucuccu ggggcugcgc cggcgaggug cgggccuucc ugcaggagaa cacccacgug 360

cggcugcgga ucuucgccgc ccggaucuac gacuacgacc cccuguacaa ggaggcccug 420

cagaugcugc gggacgccgg cgcccaggug uccaucauga ccuacgacga guucaagcac 480

ugcugggaca ccuucgugga ccaccagggc ugccccuucc agcccuggga cggccuggac 540

gagcacuccc aggcccuguc cggccggcug cgggccaucc ugcagaacca gggcaacucc 600

ggcuccgaga cccccggcac cuccgagucc gccacccccg aguccgacaa gaaguacucc 660

aucggccugg ccaucggcac caacuccgug ggcugggccg ugaucaccga cgaguacaag 720

gugcccucca agaaguucaa ggugcugggc aacaccgacc ggcacuccau caagaagaac 780

cugaucggcg cccugcuguu cgacuccggc gagaccgccg aggccacccg gcugaagcgg 840

accgcccggc ggcgguacac ccggcggaag aaccggaucu gcuaccugca ggagaucuuc 900

uccaacgaga uggccaaggu ggacgacucc uucuuccacc ggcuggagga guccuuccug 960

guggaggagg acaagaagca cgagcggcac cccaucuucg gcaacaucgu ggacgaggug 1020

gccuaccacg agaaguaccc caccaucuac caccugcgga agaagcuggu ggacuccacc 1080

gacaaggccg accugcggcu gaucuaccug gcccuggccc acaugaucaa guuccggggc 1140

cacuuccuga ucgagggcga ccugaacccc gacaacuccg acguggacaa gcuguucauc 1200

cagcuggugc agaccuacaa ccagcuguuc gaggagaacc ccaucaacgc cuccggcgug 1260

gacgccaagg ccauccuguc cgcccggcug uccaaguccc ggcggcugga gaaccugauc 1320

gcccagcugc ccggcgagaa gaagaacggc cuguucggca accugaucgc ccugucccug 1380

ggccugaccc ccaacuucaa guccaacuuc gaccuggccg aggacgccaa gcugcagcug 1440

uccaaggaca ccuacgacga cgaccuggac aaccugcugg cccagaucgg cgaccaguac 1500

gccgaccugu uccuggccgc caagaaccug uccgacgcca uccugcuguc cgacauccug 1560

cgggugaaca ccgagaucac caaggccccc cuguccgccu ccaugaucaa gcgguacgac 1620

gagcaccacc aggaccugac ccugcugaag gcccuggugc ggcagcagcu gcccgagaag 1680

uacaaggaga ucuucuucga ccaguccaag aacggcuacg ccggcuacau cgacggcggc 1740

gccucccagg aggaguucua caaguucauc aagcccaucc uggagaagau ggacggcacc 1800

gaggagcugc uggugaagcu gaaccgggag gaccugcugc ggaagcagcg gaccuucgac 1860

aacggcucca ucccccacca gauccaccug ggcgagcugc acgccauccu gcggcggcag 1920

gaggacuucu accccuuccu gaaggacaac cgggagaaga ucgagaagau ccugaccuuc 1980

cggaucccu acuacguggg cccccuggcc cggggcaacu cccgguucgc cuggaugacc 2040

cggaaguccg aggagaccau cacccccugg aacuucgagg agguggugga caagggcgcc 2100

uccgcccagu ccuucaucga gcggaugacc aacuucgaca agaaccugcc caacgagaag 2160

gugcugccca agcacucccu gcuguacgag uacuucaccg uguacaacga gcugaccaag 2220

gugaaguacg ugaccgaggg caugcggaag cccgccuucc uguccggcga gcagaagaag 2280

gccaucgugg accugcuguu caagaccaac cggaagguga ccgugaagca gcugaaggag 2340

gacuacuuca agaagaucga gugcuucgac uccguggaga ucuccggcgu ggaggaccgg 2400

uucaacgccu cccugggcac cuaccacgac cugcugaaga ucaucaagga caaggacuuc 2460

cuggacaacg aggagaacga ggacauccug gaggacaucg ugcugacccu gacccuguuc 2520

gaggaccggg agaugaucga ggagcggcug aagaccuacg cccaccuguu cgacgacaag 2580

gugaugaagc agcugaagcg gcggcgguac accggcuggg gccggcuguc ccggaagcug 2640

aucaacggca uccgggacaa gcaguccggc aagaccaucc uggacuuccu gaaguccgac 2700

ggcuucgcca accggaacuu caugcagcug auccacgacg acucccugac cuucaaggag 2760

gacauccaga aggcccaggu guccggccag ggcgacuccc ugcacgagca caucgccaac 2820

cuggccggcu cccccgccau caagaagggc auccugcaga ccgugaaggu gguggacgag 2880

cuggugaagg ugaugggccg gcacaagccc gagaacaucg ugaucgagau ggcccgggag 2940

aaccagacca cccagaaggg ccagaagaac ucccgggagc ggaugaagcg gaucgaggag 3000

ggcaucaagg agcugggcuc ccagauccug aaggagcacc ccguggagaa cacccagcug 3060

cagaacgaga agcuguaccu guacuaccug cagaacggcc gggacaugua cguggaccag 3120

gagcuggaca ucaaccggcu guccgacuac gacguggacc acaucgugcc ccaguccuuc 3180

cugaaggacg acuccaucga caacaaggug cugacccggu ccgacaagaa ccggggcaag 3240

uccgacaacg ugcccuccga ggagguggug aagaagauga agaacuacug gcggcagcug 3300

cugaacgcca agcugaucac ccagcggaag uucgacaacc ugaccaaggc cgagcggggc 3360

ggccuguccg agcuggacaa ggccggcuuc aucaagcggc agcuggugga gacccggcag 3420

aucaccaagc acguggccca gauccuggac ucccggauga acaccaagua cgacgagaac 3480

gacaagcuga uccgggaggu gaaggugauc acccugaagu ccaagcuggu guccgacuuc 3540

cggaaggacu uccaguucua caaggugcgg gagaucaaca acuaccacca cgcccacgac 3600

gccuaccuga acgccguggu gggcaccgcc cugaucaaga aguaccccaa gcuggagucc 3660

gaguucgugu acggcgacua caagguguac gacgugcgga agaugaucgc caaguccgag 3720

caggagaucg gcaaggccac cgccaaguac uucuucuacu ccaacaucau gaacuucuuc 3780

aagaccgaga ucacccuggc caacggcgag auccggaagc ggccccugau cgagaccaac 3840

ggcgagaccg gcgagaucgu gugggacaag ggccgggacu ucgccaccgu gcggaaggug 3900

cuguccaugc cccaggugaa caucgugaag aagaccgagg ugcagaccgg cggcuucucc 3960

aaggagucca uccugcccaa gcggaacucc gacaagcuga ucgcccggaa gaaggacugg 4020

gaccccaaga aguacggcgg cuucgacucc cccaccgugg ccuacuccgu gcugguggug 4080

gccaaggugg agaagggcaa guccaagaag cugaaguccg ugaaggagcu gcugggcauc 4140

accaucaugg agcgguccuc cuucgagaag aaccccaucg acuuccugga ggccaagggc 4200

uacaaggagg ugaagaagga ccugaucauc aagcugccca aguacucccu guucgagcug 4260

gagaacggcc ggaagcggau gcuggccucc gccggcgagc ugcagaaggg caacgagcug 4320

gcccugcccu ccaaguacgu gaacuuccug uaccuggccu cccacuacga gaagcugaag 4380

ggcucccccg aggacaacga gcagaagcag cuguucgugg agcagcacaa gcacuaccug 4440

gacgagauca ucgagcagau cuccgaguuc uccaagcggg ugauccuggc cgacgccaac 4500

cuggacaagg ugcuguccgc cuacaacaag caccgggaca agcccauccg ggagcaggcc 4560

gagaacauca uccaccuguu cacccugacc aaccugggcg cccccgccgc cuucaaguac 4620

uucgacacca ccaucgaccg gaagcgguac accuccacca aggaggugcu ggacgccacc 4680

cugauccacc aguccaucac cggccuguac gagacccgga ucgaccuguc ccagcugggc 4740

ggcgacggcg gcggcucccc caagaagaag cggaaggugu ga 4782

<210> 805
<211> 4839
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 805
auggaggccu cccccgccuc cggcccccgg caccugaugg acccccacau cuucaccucc 60

aacuucaaca acggcaucgg ccggcacaag accuaccugu gcuacgaggu ggagcggcug 120

gacaacggca ccuccgugaa gauggaccag caccggggcu uccugcacaa ccaggccaag 180

aaccugcugu gcggcuucua cggccggcac gccgagcugc gguuccugga ccuggugccc 240

ucccugcagc uggaccccgc ccagaucuac cgggugaccu gguucaucuc cugguccccc 300

ugcuucuccu ggggcugcgc cggcgaggug cgggccuucc ugcaggagaa cacccacgug 360

cggcugcgga ucuucgccgc ccggaucuac gacuacgacc cccuguacaa ggaggcccug 420

cagaugcugc gggacgccgg cgcccaggug uccaucauga ccuacgacga guucaagcac 480

ugcugggaca ccuucgugga ccaccagggc ugccccuucc agcccuggga cggccuggac 540

gagcacuccc aggcccuguc cggccggcug cgggccaucc ugcagaacca gggcaacucc 600

ggcuccgaga cccccggcac cuccgagucc gccacccccg aguccgacaa gaaguacucc 660

aucggccugg ccaucggcac caacuccgug ggcugggccg ugaucaccga cgaguacaag 720

gugcccucca agaaguucaa ggugcugggc aacaccgacc ggcacuccau caagaagaac 780

cugaucggcg cccugcuguu cgacuccggc gagaccgccg aggccacccg gcugaagcgg 840

accgcccggc ggcgguacac ccggcggaag aaccggaucu gcuaccugca ggagaucuuc 900

uccaacgaga uggccaaggu ggacgacucc uucuuccacc ggcuggagga guccuuccug 960

guggaggagg acaagaagca cgagcggcac cccaucuucg gcaacaucgu ggacgaggug 1020

gccuaccacg agaaguaccc caccaucuac caccugcgga agaagcuggu ggacuccacc 1080

gacaaggccg accugcggcu gaucuaccug gcccuggccc acaugaucaa guuccggggc 1140

cacuuccuga ucgagggcga ccugaacccc gacaacuccg acguggacaa gcuguucauc 1200

cagcuggugc agaccuacaa ccagcuguuc gaggagaacc ccaucaacgc cuccggcgug 1260

gacgccaagg ccauccuguc cgcccggcug uccaaguccc ggcggcugga gaaccugauc 1320

gcccagcugc ccggcgagaa gaagaacggc cuguucggca accugaucgc ccugucccug 1380

ggccugaccc ccaacuucaa guccaacuuc gaccuggccg aggacgccaa gcugcagcug 1440

uccaaggaca ccuacgacga cgaccuggac aaccugcugg cccagaucgg cgaccaguac 1500

gccgaccugu uccuggccgc caagaaccug uccgacgcca uccugcuguc cgacauccug 1560

cgggugaaca ccgagaucac caaggccccc cuguccgccu ccaugaucaa gcgguacgac 1620

gagcaccacc aggaccugac ccugcugaag gcccuggugc ggcagcagcu gcccgagaag 1680

uacaaggaga ucuucuucga ccaguccaag aacggcuacg ccggcuacau cgacggcggc 1740

gccucccagg aggaguucua caaguucauc aagcccaucc uggagaagau ggacggcacc 1800

gaggagcugc uggugaagcu gaaccgggag gaccugcugc ggaagcagcg gaccuucgac 1860

aacggcucca ucccccacca gauccaccug ggcgagcugc acgccauccu gcggcggcag 1920

gaggacuucu accccuuccu gaaggacaac cgggagaaga ucgagaagau ccugaccuuc 1980

cggauccccu acuacguggg cccccuggcc cggggcaacu cccgguucgc cuggaugacc 2040

cggaaguccg aggagaccau cacccccugg aacuucgagg agguggugga caagggcgcc 2100

uccgcccagu ccuucaucga gcggaugacc aacuucgaca agaaccugcc caacgagaag 2160

gugcugccca agcacucccu gcuguacgag uacuucaccg uguacaacga gcugaccaag 2220

gugaaguacg ugaccgaggg caugcggaag cccgccuucc uguccggcga gcagaagaag 2280

gccaucgugg accugcuguu caagaccaac cggaagguga ccgugaagca gcugaaggag 2340

gacuacuuca agaagaucga gugcuucgac uccguggaga ucuccggcgu ggaggaccgg 2400

uucaacgccu cccugggcac cuaccacgac cugcugaaga ucaucaagga caaggacuuc 2460

cuggacaacg aggagaacga ggacauccug gaggacaucg ugcugacccu gacccuguuc 2520

gaggaccggg agaugaucga ggagcggcug aagaccuacg cccaccuguu cgacgacaag 2580

gugaugaagc agcugaagcg gcggcgguac accggcuggg gccggcuguc ccggaagcug 2640

aucaacggca uccgggacaa gcaguccggc aagaccaucc uggacuuccu gaaguccgac 2700

ggcuucgcca accggaacuu caugcagcug auccacgacg acucccugac cuucaaggag 2760

gacauccaga aggcccaggu guccggccag ggcgacuccc ugcacgagca caucgccaac 2820

cuggccggcu cccccgccau caagaagggc auccugcaga ccgugaaggu gguggacgag 2880

cuggugaagg ugaugggccg gcacaagccc gagaacaucg ugaucgagau ggcccgggag 2940

aaccagacca cccagaaggg ccagaagaac ucccgggagc ggaugaagcg gaucgaggag 3000

ggcaucaagg agcugggcuc ccagauccug aaggagcacc ccguggagaa cacccagcug 3060

cagaacgaga agcuguaccu guacuaccug cagaacggcc gggacaugua cguggaccag 3120

gagcuggaca ucaaccggcu guccgacuac gacguggacc acaucgugcc ccaguccuuc 3180

cugaaggacg acuccaucga caacaaggug cugacccggu ccgacaagaa ccggggcaag 3240

uccgacaacg ugcccuccga ggagguggug aagaagauga agaacuacug gcggcagcug 3300

cugaacgcca agcugaucac ccagcggaag uucgacaacc ugaccaaggc cgagcggggc 3360

ggccuguccg agcuggacaa ggccggcuuc aucaagcggc agcuggugga gacccggcag 3420

aucaccaagc acguggccca gauccuggac ucccggauga acaccaagua cgacgagaac 3480

gacaagcuga uccgggaggu gaaggugauc acccugaagu ccaagcuggu guccgacuuc 3540

cggaaggacu uccaguucua caaggugcgg gagaucaaca acuaccacca cgcccacgac 3600

gccuaccuga acgccguggu gggcaccgcc cugaucaaga aguaccccaa gcuggagucc 3660

gaguucgugu acggcgacua caagguguac gacgugcgga agaugaucgc caaguccgag 3720

caggagaucg gcaaggccac cgccaaguac uucuucuacu ccaacaucau gaacuucuuc 3780

aagaccgaga ucacccuggc caacggcgag auccggaagc ggccccugau cgagaccaac 3840

ggcgagaccg gcgagaucgu gugggacaag ggccgggacu ucgccaccgu gcggaaggug 3900

cuguccaugc cccaggugaa caucgugaag aagaccgagg ugcagaccgg cggcuucucc 3960

aaggagucca uccugcccaa gcggaacucc gacaagcuga ucgcccggaa gaaggacugg 4020

gaccccaaga aguacggcgg cuucgacucc cccaccgugg ccuacuccgu gcugguggug 4080

gccaaggugg agaagggcaa guccaagaag cugaaguccg ugaaggagcu gcugggcauc 4140

accaucaugg agcgguccuc cuucgagaag aaccccaucg acuuccugga ggccaagggc 4200

uacaaggagg ugaagaagga ccugaucauc aagcugccca aguacucccu guucgagcug 4260

gagaacggcc ggaagcggau gcuggccucc gccggcgagc ugcagaaggg caacgagcug 4320

gcccugcccu ccaaguacgu gaacuuccug uaccuggccu cccacuacga gaagcugaag 4380

ggcuccccg aggacaacga gcagaagcag cuguucgugg agcagcacaa gcacuaccug 4440

gacgagauca ucgagcagau cuccgaguuc uccaagcggg ugauccuggc cgacgccaac 4500

cuggacaagg ugcuguccgc cuacaacaag caccgggaca agcccauccg ggagcaggcc 4560

gagaacauca uccaccuguu cacccugacc aaccugggcg cccccgccgc cuucaaguac 4620

uucgacacca ccaucgaccg gaagcgguac accuccacca aggaggugcu ggacgccacc 4680

cugauccacc aguccaucac cggccuguac gagacccgga ucgaccuguc ccagcugggc 4740

ggcgacggcg gcggcucccc caagaagaag cggaaggugu ccgaguccgc cacccccgag 4800

uccguguccg gcuggcggcu guucaagaag aucuccuga 4839

<210> 806

<400> 806
000

<210> 807
<211> 291

<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 807
augggaccga agaagaagag aaaggucgga ggaggaagca caaaccuguc ggacaucauc   60

gaaaaggaaa caggaaagca gcuggucauc caggaaucga uccugaugcu gccggaagaa   120

gucgaagaag ucaucggaaa caagccggaa ucggacaucc ugguccacac agcauacgac   180

gaaucgacag acgaaaacgu caugcugcug acaucggacg caccggaaua caagccgugg   240

gcacugguca uccaggacuc gaacggagaa aacaagauca agaugcugug a   291

<210> 808
<211> 324
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 808
augaccaacc uguccgacau caucgagaag gagaccggca agcagcuggu gauccaggag   60

uccauccuga ugcugcccga ggagguggag gaggugaucg gcaacaagcc cgaguccgac   120

auccuggugc acaccgccua cgacgagucc accgacgaga acgugaugcu gcugaccucc   180

gacgcccccg aguacaagcc cugggcccug gugauccagg acuccaacgg cgagaacaag   240

aucaagaugc uguccggcgg cuccaagcgg accgccgacg gcuccgaguu cgaguccccc   300

aagaagaagc ggaaggugga guga   324

<210> 809
<211> 1379
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 809

```
Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly Thr Asn Ser Val
1               5                   10                  15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
            20                  25                  30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
        35                  40                  45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
    50                  55                  60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65                  70                  75                  80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
                85                  90                  95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
            100                 105                 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
        115                 120                 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
    130                 135                 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145                 150                 155                 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
                165                 170                 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
            180                 185                 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
        195                 200                 205
```

```
Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
    210                 215                 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225                 230                 235                 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
                245                 250                 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
            260                 265                 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
        275                 280                 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
    290                 295                 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305                 310                 315                 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
                325                 330                 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
            340                 345                 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
        355                 360                 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
    370                 375                 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385                 390                 395                 400
```

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
405 410 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

```
Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
    610                 615                 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625                 630                 635                 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
                645                 650                 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
            660                 665                 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
        675                 680                 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
    690                 695                 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705                 710                 715                 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
                725                 730                 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
            740                 745                 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
        755                 760                 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
    770                 775                 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785                 790                 795                 800
```

```
Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
                805                 810                 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
            820                 825                 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
        835                 840                 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
    850                 855                 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865                 870                 875                 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
                885                 890                 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
            900                 905                 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
        915                 920                 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
    930                 935                 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945                 950                 955                 960

Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
                965                 970                 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
            980                 985                 990

Val Gly Thr Ala Leu Ile Lys Lys  Tyr Pro Lys Leu Glu  Ser Glu Phe
        995                 1000                1005
```

```
Val Tyr  Gly Asp Tyr Lys Val  Tyr Asp Val Arg Lys  Met Ile Ala
    1010                1015                1020

Lys Ser  Glu Gln Glu Ile Gly  Lys Ala Thr Ala Lys  Tyr Phe Phe
    1025                1030                1035

Tyr Ser  Asn Ile Met Asn Phe  Phe Lys Thr Glu Ile  Thr Leu Ala
    1040                1045                1050

Asn Gly  Glu Ile Arg Lys Arg  Pro Leu Ile Glu Thr  Asn Gly Glu
    1055                1060                1065

Thr Gly  Glu Ile Val Trp Asp  Lys Gly Arg Asp Phe  Ala Thr Val
    1070                1075                1080

Arg Lys  Val Leu Ser Met Pro  Gln Val Asn Ile Val  Lys Lys Thr
    1085                1090                1095

Glu Val  Gln Thr Gly Gly Phe  Ser Lys Glu Ser Ile  Leu Pro Lys
    1100                1105                1110

Arg Asn  Ser Asp Lys Leu Ile  Ala Arg Lys Lys Asp  Trp Asp Pro
    1115                1120                1125

Lys Lys  Tyr Gly Gly Phe Asp  Ser Pro Thr Val Ala  Tyr Ser Val
    1130                1135                1140

Leu Val  Val Ala Lys Val Glu  Lys Gly Lys Ser Lys  Lys Leu Lys
    1145                1150                1155

Ser Val  Lys Glu Leu Leu Gly  Ile Thr Ile Met Glu  Arg Ser Ser
    1160                1165                1170

Phe Glu  Lys Asn Pro Ile Asp  Phe Leu Glu Ala Lys  Gly Tyr Lys
    1175                1180                1185
```

```
Glu Val  Lys Lys Asp Leu Ile  Ile Lys Leu Pro Lys  Tyr Ser Leu
    1190                1195                1200

Phe Glu  Leu Glu Asn Gly Arg  Lys Arg Met Leu Ala  Ser Ala Gly
    1205                1210                1215

Glu Leu  Gln Lys Gly Asn Glu  Leu Ala Leu Pro Ser  Lys Tyr Val
    1220                1225                1230

Asn Phe  Leu Tyr Leu Ala Ser  His Tyr Glu Lys Leu  Lys Gly Ser
    1235                1240                1245

Pro Glu  Asp Asn Glu Gln Lys  Gln Leu Phe Val Glu  Gln His Lys
    1250                1255                1260

His Tyr  Leu Asp Glu Ile Ile  Glu Gln Ile Ser Glu  Phe Ser Lys
    1265                1270                1275

Arg Val  Ile Leu Ala Asp Ala  Asn Leu Asp Lys Val  Leu Ser Ala
    1280                1285                1290

Tyr Asn  Lys His Arg Asp Lys  Pro Ile Arg Glu Gln  Ala Glu Asn
    1295                1300                1305

Ile Ile  His Leu Phe Thr Leu  Thr Asn Leu Gly Ala  Pro Ala Ala
    1310                1315                1320

Phe Lys  Tyr Phe Asp Thr Thr  Ile Asp Arg Lys Arg  Tyr Thr Ser
    1325                1330                1335

Thr Lys  Glu Val Leu Asp Ala  Thr Leu Ile His Gln  Ser Ile Thr
    1340                1345                1350

Gly Leu  Tyr Glu Thr Arg Ile  Asp Leu Ser Gln Leu  Gly Gly Asp
    1355                1360                1365

Gly Gly  Gly Ser Pro Lys Lys  Lys Arg Lys Val
    1370                1375
```

<210> 810
<211> 1398
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 810

Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly Thr Asn Ser Val
1   5   10   15

Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
            20   25   30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
        35   40   45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
    50   55   60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65   70   75   80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
                85   90   95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
            100   105   110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
        115   120   125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
    130   135   140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
145   150   155   160

```
Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
                165                 170                 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
            180                 185                 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
        195                 200                 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
    210                 215                 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
225                 230                 235                 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
                245                 250                 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
            260                 265                 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
        275                 280                 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
    290                 295                 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
305                 310                 315                 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
                325                 330                 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
            340                 345                 350
```

```
Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
        355                 360                 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
    370                 375                 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385                 390                 395                 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
                405                 410                 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
            420                 425                 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
        435                 440                 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
    450                 455                 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465                 470                 475                 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
                485                 490                 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
            500                 505                 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
        515                 520                 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
    530                 535                 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545                 550                 555                 560
```

```
Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
                565                 570                 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
            580                 585                 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
        595                 600                 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
    610                 615                 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625                 630                 635                 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
                645                 650                 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
            660                 665                 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
        675                 680                 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
    690                 695                 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705                 710                 715                 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
                725                 730                 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
            740                 745                 750
```

```
Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
        755                 760                 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
    770                 775                 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785                 790                 795                 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
                805                 810                 815

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
            820                 825                 830

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
        835                 840                 845

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Asn Arg
    850                 855                 860

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
865                 870                 875                 880

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
                885                 890                 895

Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
            900                 905                 910

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
        915                 920                 925

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
    930                 935                 940

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
945                 950                 955                 960
```

```
Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
                965                 970                 975

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
            980                 985                 990

Val Gly Thr Ala Leu Ile Lys Lys  Tyr Pro Lys Leu Glu  Ser Glu Phe
        995                 1000                1005

Val Tyr  Gly Asp Tyr Lys Val  Tyr Asp Val Arg Lys  Met Ile Ala
    1010                 1015                 1020

Lys Ser  Glu Gln Glu Ile Gly  Lys Ala Thr Ala Lys  Tyr Phe Phe
    1025                 1030                 1035

Tyr Ser  Asn Ile Met Asn Phe  Phe Lys Thr Glu Ile  Thr Leu Ala
    1040                 1045                 1050

Asn Gly  Glu Ile Arg Lys Arg  Pro Leu Ile Glu Thr  Asn Gly Glu
    1055                 1060                 1065

Thr Gly  Glu Ile Val Trp Asp  Lys Gly Arg Asp Phe  Ala Thr Val
    1070                 1075                 1080

Arg Lys  Val Leu Ser Met Pro  Gln Val Asn Ile Val  Lys Lys Thr
    1085                 1090                 1095

Glu Val  Gln Thr Gly Gly Phe  Ser Lys Glu Ser Ile  Leu Pro Lys
    1100                 1105                 1110

Arg Asn  Ser Asp Lys Leu Ile  Ala Arg Lys Lys Asp  Trp Asp Pro
    1115                 1120                 1125

Lys Lys  Tyr Gly Gly Phe Asp  Ser Pro Thr Val Ala  Tyr Ser Val
    1130                 1135                 1140
```

Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu Lys
    1145   1150   1155

Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser Ser
    1160   1165   1170

Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr Lys
    1175   1180   1185

Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser Leu
    1190   1195   1200

Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala Gly
    1205   1210   1215

Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr Val
    1220   1225   1230

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
    1235   1240   1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
    1250   1255   1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
    1265   1270   1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
    1280   1285   1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
    1295   1300   1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
    1310   1315   1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
    1325   1330   1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
    1340   1345   1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
    1355   1360   1365

Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val Ser Glu Ser Ala
    1370   1375   1380

Thr Pro Glu Ser Val Ser Gly Trp Arg Leu Phe Lys Lys Ile Ser
    1385   1390   1395

<210> 811
<211> 1593
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 811

Met Glu Ala Ser Pro Ala Ser Gly Pro Arg His Leu Met Asp Pro His
1   5   10   15

Ile Phe Thr Ser Asn Phe Asn Asn Gly Ile Gly Arg His Lys Thr Tyr
            20   25   30

Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
        35   40   45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
    50   55   60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65   70   75   80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
                85   90   95

```
Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
            100                 105                 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
                165                 170                 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
            180                 185                 190

Ile Leu Gln Asn Gln Gly Asn Ser Gly Ser Glu Thr Pro Gly Thr Ser
        195                 200                 205

Glu Ser Ala Thr Pro Glu Ser Asp Lys Lys Tyr Ser Ile Gly Leu Ala
    210                 215                 220

Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys
225                 230                 235                 240

Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser
                245                 250                 255

Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr
            260                 265                 270

Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg
        275                 280                 285
```

Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met
    290   295   300

Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu
305   310   315   320

Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile
                325   330   335

Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu
            340   345   350

Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile
        355   360   365

Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile
    370   375   380

Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile
385   390   395   400

Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn
                405   410   415

Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys
            420   425   430

Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys
        435   440   445

Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro
    450   455   460

Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu
465   470   475   480

Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile
                485   490   495

```
Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp
            500                 505                 510

Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys
        515                 520                 525

Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln
    530                 535                 540

Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys
545                 550                 555                 560

Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr
                565                 570                 575

Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro
            580                 585                 590

Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn
        595                 600                 605

Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile
    610                 615                 620

Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln
625                 630                 635                 640

Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys
                645                 650                 655

Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly
            660                 665                 670

Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr
        675                 680                 685
```

Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser
    690   695   700

Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys
705   710   715   720

Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn
                725   730   735

Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala
            740   745   750

Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys
        755   760   765

Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys
    770   775   780

Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg
785   790   795   800

Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys
                805   810   815

Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp
            820   825   830

Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu
        835   840   845

Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln
    850   855   860

Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu
865   870   875   880

Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe
                885   890   895

```
Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His
            900                 905                 910

Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser
        915                 920                 925

Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser
    930                 935                 940

Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu
945                 950                 955                 960

Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu
                965                 970                 975

Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg
            980                 985                 990

Glu Arg Met Lys Arg Ile Glu Glu  Gly Ile Lys Glu Leu  Gly Ser Gln
        995                 1000                1005

Ile Leu  Lys Glu His Pro Val  Glu Asn Thr Gln Leu  Gln Asn Glu
    1010                1015                1020

Lys Leu  Tyr Leu Tyr Tyr Leu  Gln Asn Gly Arg Asp  Met Tyr Val
    1025                1030                1035

Asp Gln  Glu Leu Asp Ile Asn  Arg Leu Ser Asp Tyr  Asp Val Asp
    1040                1045                1050

His Ile  Val Pro Gln Ser Phe  Leu Lys Asp Asp Ser  Ile Asp Asn
    1055                1060                1065

Lys Val  Leu Thr Arg Ser Asp  Lys Asn Arg Gly Lys  Ser Asp Asn
    1070                1075                1080
```

Val Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg
1085 1090 1095

Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn
1100 1105 1110

Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala
1115 1120 1125

Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys
1130 1135 1140

His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
1145 1150 1155

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys
1160 1165 1170

Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys
1175 1180 1185

Val Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu
1190 1195 1200

Asn Ala Val Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu
1205 1210 1215

Glu Ser Glu Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg
1220 1225 1230

Lys Met Ile Ala Lys Ser Glu Gln Glu Ile Gly Lys Ala Thr Ala
1235 1240 1245

Lys Tyr Phe Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu
1250 1255 1260

Ile Thr Leu Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu
1265 1270 1275

Thr Asn Gly Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp
1280 1285 1290

Phe Ala Thr Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile
1295 1300 1305

Val Lys Lys Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser
1310 1315 1320

Ile Leu Pro Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys
1325 1330 1335

Asp Trp Asp Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val
1340 1345 1350

Ala Tyr Ser Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser
1355 1360 1365

Lys Lys Leu Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met
1370 1375 1380

Glu Arg Ser Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala
1385 1390 1395

Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro
1400 1405 1410

Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu
1415 1420 1425

Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro
1430 1435 1440

Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys
1445 1450 1455

Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val
    1460   1465   1470

Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser
    1475   1480   1485

Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys
    1490   1495   1500

Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu
    1505   1510   1515

Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly
    1520   1525   1530

Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys
    1535   1540   1545

Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His
    1550   1555   1560

Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln
    1565   1570   1575

Leu Gly Gly Asp Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
    1580   1585   1590

<210> 812
<211> 1612
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 812

Met Glu Ala Ser Pro Ala Ser Gly Pro Arg His Leu Met Asp Pro His
1   5   10   15

```
Ile Phe Thr Ser Asn Phe Asn Asn Gly Ile Gly Arg His Lys Thr Tyr
            20                  25                  30

Leu Cys Tyr Glu Val Glu Arg Leu Asp Asn Gly Thr Ser Val Lys Met
        35                  40                  45

Asp Gln His Arg Gly Phe Leu His Asn Gln Ala Lys Asn Leu Leu Cys
    50                  55                  60

Gly Phe Tyr Gly Arg His Ala Glu Leu Arg Phe Leu Asp Leu Val Pro
65                  70                  75                  80

Ser Leu Gln Leu Asp Pro Ala Gln Ile Tyr Arg Val Thr Trp Phe Ile
                85                  90                  95

Ser Trp Ser Pro Cys Phe Ser Trp Gly Cys Ala Gly Glu Val Arg Ala
            100                 105                 110

Phe Leu Gln Glu Asn Thr His Val Arg Leu Arg Ile Phe Ala Ala Arg
        115                 120                 125

Ile Tyr Asp Tyr Asp Pro Leu Tyr Lys Glu Ala Leu Gln Met Leu Arg
    130                 135                 140

Asp Ala Gly Ala Gln Val Ser Ile Met Thr Tyr Asp Glu Phe Lys His
145                 150                 155                 160

Cys Trp Asp Thr Phe Val Asp His Gln Gly Cys Pro Phe Gln Pro Trp
                165                 170                 175

Asp Gly Leu Asp Glu His Ser Gln Ala Leu Ser Gly Arg Leu Arg Ala
            180                 185                 190

Ile Leu Gln Asn Gln Gly Asn Ser Gly Ser Glu Thr Pro Gly Thr Ser
        195                 200                 205

Glu Ser Ala Thr Pro Glu Ser Asp Lys Lys Tyr Ser Ile Gly Leu Ala
    210                 215                 220
```

```
Ile Gly Thr Asn Ser Val Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys
225                 230                 235                 240

Val Pro Ser Lys Lys Phe Lys Val Leu Gly Asn Thr Asp Arg His Ser
                245                 250                 255

Ile Lys Lys Asn Leu Ile Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr
            260                 265                 270

Ala Glu Ala Thr Arg Leu Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg
        275                 280                 285

Arg Lys Asn Arg Ile Cys Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met
    290                 295                 300

Ala Lys Val Asp Asp Ser Phe Phe His Arg Leu Glu Glu Ser Phe Leu
305                 310                 315                 320

Val Glu Glu Asp Lys Lys His Glu Arg His Pro Ile Phe Gly Asn Ile
                325                 330                 335

Val Asp Glu Val Ala Tyr His Glu Lys Tyr Pro Thr Ile Tyr His Leu
            340                 345                 350

Arg Lys Lys Leu Val Asp Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile
        355                 360                 365

Tyr Leu Ala Leu Ala His Met Ile Lys Phe Arg Gly His Phe Leu Ile
    370                 375                 380

Glu Gly Asp Leu Asn Pro Asp Asn Ser Asp Val Asp Lys Leu Phe Ile
385                 390                 395                 400

Gln Leu Val Gln Thr Tyr Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn
                405                 410                 415
```

```
Ala Ser Gly Val Asp Ala Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys
            420                 425                 430

Ser Arg Arg Leu Glu Asn Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys
        435                 440                 445

Asn Gly Leu Phe Gly Asn Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro
    450                 455                 460

Asn Phe Lys Ser Asn Phe Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu
465                 470                 475                 480

Ser Lys Asp Thr Tyr Asp Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile
                485                 490                 495

Gly Asp Gln Tyr Ala Asp Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp
            500                 505                 510

Ala Ile Leu Leu Ser Asp Ile Leu Arg Val Asn Thr Glu Ile Thr Lys
        515                 520                 525

Ala Pro Leu Ser Ala Ser Met Ile Lys Arg Tyr Asp Glu His His Gln
    530                 535                 540

Asp Leu Thr Leu Leu Lys Ala Leu Val Arg Gln Gln Leu Pro Glu Lys
545                 550                 555                 560

Tyr Lys Glu Ile Phe Phe Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr
                565                 570                 575

Ile Asp Gly Gly Ala Ser Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro
            580                 585                 590

Ile Leu Glu Lys Met Asp Gly Thr Glu Glu Leu Leu Val Lys Leu Asn
        595                 600                 605

Arg Glu Asp Leu Leu Arg Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile
    610                 615                 620
```

```
Pro His Gln Ile His Leu Gly Glu Leu His Ala Ile Leu Arg Arg Gln
625                 630                 635                 640

Glu Asp Phe Tyr Pro Phe Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys
                645                 650                 655

Ile Leu Thr Phe Arg Ile Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly
            660                 665                 670

Asn Ser Arg Phe Ala Trp Met Thr Arg Lys Ser Glu Glu Thr Ile Thr
        675                 680                 685

Pro Trp Asn Phe Glu Glu Val Val Asp Lys Gly Ala Ser Ala Gln Ser
    690                 695                 700

Phe Ile Glu Arg Met Thr Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys
705                 710                 715                 720

Val Leu Pro Lys His Ser Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn
                725                 730                 735

Glu Leu Thr Lys Val Lys Tyr Val Thr Glu Gly Met Arg Lys Pro Ala
            740                 745                 750

Phe Leu Ser Gly Glu Gln Lys Lys Ala Ile Val Asp Leu Leu Phe Lys
        755                 760                 765

Thr Asn Arg Lys Val Thr Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys
    770                 775                 780

Lys Ile Glu Cys Phe Asp Ser Val Glu Ile Ser Gly Val Glu Asp Arg
785                 790                 795                 800

Phe Asn Ala Ser Leu Gly Thr Tyr His Asp Leu Leu Lys Ile Ile Lys
                805                 810                 815
```

```
Asp Lys Asp Phe Leu Asp Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp
            820                 825                 830

Ile Val Leu Thr Leu Thr Leu Phe Glu Asp Arg Glu Met Ile Glu Glu
        835                 840                 845

Arg Leu Lys Thr Tyr Ala His Leu Phe Asp Asp Lys Val Met Lys Gln
    850                 855                 860

Leu Lys Arg Arg Arg Tyr Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu
865                 870                 875                 880

Ile Asn Gly Ile Arg Asp Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe
                885                 890                 895

Leu Lys Ser Asp Gly Phe Ala Asn Arg Asn Phe Met Gln Leu Ile His
            900                 905                 910

Asp Asp Ser Leu Thr Phe Lys Glu Asp Ile Gln Lys Ala Gln Val Ser
        915                 920                 925

Gly Gln Gly Asp Ser Leu His Glu His Ile Ala Asn Leu Ala Gly Ser
    930                 935                 940

Pro Ala Ile Lys Lys Gly Ile Leu Gln Thr Val Lys Val Val Asp Glu
945                 950                 955                 960

Leu Val Lys Val Met Gly Arg His Lys Pro Glu Asn Ile Val Ile Glu
                965                 970                 975

Met Ala Arg Glu Asn Gln Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg
            980                 985                 990

Glu Arg Met Lys Arg Ile Glu Glu  Gly Ile Lys Glu Leu  Gly Ser Gln
        995                 1000                1005

Ile Leu  Lys Glu His Pro Val  Glu Asn Thr Gln Leu  Gln Asn Glu
    1010                1015                1020
```

Lys Leu Tyr Leu Tyr Tyr Leu Gln Asn Gly Arg Asp Met Tyr Val
1025 1030 1035

Asp Gln Glu Leu Asp Ile Asn Arg Leu Ser Asp Tyr Asp Val Asp
1040 1045 1050

His Ile Val Pro Gln Ser Phe Leu Lys Asp Asp Ser Ile Asp Asn
1055 1060 1065

Lys Val Leu Thr Arg Ser Asp Lys Asn Arg Gly Lys Ser Asp Asn
1070 1075 1080

Val Pro Ser Glu Glu Val Val Lys Lys Met Lys Asn Tyr Trp Arg
1085 1090 1095

Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys Phe Asp Asn
1100 1105 1110

Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp Lys Ala
1115 1120 1125

Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr Lys
1130 1135 1140

His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
1145 1150 1155

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys
1160 1165 1170

Ser Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys
1175 1180 1185

Val Arg Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu
1190 1195 1200

```
Asn Ala  Val Val Gly Thr Ala  Leu Ile Lys Lys Tyr  Pro Lys Leu
    1205                 1210                 1215

Glu Ser  Glu Phe Val Tyr Gly  Asp Tyr Lys Val Tyr  Asp Val Arg
    1220                 1225                 1230

Lys Met  Ile Ala Lys Ser Glu  Gln Glu Ile Gly Lys  Ala Thr Ala
    1235                 1240                 1245

Lys Tyr  Phe Phe Tyr Ser Asn  Ile Met Asn Phe Phe  Lys Thr Glu
    1250                 1255                 1260

Ile Thr  Leu Ala Asn Gly Glu  Ile Arg Lys Arg Pro  Leu Ile Glu
    1265                 1270                 1275

Thr Asn  Gly Glu Thr Gly Glu  Ile Val Trp Asp Lys  Gly Arg Asp
    1280                 1285                 1290

Phe Ala  Thr Val Arg Lys Val  Leu Ser Met Pro Gln  Val Asn Ile
    1295                 1300                 1305

Val Lys  Lys Thr Glu Val Gln  Thr Gly Gly Phe Ser  Lys Glu Ser
    1310                 1315                 1320

Ile Leu  Pro Lys Arg Asn Ser  Asp Lys Leu Ile Ala  Arg Lys Lys
    1325                 1330                 1335

Asp Trp  Asp Pro Lys Lys Tyr  Gly Gly Phe Asp Ser  Pro Thr Val
    1340                 1345                 1350

Ala Tyr  Ser Val Leu Val Val  Ala Lys Val Glu Lys  Gly Lys Ser
    1355                 1360                 1365

Lys Lys  Leu Lys Ser Val Lys  Glu Leu Leu Gly Ile  Thr Ile Met
    1370                 1375                 1380

Glu Arg  Ser Ser Phe Glu Lys  Asn Pro Ile Asp Phe  Leu Glu Ala
    1385                 1390                 1395
```

Lys Gly Tyr Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro
1400 1405 1410

Lys Tyr Ser Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu
1415 1420 1425

Ala Ser Ala Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro
1430 1435 1440

Ser Lys Tyr Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys
1445 1450 1455

Leu Lys Gly Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val
1460 1465 1470

Glu Gln His Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser
1475 1480 1485

Glu Phe Ser Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys
1490 1495 1500

Val Leu Ser Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu
1505 1510 1515

Gln Ala Glu Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly
1520 1525 1530

Ala Pro Ala Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys
1535 1540 1545

Arg Tyr Thr Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His
1550 1555 1560

Gln Ser Ile Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln
1565 1570 1575

Leu Gly Gly Asp Gly Gly Gly Ser Pro Lys Lys Lys Arg Lys Val
    1580   1585   1590

Ser Glu Ser Ala Thr Pro Glu Ser Val Ser Gly Trp Arg Leu Phe
    1595   1600   1605

Lys Lys Ile Ser
    1610

<210> 813

<400> 813
000

<210> 814
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 814

Met Thr Asn Leu Ser Asp Ile Ile Glu Lys Glu Thr Gly Lys Gln Leu
1   5   10   15

Val Ile Gln Glu Ser Ile Leu Met Leu Pro Glu Glu Val Glu Glu Val
            20   25   30

Ile Gly Asn Lys Pro Glu Ser Asp Ile Leu Val His Thr Ala Tyr Asp
        35   40   45

Glu Ser Thr Asp Glu Asn Val Met Leu Leu Thr Ser Asp Ala Pro Glu
    50   55   60

Tyr Lys Pro Trp Ala Leu Val Ile Gln Asp Ser Asn Gly Glu Asn Lys
65   70   75   80

Ile Lys Met Leu Ser Gly Gly Ser Lys Arg Thr Ala Asp Gly Ser Glu
                85   90   95

```
Phe Glu Ser Pro Lys Lys Lys Arg Lys Val Glu
            100                 105


<210>  815

<400>  815
000

<210>  816
<211>  91
<212>  RNA
<213>  Artificial Sequence

<220>
<223>  Synthetic


<220>
<221>  misc_feature
<223>  contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400>  816
acucacgcug gauagccucc guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc       60

cguuaucacg aaagggcacc gagucggugc u                                      91


<210>  817
<211>  4140
<212>  RNA
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  817
auggacaaga aguacagcau cggacuggac aucggaacaa acagcgucgg augggcaguc       60

aucacagacg aauacaaggu cccgagcaag aaguucaagg uccugggaaa cacagacaga      120

cacagcauca agaagaaccu gaucggagca cugcuguucg acagcggaga aacagcagaa      180

gcaacaagac ugaagagaac agcaagaaga agauacacaa gaagaaagaa cagaaucugc      240

uaccugcagg aaaucuucag caacgaaaug gcaaaggucg acgacagcuu cuuccacaga      300
```

```
cuggaagaaa gcuuccuggu cgaagaagac aagaagcacg aaagacaccc gaucuucgga      360
aacaucgucg acgaagucgc auaccacgaa aaguacccga caaucuacca ccugagaaag      420
aagcuggucg acagcacaga caaggcagac cugagacuga ucuaccuggc acuggcacac      480
augaucaagu ucagaggaca cuuccugauc gaaggagacc ugaacccgga caacagcgac      540
gucgacaagc uguucaucca gcugguccag acauacaacc agcuguucga agaaaacccg      600
aucaacgcaa gcggagucga cgcaaaggca auccugagcg caagacugag caagagcaga      660
agacuggaaa accugaucgc acagcugccg ggagaaaaga agaacggacu guucggaaac      720
cugaucgcac ugagccuggg acugacaccg aacuucaaga gcaacuucga ccuggcagaa      780
gacgcaaagc ugcagcugag caaggacaca uacgacgacg accuggacaa ccugcuggca      840
cagaucggag accaguacgc agaccuguuc cuggcagcaa agaaccugag cgacgcaauc      900
cugcugagcg acauccugag agucaacaca gaaaucacaa aggcaccgcu gagcgcaagc      960
augaucaaga gauacgacga acaccaccag gaccugacac ugcugaaggc acuggucaga     1020
cagcagcugc cggaaaagua caaggaaauc uucuucgacc agagcaagaa cggauacgca     1080
ggauacaucg acggaggagc aagccaggaa gaauucuaca aguucaucaa gccgauccug     1140
gaaaagaugg acggaacaga agaacugcug gucaagcuga acagagaaga ccugcugaga     1200
aagcagagaa cauucgacaa cggaagcauc ccgcaccaga uccaccuggg agaacugcac     1260
gcaauccuga gaagacagga agacuucuac ccguuccuga aggacaacag agaaaagauc     1320
gaaaagaucc ugacauucag aaucccguac uacgucggac cgcuggcaag aggaaacagc     1380
agauucgcau ggaugacaag aaagagcgaa gaaacaauca caccguggaa cuucgaagaa     1440
gucgucgaca agggagcaag cgcacagagc uucaucgaaa gaaugacaaa cuucgacaag     1500
aaccugccga acgaaaaggu ccugccgaag cacagccugc uguacgaaua cuucacaguc     1560
uacaacgaac ugacaaaggu caaguacguc acagaaggaa ugagaaagcc ggcauuccug     1620
agcggagaac agaagaaggc aaucgucgac cugcuguuca agacaaacag aaaggucaca     1680
gucaagcagc ugaaggaaga cuacuucaag aagaucgaau gcuucgacag cgucgaaauc     1740
agcggagucg aagacagauu caacgcaagc cugggaacau accacgaccu gcugaagauc     1800
```

```
aucaaggaca aggacuuccu ggacaacgaa gaaaacgaag acauccugga agacaucguc     1860
cugacacuga cacuguucga agacagagaa augaucgaag aaagacugaa gacauacgca     1920
caccuguucg acgacaaggu caugaagcag cugaagagaa gaagauacac aggaugggga     1980
agacugagca gaaagcugau caacggaauc agagacaagc agagcggaaa gacaauccug     2040
gacuuccuga agagcgacgg auucgcaaac agaaacuuca ugcagcugau ccacgacgac     2100
agccugacau ucaaggaaga cauccagaag gcacagguca gcggacaggg agacagccug     2160
cacgaacaca ucgcaaaccu ggcaggaagc ccggcaauca agaagggaau ccugcagaca     2220
gucaaggucg ucgacgaacu ggucaagguc augggaagac acaagccgga aaacaucguc     2280
aucgaaaugg caagagaaaa ccagacaaca cagaagggac agaagaacag cagagaaaga     2340
augaagagaa ucgaagaagg aaucaaggaa cugggaagcc agauccugaa ggaacacccg     2400
gucgaaaaca cacagcugca gaacgaaaag cuguaccugu acuaccugca gaacggaaga     2460
gacauguacg ucgaccagga acuggacauc aacagacuga gcgacuacga cgucgaccac     2520
aucgucccgc agagcuuccu gaaggacgac agcaucgaca acaagguccu gacaagaagc     2580
gacaagaaca gaggaaagag cgacaacguc ccgagcgaag aagucgucaa gaagaugaag     2640
aacuacugga gacagcugcu gaacgcaaag cugaucacac agagaaaguu cgacaaccug     2700
acaaaggcag agagaggagg acugagcgaa cuggacaagg caggauucau caagagacag     2760
cuggucgaaa caagacagau cacaaagcac gucgcacaga uccuggacag cagaaugaac     2820
acaaaguacg acgaaaacga caagcugauc agagaaguca aggucaucac acugaagagc     2880
aagcugguca gcgacuucag aaaggacuuc caguucuaca aggucagaga aaucaacaac     2940
uaccaccacg cacacgacgc auaccugaac gcagucgucg gaacagcacu gaucaagaag     3000
uacccgaagc uggaaagcga auucgucuac ggagacuaca aggucuacga cgucagaaag     3060
augaucgcaa agagcgaaca ggaaaucgga aaggcaacag caaaguacuu cuucuacagc     3120
aacaucauga acuucuucaa gacagaaauc acacuggcaa acggagaaau cagaaagaga     3180
ccgcugaucg aaacaaacgg agaaacagga gaaaucgucu gggacaaggg aagagacuuc     3240
gcaacaguca gaaagguccu gagcaugccg caggucaaca ucgucaagaa gacagaaguc     3300
```

cagacaggag gauucagcaa ggaaagcauc cugccgaaga gaaacagcga caagcugauc 3360

gcaagaaaga aggacuggga cccgaagaag uacggaggau ucgacagccc gacagucgca 3420

uacagcgucc uggucgucgc aaaggucgaa aagggaaaga gcaagaagcu gaagagcguc 3480

aaggaacugc ugggaaucac aaucauggaa agaagcagcu ucgaaaagaa cccgaucgac 3540

uuccuggaag caaagggaua caaggaaguc aagaaggacc ugaucaucaa gcugccgaag 3600

uacagccugu ucgaacugga aaacggaaga aagagaaugc uggcaagcgc aggagaacug 3660

cagaagggaa acgaacuggc acugccgagc aaguacguca acuuccugua ccuggcaagc 3720

cacuacgaaa agcugaaggg aagcccggaa gacaacgaac agaagcagcu guucgucgaa 3780

cagcacaagc acuaccugga cgaaaucauc gaacagauca gcgaauucag caagagaguc 3840

auccuggcag acgcaaaccu ggacaagguc cugagcgcau acaacaagca cagagacaag 3900

ccgaucagag aacaggcaga aaacaucauc caccuguuca cacugacaaa ccugggagca 3960

ccggcagcau ucaaguacuu cgacacaaca aucgacagaa agagauacac aagcacaaag 4020

gaaguccugg acgcaacacu gauccaccag agcaucacag gacuguacga aacaagaauc 4080

gaccugagcc agcugggagg agacggagga ggaagcccga agaagaagag aaaggucuag 4140

<210> 818
<211> 5043
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 818
auggaagcaa gcccggcaag cggaccgaga caccugaugg acccgcacau cuucacaagc 60

aacuucaaca acggaaucgg aagacacaag acauaccugu gcuacgaagu cgaaagacug 120

gacaacggaa caagcgucaa gauggaccag cacagaggau uccugcacaa ccaggcaaag 180

aaccugcugu gcggauucua cggaagacac gcagaacuga gauuccugga ccuggucccg 240

agccugcagc uggacccggc acagaucuac agagucacau gguucaucag cuggagcccg 300

ugcuucagcu ggggaugcgc aggagaaguc agagcauuuc ugcaggaaaa cacacacguc 360

agacugagaa ucuucgcagc aagaaucuac gacuacgacc cgcuguacaa ggaagcacug 420

cagaugcuga gagacgcagg agcacagguc agcaucauga cauacgacga auucaagcac 480

ugcugggaca cauucgucga ccaccaggga ugcccguucc agccguggga cggacuggac 540

gaacacagcc aggcacugag cggaagacug agagcaaucc ugcagaacca gggaaacagc 600

ggaagcgaaa caccgggaac aagcgaaagc gcaacaccgg aaagcgacaa gaaguacagc 660

aucggacugg ccaucggaac aaacagcguc ggaugggcag ucaucacaga cgaauacaag 720

gucccgagca agaaguucaa gguccuggga aacacagaca gacacagcau caagaagaac 780

cugaucggag cacugcuguu cgacagcgga gaaacagcag aagcaacaag acugaagaga 840

acagcaagaa gaagauacac aagaagaaag aacagaaucu gcuaccugca ggaaaucuuc 900

agcaacgaaa uggcaaaggu cgacgacagc uucuuccaca gacuggaaga aagcuuccug 960

gucgaagaag acaagaagca cgaaagacac ccgaucuucg gaaacaucgu cgacgaaguc 1020

gcauaccacg aaaaguaccc gacaaucuac caccugagaa agaagcuggu cgacagcaca 1080

gacaaggcag accugagacu gaucuaccug gcacuggcac acaugaucaa guucagagga 1140

cacuuccuga ucgaaggaga ccugaacccg gacaacagcg acgucgacaa gcuguucauc 1200

cagcuggucc agacauacaa ccagcuguuc gaagaaaacc cgaucaacgc aagcggaguc 1260

gacgcaaagg caauccugag cgcaagacug agcaagagca gaagacugga aaaccugauc 1320

gcacagcugc cgggagaaaa gaagaacgga cuguucggaa accugaucgc acugagccug 1380

ggacugacac cgaacuucaa gagcaacuuc gaccuggcag aagacgcaaa gcugcagcug 1440

agcaaggaca cauacgacga cgaccuggac aaccugcugg cacagaucgg agaccaguac 1500

gcagaccugu uccuggcagc aaagaaccug agcgacgcaa uccugcugag cgacauccug 1560

agagucaaca cagaaaucac aaaggcaccg cugagcgcaa gcaugaucaa gagauacgac 1620

gaacaccacc aggaccugac acugcugaag gcacugguca gacagcagcu gccggaaaag 1680

uacaaggaaa ucuucuucga ccagagcaag aacggauacg caggauacau cgacggagga 1740

gcaagccagg aagaauucua caaguucauc aagccgaucc uggaaaagau ggacggaaca 1800

gaagaacugc uggucaagcu gaacagagaa gaccugcuga gaaagcagag aacauucgac 1860

aacggaagca ucccgcacca gauccaccug ggagaacugc acgcaauccu gagaagacag 1920

gaagacuucu acccguuccu gaaggacaac agagaaaaga ucgaaaagau ccugacauuc 1980

agaaucccgu acuacgucgg accgcuggca agaggaaaca gcagauucgc auggaugaca 2040

agaaagagcg aagaaacaau cacaccgugg aacuucgaag aagucgucga caagggagca 2100

agcgcacaga gcuucaucga aagaaugaca aacuucgaca agaaccugcc gaacgaaaag 2160

guccugccga agcacagccu gcuguacgaa uacuucacag ucuacaacga acugacaaag 2220

gucaaguacg ucacagaagg aaugagaaag ccggcauucc ugagcggaga acagaagaag 2280

gcaaucgucg accugcuguu caagacaaac agaaagguca cagucaagca gcugaaggaa 2340

gacuacuuca agaagaucga augcuucgac agcgucgaaa ucagcggagu cgaagacaga 2400

uucaacgcaa gccugggaac auaccacgac cugcugaaga ucaucaagga caaggacuuc 2460

cuggacaacg aagaaaacga agacauccug gaagacaucg uccugacacu gacacuguuc 2520

gaagacagag aaaugaucga agaaagacug aagacauacg cacaccuguu cgacgacaag 2580

gucaugaagc agcugaagag aagaagauac acaggauggg gaagacugag cagaaagcug 2640

aucaacggaa ucagagacaa gcagagcgga aagacaaucc uggacuuccu gaagagcgac 2700

ggauucgcaa acagaaacuu caugcagcug auccacgacg acagccugac auucaaggaa 2760

gacauccaga aggcacaggu cagcggacag ggagacagcc ugcacgaaca caucgcaaac 2820

cuggcaggaa gcccggcaau caagaaggga auccugcaga cagucaaggu cgucgacgaa 2880

cuggucaagg ucaugggaag acacaagccg gaaaacaucg ucaucgaaau ggcaagagaa 2940

aaccagacaa cacagaaggg acagaagaac agcagagaaa gaaugaagag aaucgaagaa 3000

ggaaucaagg aacugggaag ccagauccug aaggaacacc cggucgaaaa cacacagcug 3060

cagaacgaaa agcuguaccu guacuaccug cagaacggaa gagacaugua cgucgaccag 3120

gaacuggaca ucaacagacu gagcgacuac gacgucgacc acaucguccc gcagagcuuc 3180

cugaaggacg acagcaucga caacaagguc cugacaagaa gcgacaagaa cagaggaaag 3240

agcgacaacg ucccgagcga agaagucguc aagaagauga agaacuacug gagacagcug 3300

cugaacgcaa agcugaucac acagagaaag uucgacaacc ugacaaaggc agagagagga 3360

ggacugagcg aacuggacaa ggcaggauuc aucaagagac agcuggucga aacaagacag 3420

aucacaaagc acgucgcaca gauccuggac agcagaauga acacaaagua cgacgaaaac 3480

gacaagcuga ucagagaagu caaggucauc acacugaaga gcaagcuggu cagcgacuuc 3540

agaaaggacu uccaguucua caaggucaga gaaaucaaca acuaccacca cgcacacgac 3600

gcauaccuga acgcagucgu cggaacagca cugaucaaga aguacccgaa gcuggaaagc 3660

gaauucgucu acggagacua caaggucuac gacgucagaa agaugaucgc aaagagcgaa 3720

caggaaaucg gaaaggcaac agcaaaguac uucuucuaca gcaacaucau gaacuucuuc 3780

aagacagaaa ucacacuggc aaacggagaa aucagaaaga gaccgcugau cgaaacaaac 3840

ggagaaacag gagaaaucgu cugggacaag ggaagagacu ucgcaacagu cagaaagguc 3900

cugagcaugc cgcaggucaa caucgucaag aagacagaag uccagacagg aggauucagc 3960

aaggaaagca uccugccgaa gagaaacagc gacaagcuga ucgcaagaaa gaaggacugg 4020

gacccgaaga aguacggagg auucgacagc ccgacagucg cauacagcgu ccuggucguc 4080

gcaaaggucg aaaagggaaa gagcaagaag cugaagagcg ucaaggaacu gcugggaauc 4140

acaaucaugg aaagaagcag cuucgaaaag aacccgaucg acuuccugga agcaaaggga 4200

uacaaggaag ucaagaagga ccugaucauc aagcugccga aguacagccu guucgaacug 4260

gaaaacggaa gaaagagaau gcuggcaagc gcaggagaac ugcagaaggg aaacgaacug 4320

gcacugccga gcaaguacgu caacuuccug uaccuggcaa gccacuacga aaagcugaag 4380

ggaagcccgg aagacaacga acagaagcag cuguucgucg aacagcacaa gcacuaccug 4440

gacgaaauca ucgaacagau cagcgaauuc agcaagagag ucauccuggc agacgcaaac 4500

cuggacaagg uccugagcgc auacaacaag cacagagaca agccgaucag agaacaggca 4560

gaaaacauca uccaccuguu cacacugaca aaccugggag caccggcagc auucaaguac 4620

uucgacacaa caaucgacag aaagagauac acaagcacaa aggaaguccu ggacgcaaca 4680

cugauccacc agagcaucac aggacuguac gaaacaagaa ucgaucugag ccagcuggga 4740

ggagacagcg gaggaagcac aaaccugagc gacaucaucg aaaaggaaac aggaaagcag 4800

cuggucaucc aggaaagcau ccugaugcug ccggaagaag ucgaagaagu caucggaaac 4860

aagccggaaa gcgacauccu gguccacaca gcauacgacg aaagcacaga cgaaaacguc   4920

augcugcuga caagcgacgc accggaauac aagccguggg cacuggucau ccaggacagc   4980

aacggagaaa acaagaucaa gaugcugagc ggaggaagcc cgaagaagaa gagaaagguc   5040

uaa   5043

<210> 819
<211> 291
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 819
augggaccga agaagaagag aaaggucgga ggaggaagca caaaccuguc ggacaucauc   60

gaaaaggaaa caggaaagca gcuggucauc caggaaucga uccugaugcu gccggaagaa   120

gucgaagaag ucaucggaaa caagccggaa ucggacaucc ugguccacac agcauacgac   180

gaaucgacag acgaaaacgu caugcugcug acaucggacg caccggaaua caagccgugg   240

gcacugguca uccaggacuc gaacggagaa aacaagauca agaugcugug a   291

<210> 820

<400> 820
000

<210> 821

<400> 821
000

<210> 822

<400> 822
000

<210> 823

<400> 823
000

<210> 824

<400> 824
000

<210> 825

<400> 825
000

<210> 826

<400> 826
000

<210> 827

<400> 827
000

<210> 828

<400> 828
000

<210> 829

<400> 829
000

<210> 830

<400> 830
000

<210> 831

<400> 831
000

<210> 832

<400> 832
000

<210> 833

<400> 833
000

<210> 834

<400> 834
000

<210> 835

<400> 835
000

<210> 836

<400> 836
000

<210> 837

<400> 837
000

<210> 838

<400> 838
000

<210> 839

<400> 839
000

<210> 840

<400> 840
000

<210> 841

<400> 841
000

<210> 842

<400> 842
000

<210> 843

<400> 843
000

<210> 844

<400> 844
000

<210> 845

<400> 845
000

<210> 846

<400> 846
000

<210> 847

<400> 847
000

<210> 848

<400> 848
000

<210> 849

<400> 849
000

<210> 850

<400> 850
000

<210> 851

<400> 851
000

<210> 852

<400> 852
000

<210> 853

<400> 853
000

<210> 854

<400> 854
000

<210> 855

<400> 855
000

<210> 856

<400> 856
000

<210> 857

<400> 857
000

<210> 858

<400> 858
000

<210> 859

<400> 859
000

<210> 860

<400> 860
000

<210> 861

<400> 861
000

<210> 862

<400> 862
000

<210> 863

<400> 863
000

<210> 864

<400> 864
000

<210> 865

<400> 865
000

<210> 866

<400> 866
000

<210> 867

<400> 867
000

<210> 868

<400> 868
000

<210> 869

<400> 869
000

<210> 870

<400> 870
000

<210> 871

<400> 871
000

<210> 872

<400> 872
000

<210> 873

<400> 873
000

<210> 874

<400> 874
000

<210> 875

<400> 875
000

<210> 876

<400> 876
000

<210> 877

<400> 877
000

<210> 878

<400> 878
000

<210> 879

<400> 879
000

<210> 880

<400> 880
000

<210> 881

<400> 881
000

<210> 882

<400> 882
000

<210> 883

<400> 883
000

<210> 884

<400> 884
000

<210> 885

<400> 885
000

<210> 886

<400> 886
000

<210> 887

<400> 887
000

<210> 888

<400> 888
000

<210> 889

<400> 889
000

<210> 890

<400> 890
000

<210> 891

<400> 891
000

<210> 892

<400> 892
000

<210> 893

<400> 893
000

<210> 894

<400> 894
000

<210> 895

<400> 895
000

<210> 896

<400> 896
000

<210> 897

<400> 897
000

<210> 898

<400> 898
000

<210> 899

<400> 899
000

<210> 900
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 900

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
1   5   10   15

<210> 901
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 901

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala
1   5   10

<210> 902
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 902

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Gly
1   5   10   15

Gly Ser Gly Gly Ser
            20

<210> 903

<400> 903
000

<210> 904

<400> 904
000

<210> 905

<400> 905
000

<210> 906

<400> 906
000

<210> 907

<400> 907
000

<210> 908

<400> 908
000

<210> 909

<400> 909
000

<210> 910

<400> 910
000

<210> 911

<400> 911
000

<210> 912

<400> 912
000

<210> 913

<400> 913
000

<210> 914

<400> 914
000

<210> 915

<400> 915
000

<210> 916

<400> 916
000

<210> 917

<400> 917
000

<210> 918

<400> 918
000

<210> 919

<400> 919
000

<210> 920

<400> 920
000

<210> 921

<400> 921
000

<210> 922

<400> 922
000

<210> 923

<400> 923
000

<210> 924

<400> 924
000

<210> 925

<400> 925
000

<210> 926

<400> 926
000

<210> 927

<400> 927
000

<210> 928

<400> 928
000

<210> 929

<400> 929
000

<210> 930

<400> 930
000

<210> 931

<400> 931
000

<210> 932

<400> 932
000

<210> 933

<400> 933
000

<210> 934

<400> 934
000

<210> 935

<400> 935
000

<210> 936

<400> 936
000

<210> 937

<400> 937
000

<210> 938

<400> 938
000

<210> 939

<400> 939
000

<210> 940

<400> 940
000

<210> 941

<400> 941
000

<210> 942

<400> 942
000

<210> 943

<400> 943
000

<210> 944

<400> 944
000

<210> 945

<400> 945
000

<210> 946

<400> 946
000

<210> 947

<400> 947
000

<210> 948

<400> 948
000

<210> 949

<400> 949
000

<210> 950

<400> 950
000

<210> 951

<400> 951
000

<210> 952

<400> 952
000

<210> 953

<400> 953
000

<210> 954

<400> 954
000

<210> 955

<400> 955
000

<210> 956

<400> 956
000

<210> 957

<400> 957
000

<210> 958

<400> 958
000

<210> 959

<400> 959
000

<210> 960

<400> 960
000

<210> 961

<400> 961
000

<210> 962

<400> 962
000

<210> 963

<400> 963
000

<210> 964

<400> 964
000

<210> 965

<400> 965
000

<210> 966

<400> 966
000

<210> 967

<400> 967
000

<210> 968

<400> 968
000

<210> 969

<400> 969
000

<210> 970

<400> 970
000

<210> 971

<400> 971
000

<210> 972
<211> 5342
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 972
gggaagcuca gaauaaacgc ucaacuuugg ccggaucugc caccauggag gccuccccg   60

ccuccggccc ccggcaccug auggaccccc acaucuucac cuccaacuuc aacaacggca   120

ucggccggca caagaccuac cugugcuacg agguggagcg gcuggacaac ggcaccuccg   180

ugaagaugga ccagcaccgg ggcuuccugc acaaccaggc caagaaccug cugugcggcu   240

ucuacggccg gcacgccgag cugcgguucc uggaccuggu gcccucccug cagcuggacc   300

ccgcccagau cuaccgggug accugguuca ucuccugguc ccccugcuuc uccuggggcu   360

gcgccggcga ggugcgggcc uuccugcagg agaacaccca cgugcggcug cggaucuucg   420

ccgcccggau cuacgacuac gacccccugu acaaggaggc ccugcagaug cugcgggacg   480

ccggcgccca gguguccauc augaccuacg acgaguucaa gcacugcugg gacaccuucg   540

uggaccacca gggcugcccc uuccagcccu gggacggccu ggacgagcac ucccaggccc   600

uguccggccg gcugcgggcc auccugcaga accagggcaa cuccggcucc gagacccccg   660

gcaccuccga guccgccacc cccgaguccg acaagaagua cuccaucggc cuggccaucg 720

gcaccaacuc cgugggcugg gccgugauca ccgacgagua caaggugccc uccaagaagu 780

ucaaggugcu gggcaacacc gaccggcacu ccaucaagaa gaaccugauc ggcgcccugc 840

uguucgacuc cggcgagacc gccgaggcca cccggcugaa gcggaccgcc cggcggcggu 900

acacccggcg gaagaaccgg aucugcuacc ugcaggagau cuucuccaac gagauggcca 960

agguggacga cuccuucuuc caccggcugg aggaguccuu ccugguggag gaggacaaga 1020

agcacgagcg gcaccccauc uucggcaaca ucguggacga gguggccuac cacgagaagu 1080

accccaccau cuaccaccug cggaagaagc ugguggacuc caccgacaag gccgaccugc 1140

ggcugaucua ccuggcccug gcccacauga ucaaguuccg gggccacuuc cugaucgagg 1200

gcgaccugaa ccccgacaac uccgacgugg acaagcuguu cauccagcug gugcagaccu 1260

acaaccagcu guucgaggag aaccccauca acgccuccgg cguggacgcc aaggccaucc 1320

uguccgcccg gcuguccaag ucccggcggc uggagaaccu gaucgcccag cugcccggcg 1380

agaagaagaa cggccuguuc ggcaaccuga ucgcccuguc ccugggccug acccccaacu 1440

ucaaguccaa cuucgaccug gccgaggacg ccaagcugca gcuguccaag gacaccuacg 1500

acgacgaccu ggacaaccug cuggcccaga ucggcgacca guacgccgac cuguuccugg 1560

ccgccaagaa ccuguccgac gccauccugc uguccgacau ccugcgggug aacaccgaga 1620

ucaccaaggc cccccugucc gccuccauga ucaagcggua cgacgagcac caccaggacc 1680

ugacccugcu gaaggcccug gugcggcagc agcugcccga gaaguacaag gagaucuucu 1740

ucgaccaguc caagaacggc uacgccggcu acaucgacgg cggcgccucc caggaggagu 1800

ucuacaaguu caucaagccc auccuggaga agauggacgg caccgaggag cugcugguga 1860

agcugaaccg ggaggaccug cugcggaagc agcggaccuu cgacaacggc uccauccccc 1920

accagaucca ccugggcgag cugcacgcca uccugcggcg gcaggaggac uucuaccccu 1980

uccugaagga caaccgggag aagaucgaga agauccugac cuuccggauc cccuacuacg 2040

ugggcccccu ggcccggggc aacucccggu ucgccuggau gacccggaag uccgaggaga 2100

ccaucacccc cuggaacuuc gaggaggugg uggacaaggg cgccuccgcc caguccuuca 2160

ucgagcggau gaccaacuuc gacaagaacc ugcccaacga gaaggugcug cccaagcacu 2220

cccugcugua cgaguacuuc accguguaca acgagcugac caaggugaag uacgugaccg 2280

agggcaugcg gaagcccgcc uuccuguccg gcgagcagaa gaaggccauc guggaccugc 2340

uguucaagac caaccggaag gugaccguga agcagcugaa ggaggacuac uucaagaaga 2400

ucgagugcuu cgacuccgug gagaucuccg gcguggagga ccgguucaac gccucccugg 2460

gcaccuacca cgaccugcug aagaucauca aggacaagga cuuccuggac aacgaggaga 2520

acgaggacau ccuggaggac aucgugcuga cccugacccu guucgaggac cgggagauga 2580

ucgaggagcg gcugaagacc uacgcccacc uguucgacga caaggugaug aagcagcuga 2640

agcggcggcg guacaccggc uggggccggc ugucccggaa gcugaucaac ggcauccggg 2700

acaagcaguc cggcaagacc auccuggacu uccugaaguc cgacggcuuc gccaaccgga 2760

acuucaugca gcugauccac gacgacuccc ugaccuucaa ggaggacauc cagaaggccc 2820

agguguccgg ccagggcgac ucccugcacg agcacaucgc caaccuggcc ggcuccccg 2880

ccaucaagaa gggcauccug cagaccguga agguggugga cgagcuggug aaggugaugg 2940

gccggcacaa gcccgagaac aucgugaucg agauggcccg ggagaaccag accacccaga 3000

agggccagaa gaacucccgg gagcggauga agcggaucga ggagggcauc aaggagcugg 3060

gcucccagau ccugaaggag caccccgugg agaacaccca gcugcagaac gagaagcugu 3120

accuguacua ccugcagaac ggccgggaca uguacgugga ccaggagcug gacaucaacc 3180

ggcuguccga cuacgacgug gaccacaucg ugccccaguc cuuccugaag gacgacucca 3240

ucgacaacaa ggugcugacc cgguccgaca agaaccgggg caaguccgac aacgugcccu 3300

ccgaggaggu ggugaagaag augaagaacu acuggcggca gcugcugaac gccaagcuga 3360

ucacccagcg gaaguucgac aaccugacca aggccgagcg gggcggccug uccgagcugg 3420

acaaggccgg cuucaucaag cggcagcugg uggagacccg gcagaucacc aagcacgugg 3480

cccagauccu ggacucccgg augaacacca aguacgacga gaacgacaag cugauccggg 3540

aggugaaggu gaucacccug aaguccaagc ugguguccga cuuccggaag gacuuccagu 3600

ucuacaaggu gcgggagauc aacaacuacc accacgccca cgacgccuac cugaacgccg 3660

ugguggcac cgcccugauc aagaaguacc ccaagcugga guccgaguuc guguacggcg 3720

acuacaaggu guacgacgug cggaagauga ucgccaaguc cgagcaggag aucggcaagg 3780

ccaccgccaa guacuucuuc uacuccaaca ucaugaacuu cuucaagacc gagaucaccc 3840

uggccaacgg cgagauccgg aagcggcccc ugaucgagac caacggcgag accggcgaga 3900

ucgugugga caagggccgg gacuucgcca ccgugcggaa ggugcugucc augccccagg 3960

ugaacaucgu gaagaagacc gaggugcaga ccggcggcuu cuccaaggag uccauccugc 4020

ccaagcggaa cuccgacaag cugaucgccc ggaagaagga cugggacccc aagaaguacg 4080

gcggcuucga cucccccacc guggccuacu ccgugcuggu gguggccaag guggagaagg 4140

gcaaguccaa gaagcugaag uccgugaagg agcugcuggg caucaccauc auggagcggu 4200

ccuccuucga gaagaacccc aucgacuucc uggaggccaa gggcuacaag gaggugaaga 4260

aggaccugau caucaagcug cccaaguacu cccuguucga gcuggagaac ggccggaagc 4320

ggaugcuggc cuccgccggc gagcugcaga agggcaacga gcuggcccug cccuccaagu 4380

acgugaacuu ccuguaccug gccucccacu acgagaagcu gaagggcucc cccgaggaca 4440

acgagcagaa gcagcuguuc guggagcagc acaagcacua ccuggacgag aucaucgagc 4500

agaucuccga guucuccaag cgggugaucc uggccgacgc caaccuggac aaggugcugu 4560

ccgccuacaa caagcaccgg gacaagccca uccgggagca ggccgagaac aucauccacc 4620

uguucacccu gaccaaccug ggcgcccccg ccgccuucaa guacuucgac accaccaucg 4680

accggaagcg guacaccucc accaaggagg ugcuggacgc cacccugauc caccagucca 4740

ucaccggccu guacgagacc cggaucgacc ugucccagcu gggcggcgac ggcggcggcu 4800

cccccaagaa gaagcggaag gugugacuag caccagccuc aagaacaccc gaauggaguc 4860

ucuaagcuac auaauaccaa cuuacacuuu acaaaauguu gucccccaaa auguagccau 4920

ucguaucugc uccuaauaaa aagaaaguuu cuucacauuc ucucgagaaa aaaaaaaaau 4980

ggaaaaaaaa aaaacggaaa aaaaaaaaag guaaaaaaaa aaaauauaaa aaaaaaaaac 5040

auaaaaaaaa aaaacgaaaa aaaaaaaacg uaaaaaaaaa aaacucaaaa aaaaaaaaga 5100

uaaaaaaaaa aaaccuaaaa aaaaaaaaug uaaaaaaaaa aaagggaaaa aaaaaaaacg 5160

caaaaaaaaa aaacacaaaa aaaaaaaaug caaaaaaaaa aaaucgaaaa aaaaaaaauc 5220

uaaaaaaaaa aaacgaaaaa aaaaaaaccc aaaaaaaaaa aagacaaaaa aaaaaaauag 5280

aaaaaaaaaa aaguuaaaaa aaaaaaacug aaaaaaaaaa aauuuaaaaa aaaaaaaucu 5340

ag 5342

<210> 973
<211> 5399
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 973
gggaagcuca gaauaaacgc ucaacuuugg ccggaucugc caccauggag gccucccccg 60

ccuccggccc ccggcaccug auggaccccc acaucuucac cuccaacuuc aacaacggca 120

ucggccggca caagaccuac cugugcuacg agguggagcg gcuggacaac ggcaccuccg 180

ugaagaugga ccagcaccgg ggcuuccugc acaaccaggc caagaaccug cugugcggcu 240

ucuacggccg gcacgccgag cugcgguucc uggaccuggu gcccucccug cagcuggacc 300

ccgcccagau cuaccgggug accugguuca ucuccugguc ccccugcuuc uccuggggcu 360

gcgccggcga ggugcgggcc uuccugcagg agaacaccca cgugcggcug cggaucuucg 420

ccgcccggau cuacgacuac gacccccugu acaaggaggc ccugcagaug cugcgggacg 480

ccggcgccca gguguccauc augaccuacg acgaguucaa gcacugcugg gacaccuucg 540

uggaccacca gggcugcccc uuccagcccu gggacggccu ggacgagcac ucccaggccc 600

uguccggccg gcugcgggcc auccugcaga accagggcaa cuccggcucc gagacccccg 660

gcaccuccga guccgccacc cccgaguccg acaagaagua cuccaucggc cuggccaucg 720

gcaccaacuc cgugggcugg gccgugauca ccgacgagua caaggugccc uccaagaagu 780

ucaaggugcu gggcaacacc gaccggcacu ccaucaagaa gaaccugauc ggcgcccugc 840

uguucgacuc cggcgagacc gccgaggcca cccggcugaa gcggaccgcc cggcggcggu 900

acacccggcg gaagaaccgg aucugcuacc ugcaggagau cuucuccaac gagauggcca 960

agguggacga cuccuucuuc caccggcugg aggaguccuu ccugguggag gaggacaaga 1020

agcacgagcg gcaccccauc uucggcaaca ucguggacga gguggccuac cacgagaagu 1080

accccaccau cuaccaccug cggaagaagc ugguggacuc caccgacaag gccgaccugc 1140

ggcugaucua ccuggcccug gcccacauga ucaaguuccg gggccacuuc cugaucgagg 1200

gcgaccugaa ccccgacaac uccgacgugg acaagcuguu cauccagcug gugcagaccu 1260

acaaccagcu guucgaggag aaccccauca acgccuccgg cguggacgcc aaggccaucc 1320

uguccgcccg gcuguccaag ucccggcggc uggagaaccu gaucgcccag cugcccggcg 1380

agaagaagaa cggccuguuc ggcaaccuga ucgcccuguc ccugggccug acccccaacu 1440

ucaaguccaa cuucgaccug gccgaggacg ccaagcugca gcuguccaag gacaccuacg 1500

acgacgaccu ggacaaccug cuggcccaga ucggcgacca guacgccgac cuguuccugg 1560

ccgccaagaa ccuguccgac gccauccugc uguccgacau ccugcgggug aacaccgaga 1620

ucaccaaggc cccccugucc gccuccauga ucaagcggua cgacgagcac caccaggacc 1680

ugacccugcu gaaggcccug gugcggcagc agcugcccga gaaguacaag gagaucuucu 1740

ucgaccaguc caagaacggc uacgccggcu acaucgacgg cggcgccucc caggaggagu 1800

ucuacaaguu caucaagccc auccuggaga agauggacgg caccgaggag cugcugguga 1860

agcugaaccg ggaggaccug cugcggaagc agcggaccuu cgacaacggc uccauccccc 1920

accagaucca ccugggcgag cugcacgcca uccugcggcg gcaggaggac uucuaccccu 1980

uccugaagga caaccgggag aagaucgaga agauccugac cuuccggauc ccuacuacg 2040

ugggcccccu ggcccggggc aacucccggu ucgccuggau gacccggaag uccgaggaga 2100

ccaucacccc cuggaacuuc gaggaggugg uggacaaggg cgccuccgcc caguccuuca 2160

ucgagcggau gaccaacuuc gacaagaacc ugcccaacga gaaggugcug cccaagcacu 2220

cccugcugua cgaguacuuc accguguaca acgagcugac caaggugaag uacgugaccg 2280

agggcaugcg gaagcccgcc uuccuguccg gcgagcagaa gaaggccauc guggaccugc 2340

uguucaagac caaccggaag gugaccguga agcagcugaa ggaggacuac uucaagaaga 2400

ucgagugcuu cgacuccgug gagaucuccg gcguggagga ccgguucaac gccucccugg 2460

```
gcaccuacca cgaccugcug aagaucauca aggacaagga cuuccuggac aacgaggaga     2520
acgaggacau ccuggaggac aucgugcuga cccugacccu guucgaggac cgggagauga     2580
ucgaggagcg gcugaagacc uacgcccacc uguucgacga caaggugaug aagcagcuga     2640
agcggcggcg guacaccggc uggggccggc ugucccggaa gcugaucaac ggcauccggg     2700
acaagcaguc cggcaagacc auccuggacu uccugaaguc cgacggcuuc gccaaccgga     2760
acuucaugca gcugauccac gacgacuccc ugaccuucaa ggaggacauc cagaaggccc     2820
agguguccgg ccagggcgac ucccugcacg agcacaucgc caaccuggcc ggcucccccg     2880
ccaucaagaa gggcauccug cagaccguga agguggugga cgagcuggug aaggugaugg     2940
gccggcacaa gcccgagaac aucgugaucg agauggcccg ggagaaccag accacccaga     3000
agggccagaa gaacucccgg gagcggauga agcggaucga ggagggcauc aaggagcugg     3060
gcucccagau ccugaaggag caccccgugg agaacaccca gcugcagaac gagaagcugu     3120
accuguacua ccugcagaac ggccgggaca uguacgugga ccaggagcug gacaucaacc     3180
ggcuguccga cuacgacgug gaccacaucg ugccccaguc cuuccugaag gacgacucca     3240
ucgacaacaa ggugcugacc cgguccgaca agaaccgggg caaguccgac aacgugcccu     3300
ccgaggaggu ggugaagaag augaagaacu acuggcggca gcugcugaac gccaagcuga     3360
ucacccagcg gaaguucgac aaccugacca aggccgagcg gggcggccug uccgagcugg     3420
acaaggccgg cuucaucaag cggcagcugg uggagacccg gcagaucacc aagcacgugg     3480
cccagauccu ggacucccgg augaacacca aguacgacga gaacgacaag cugauccggg     3540
aggugaaggu gaucacccug aaguccaagc ugguguccga cuuccggaag gacuuccagu     3600
ucuacaaggu gcgggagauc aacaacuacc accacgccca cgacgccuac cugaacgccg     3660
uggugggcac cgcccugauc aagaaguacc ccaagcugga guccgaguuc guguacggcg     3720
acuacaaggu guacgacgug cggaagauga ucgccaaguc cgagcaggag aucggcaagg     3780
ccaccgccaa guacuucuuc uacuccaaca ucaugaacuu cuucaagacc gagaucaccc     3840
uggccaacgg cgagauccgg aagcggcccc ugaucgagac caacggcgag accggcgaga     3900
ucgugaggga caagggccgg gacuucgcca ccgugcggaa ggugcugucc augccccagg     3960
```

ugaacaucgu gaagaagacc gaggugcaga ccggcggcuu cuccaaggag uccauccugc 4020
ccaagcggaa cuccgacaag cugaucgccc ggaagaagga cugggacccc aagaaguacg 4080
gcggcuucga cucccccacc guggccuacu ccgugcuggu gguggccaag guggagaagg 4140
gcaaguccaa gaagcugaag uccgugaagg agcugcuggg caucaccauc auggagcggu 4200
ccuccuucga gaagaacccc aucgacuucc uggaggccaa gggcuacaag gaggugaaga 4260
aggaccugau caucaagcug cccaaguacu cccuguucga gcuggagaac ggccggaagc 4320
ggaugcuggc cuccgccggc gagcugcaga agggcaacga gcuggcccug cccuccaagu 4380
acgugaacuu ccuguaccug gccucccacu acgagaagcu gaagggcucc cccgaggaca 4440
acgagcagaa gcagcuguuc guggagcagc acaagcacua ccuggacgag aucaucgagc 4500
agaucuccga guucuccaag cgggugaucc uggccgacgc caaccuggac aaggugcugu 4560
ccgccuacaa caagcaccgg gacaagccca uccgggagca ggccgagaac aucauccacc 4620
uguucacccu gaccaaccug ggcgcccccg ccgccuucaa guacuucgac accaccaucg 4680
accggaagcg guacaccucc accaaggagg ugcuggacgc cacccugauc caccagucca 4740
ucaccggccu guacgagacc cggaucgacc ugucccagcu gggcggcgac ggcggcggcu 4800
cccccaagaa gaagcggaag guguccgagu ccgccacccc cgaguccgug uccggcuggc 4860
ggcuguucaa gaagaucucc ugacuagcac cagccucaag aacacccgaa uggagucucu 4920
aagcuacaua auaccaacuu acacuuuaca aaauguuguc ccccaaaaug uagccauucg 4980
uaucugcucc uaauaaaaag aaaguuucuu cacauucucu cgagaaaaaa aaaaaaugga 5040
aaaaaaaaaa acggaaaaaa aaaaaaggua aaaaaaaaaa auauaaaaaa aaaaaacaua 5100
aaaaaaaaaa acgaaaaaaa aaaaacguaa aaaaaaaaaa cucaaaaaaa aaaaagauaa 5160
aaaaaaaaaa ccuaaaaaaa aaaaauguaa aaaaaaaaaa gggaaaaaaa aaaaacgcaa 5220
aaaaaaaaaa cacaaaaaaa aaaaaugcaa aaaaaaaaaa ucgaaaaaaa aaaaaucuaa 5280
aaaaaaaaaa cgaaaaaaaa aaaacccaaa aaaaaaaaag acaaaaaaaa aaaauagaaa 5340
aaaaaaaaag uuaaaaaaaa aaaacugaaa aaaaaaaaau uuaaaaaaaa aaaaucuag 5399

<210> 974

<400> 974
000

<210> 975
<211> 589
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 975
gggagaccca agcuggcuag cucccgcagu cggcguccag cggcucugcu uguucgugug 60

ugugucguug caggccuuau ucggauccgc caccauggga ccgaagaaga agagaaaggu 120

cggaggagga agcacaaacc ugucggacau caucgaaaag gaaacaggaa agcagcuggu 180

cauccaggaa ucgauccuga ugcugccgga agaagucgaa gaagucaucg gaaacaagcc 240

ggaaucggac auccuggucc acacagcaua cgacgaaucg acagacgaaa acgucaugcu 300

gcugacaucg gacgcaccgg aauacaagcc gugggcacug gucauccagg acucgaacgg 360

agaaaacaag aucaagaugc ugugauaguc uagacaucac auuuaaaagc aucucagccu 420

accaugagaa uaagagaaag aaaaugaaga ucaauagcuu auucaucucu uuuucuuuuu 480

cguuggugua aagccaacac ccugucuaaa aaacauaaau uucuuuaauc auuuugccuc 540

uuuucucugu gcuucaauua auaaaaaaug gaaagaaccu cgagucuag 589

<210> 976

<400> 976
000

<210> 977

<400> 977
000

<210> 978

<400> 978
000

<210> 979

<400> 979
000

<210> 980

<400> 980
000

<210> 981

<400> 981
000

<210> 982

<400> 982
000

<210> 983

<400> 983
000

<210> 984

<400> 984
000

<210> 985

<400> 985
000

<210> 986

<400> 986
000

<210> 987

<400> 987
000

<210> 988

<400> 988
000

<210> 989

<400> 989
000

<210> 990

<400> 990
000

<210> 991

<400> 991
000

<210> 992

<400> 992
000

<210> 993

<400> 993
000

<210> 994

<400> 994
000

<210> 995

<400> 995
000

<210> 996

<400> 996
000

<210> 997

<400> 997
000

<210> 998

<400> 998
000

<210> 999

<400> 999
000

<210> 1000
<211> 8540
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 1000
gcgatcgcag taatcaatta cggggtcatt agttcatagc ccatatatgg agttccgcgt   60

tacataactt acggtaaatg gcccgcctgg ctgaccgccc aacgaccccc gcccattgac   120

gtcaataatg acgtatgttc ccatagtaac gccaataggg actttccatt gacgtcaatg   180

ggtggagtat ttacggtaaa ctgcccactt ggcagtacat caagtgtatc atatgccaag   240

tacgccccct attgacgtca atgacggtaa atggcccgcc tggcattatg cccagtacat   300

gaccttatgg gactttccta cttggcagta catctacgta ttagtcatcg ctattaccat   360

ggtgatgcgg ttttggcagt acatcaatgg gcgtggatag cggtttgact cacggggatt   420

tccaagtctc caccccattg acgtcaatgg gagtttgttt tggcaccaaa atcaacggga   480

ctttccaaaa tgtcgtaaca actccgcccc attgacgcaa atgggcggta ggcgtgtacg   540

gtgggaggtc tatataagca gagctcgttt agtgaaccgg ggtctctctg gttagaccag   600

atctgagcct gggagctctc tggctaacta gggaacccac tgcttaagcc tcaataaagc   660

ttgccttgag tgcttcaagt agtgtgtgcc cgtctgttgt gtgactctgg taactagaga   720

tccctcagac ccttttagtc agtgtggaaa atctctagca gtggcgcccg aacagggacc   780

tgaaagcgaa agggaaacca gagctctctc gacgcaggac tcggcttgct gaagcgcgca   840

cggcaagagg cgaggggcgg cgactggtga gtacgccaaa aattttgact agcggaggct   900

agaaggagag agatgggtgc gagagcgtca gtattaagcg ggggagaatt agatcgcgat   960

gggaaaaaat tcggttaagg ccagggggaa agaaaaaata taaattaaaa catatagtat   1020

gggcaagcag ggagctagaa cgattcgcag ttaatcctgg cctgttagaa acatcagaag   1080

gctgtagaca aatactggga cagctacaac catcccttca gacaggatca gaagaactta 1140

gatcattata taatacagta gcaaccctct attgtgtgca tcaaaggata gagataaaag 1200

acaccaagga agctttagac aagatagagg aagagcaaaa caaaagtaag accaccgcac 1260

agcaagcggc cgctgatctt cagacctgga ggaggagata tgagggacaa ttggagaagt 1320

gaattatata aatataaagt agtaaaaatt gaaccattag gagtagcacc caccaaggca 1380

aagagaagag tggtgcagag agaaaaaaga gcagtgggaa taggagcttt gttccttggg 1440

ttcttgggag cagcaggaag cactatgggc gcagcctcaa tgacgctgac ggtacaggcc 1500

agacaattat tgtctggtat agtgcagcag cagaacaatt tgctgagggc tattgaggcg 1560

caacagcatc tgttgcaact cacagtctgg ggcatcaagc agctccaggc aagaatcctg 1620

gctgtggaaa gatacctaaa ggatcaacag ctcctgggga tttggggttg ctctggaaaa 1680

ctcatttgca ccactgctgt gccttggaat gctagttgga gtaataaatc tctggaacag 1740

atttggaatc acacgacctg gatggagtgg gacagagaaa ttaacaatta cacaagctta 1800

atacactcct taattgaaga atcgcaaaac cagcaagaaa agaatgaaca agaattattg 1860

gaattagata aatgggcaag tttgtggaat tggtttaaca taacaaattg gctgtggtat 1920

ataaaattat tcataatgat agtaggaggc ttggtaggtt taagaatagt ttttgctgta 1980

ctttctatag tgaatagagt taggcaggga tattcaccat tatcgtttca gacccacctc 2040

ccaaccccga ggggacccga caggcccgaa ggaatagaag aagaaggtgg agagagagac 2100

agagacagat ccattcgatt agtgaacgga tctcgacggt atcggttaac ttttaaaaga 2160

aaagggggga ttggggggta cagtgcaggg gaaagaatag tagacataat agcaacagac 2220

atacaaacta aagaattaca aaaacaaatt acaaaaattc aaaattttgg ctcccgatcg 2280

ttgcgttaca cacacaatta ctgctgatcg agtgtagcct tcccacagtc cccgagaagt 2340

tggggggagg ggtcggcaat tgaaccggtg cctagagaag gtggcgcggg gtaaactggg 2400

aaagtgatgt cgtgtactgg ctccgccttt ttcccgaggg tgggggagaa ccgtatataa 2460

gtgcagtagt cgccgtgaac gttctttttc gcaacgggtt tgccgccaga acacaggtaa 2520

gtgccgtgtg tggttcccgc gggcctggcc tctttacggg ttatggccct tgcgtgcctt 2580

gaattacttc cacgcccctg gctgcagtac gtgattcttg atcccgagct tcgggttgga 2640

agtgggtggg agagttcgag gccttgcgct taaggagccc cttcgcctcg tgcttgagtt 2700

gaggcctggc ttgggcgctg gggccgccgc gtgcgaatct ggtggcacct tcgcgcctgt 2760

ctcgctgctt tcgataagtc tctagccatt taaaattttt gatgacctgc tgcgacgctt 2820

tttttctggc aagatagtct tgtaaatgcg ggccaagatg tgcacactgg tatttcggtt 2880

tttggggccg cgggcggcga cggggcccgt gcgtcccagc gcacatgttc ggcgaggcgg 2940

ggcctgcgag cgcggccacc gagaatcgga cgggggtagt ctcaagctgg ccggcctgct 3000

ctggtgcctg gcctcgcgcc gccgtgtatc gccccgccct gggcggcaag gctggcccgg 3060

tcggcaccag ttgcgtgagc ggaaagatgg ccgcttcccg gccctgctgc agggagctca 3120

aaatggagga cgcggcgctc gggagagcgg gcgggtgagt cacccacaca aaggaaaagg 3180

gcctttccgt cctcagccgt cgcttcatgt gactccacgg agtaccgggc gccgtccagg 3240

cacctcgatt agttctcgag cttttggagt acgtcgtctt taggttgggg ggaggggttt 3300

tatgcgatgg agtttcccca cactgagtgg gtggagactg aagttaggcc agcttggcac 3360

ttgatgtaat tctccttgga atttgccctt tttgagtttg gatcttggtt cattctcaag 3420

cctcagacag tggttcaaag tttttttctt ccatttcagg tgtcgtgatc tagacgccac 3480

catgtctcgc tccgtggcct tagctgtgct cgcgctactc tctctttctg gcctagaggc 3540

tgttatggct ccgcggactt taattttagg tggtggcgga tccggtggag gcggttctgg 3600

tggaggcggc tccatccagc gtacgccaaa gattcaggtt tactcacgtc atccagcaga 3660

gaatggaaag tcaaatttcc tgaattgcta tgtgtctggg tttcatccat ccgacattga 3720

agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag acttgtcttt 3780

cagcaaggac tggtctttct atctcttgta ctacactgaa ttcaccccca ctgaaaaaga 3840

tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatag ttaagtggga 3900

tcgcgacatg ggtggtggcg gttctggtgg tggcggtagt ggcggcggag gaagcggtgg 3960

tggcggttcc ggatctcact ccttgaagta tttccacact tccgtgtccc ggcccggccg 4020

cggggagccc cgcttcatct ctgtgggcta cgtggacgac acccagttcg tgcgcttcga 4080

caacgacgcc gcgagtccga ggatggtgcc gcgggcgccg tggatggagc aggaggggtc 4140

agagtattgg gaccgggaga cacggagcgc cagggacacc gcacagattt tccgagtgaa 4200

cctgcggacg ctgcgcggct actacaatca gagcgaggcc gggtctcaca ccctgcagtg 4260

gatgcatggc tgcgagctgg ggcccgacag gcgcttcctc cgcgggtatg aacagttcgc 4320

ctacgacggc aaggattatc tcaccctgaa tgaggacctg cgctcctgga ccgcggtgga 4380

cacggcggct cagatctccg agcaaaagtc aaatgatgcc tctgaggcgg agcaccagag 4440

agcctacctg gaagacacat gcgtggagtg gctccacaaa tacctggaga aggggaagga 4500

gacgctgctt cacctggagc ccccaaagac acacgtgact caccacccca tctctgacca 4560

tgaggccacc ctgaggtgct gggctctggg cttctaccct gcggagatca cactgacctg 4620

gcagcaggat ggggagggcc atacccagga cacggagctc gtggagacca ggcctgctgg 4680

ggatggaacc ttccagaagt gggcagctgt ggtggtgcct tctggagagg agcagagata 4740

cacgtgccat gtgcagcatg aggggctacc cgagcccgtc accctgagat ggaagccggc 4800

ttcccagccc accatcccca tcgtgggcat cattgctggc ctggttctcc ttggatctgt 4860

ggtctctgga gctgtggttg ctgctgtgat atggaggaag aagagctcag gtggaaaagg 4920

agggagctac tataaggctg agtggagcga cagtgcccag gggtctgagt ctcacagctt 4980

gtaaaagtag aagttgtctc ctcctgcact gactgactga tacaatcgat ttctggatcc 5040

gcaggcctct gctagaagtt gtctcctcct gcactgactg actgatacaa tcgatttctg 5100

gatccgcagg cctctgctag cttgactgac tgagtcgaca atcaacctct ggattacaaa 5160

atttgtgaaa gattgactgg tattcttaac tatgttgctc cttttacgct atgtggatac 5220

gctgctttaa tgcctttgta tcatgctatt gcttcccgta tggctttcat tttctcctcc 5280

ttgtataaat cctggttgct gtctctttat gaggagttgt ggcccgttgt caggcaacgt 5340

ggcgtggtgt gcactgtgtt tgctgacgca acccccactg gttggggcat tgccaccacc 5400

tgtcagctcc tttccgggac tttcgctttc cccctcccta ttgccacggc ggaactcatc 5460

gccgcctgcc ttgcccgctg ctggacaggg gctcggctgt tgggcactga caattccgtg 5520

gtgttgtcgg ggaagctgac gtcctttcca tggctgctcg cctgtgttgc cacctggatt 5580

ctgcgcggga cgtccttctg ctacgtccct tcggccctca atccagcgga ccttccttcc 5640

cgcggcctgc tgccggctct gcggcctctt ccgcgtcttc gccttcgccc tcagacgagt 5700

cggatctccc tttgggccgc ctccccgcct ggaattcgag ctcggtacct ttaagaccaa 5760

tgacttacaa ggcagctgta gatcttagcc actttttaaa agaaaagggg ggactggaag 5820

ggctaattca ctcccaacga agacaagatc tgctttttgc ttgtactggg tctctctggt 5880

tagaccagat ctgagcctgg gagctctctg gctaactagg gaacccactg cttaagcctc 5940

aataaagctt gccttgagtg cttcaagtag tgtgtgcccg tctgttgtgt gactctggta 6000

actagagatc cctcagaccc ttttagtcag tgtggaaaat ctctagcagt cctggccaac 6060

gtgagcaccg tgctgacctc caaatatcgt taagctggag cctgggagcc ggcctggccc 6120

tccgcccccc ccacccccgc agcccacccc tggtctttga ataaagtctg agtgagtggc 6180

cgacagtgcc cgtggagttc tcgtgacctg aggtgcaggg ccggcgctag ggacacgtcc 6240

gtgcacgtgc cgaggccccc tgtgcagctg caagggacag gcctagccct gcaggcctaa 6300

ctccgcccat cccgccccta actccgccca gttccgccca ttctccgcct catggctgac 6360

taattttttt tatttatgca gaggccgagg ccgcctcggc ctctgagcta ttccagaagt 6420

agtgaggacg cttttttgga ggccgaggct tttgcaaaga tcgaacaaga gacaggacct 6480

gcaggttaat taaatttaaa tcatgtgagc aaaaggccag caaaaggcca ggaaccgtaa 6540

aaaggccgcg ttgctggcgt ttttccatag gctccgcccc cctgacgagc atcacaaaaa 6600

tcgacgctca agtcagaggt ggcgaaaccc gacaggacta taaagatacc aggcgtttcc 6660

ccctggaagc tccctcgtgc gctctcctgt tccgaccctg ccgcttaccg gatacctgtc 6720

cgcctttctc ccttcgggaa gcgtggcgct ttctcatagc tcacgctgta ggtatctcag 6780

ttcggtgtag gtcgttcgct ccaagctggg ctgtgtgcac gaaccccccg ttcagcccga 6840

ccgctgcgcc ttatccggta actatcgtct tgagtccaac ccggtaagac acgacttatc 6900

gccactggca gcagccactg gtaacaggat tagcagagcg aggtatgtag gcggtgctac 6960

agagttcttg aagtggtggc ctaactacgg ctacactaga agaacagtat ttggtatctg 7020

cgctctgctg aagccagtta ccttcggaaa aagagttggt agctcttgat ccggcaaaca 7080

aaccaccgct ggtagcggtg gtttttttgt ttgcaagcag cagattacgc gcagaaaaaa 7140

aggatctcaa gaagatcctt tgatcttttc tacggggtct gacgctcagt ggaacgaaaa 7200

ctcacgttaa gggattttgg tcatgagatt atcaaaaagg atcttcacct agatcctttt 7260

aaattaaaaa tgaagtttta aatcaatcta aagtatatat gagtaaactt ggtctgacag 7320

ttaccaatgc ttaatcagtg aggcacctat ctcagcgatc tgtctatttc gttcatccat 7380

agttgcattt aaatggccgg cctggcgcgc cgtttaaacc tagatattga tagtctgatc 7440

ggtcaacgta taatcgagtc ctagcttttg caaacatcta tcaagagaca ggatcagcag 7500

gaggctttcg catgagtatt caacatttcc gtgtcgccct tattcccttt tttgcggcat 7560

tttgccttcc tgtttttgct cacccagaaa cgctggtgaa agtaaaagat gctgaagatc 7620

agttgggtgc gcgagtgggt tacatcgaac tggatctcaa cagcggtaag atccttgaga 7680

gttttcgccc cgaagaacgc tttccaatga tgagcacttt taaagttctg ctatgtggcg 7740

cggtattatc ccgtattgac gccgggcaag agcaactcgg tcgccgcata cactattctc 7800

agaatgactt ggttgagtat tcaccagtca cagaaaagca tcttacggat ggcatgacag 7860

taagagaatt atgcagtgct gccataacca tgagtgataa cactgcggcc aacttacttc 7920

tgacaacgat tggaggaccg aaggagctaa ccgctttttt gcacaacatg ggggatcatg 7980

taactcgcct tgatcgttgg gaaccggagc tgaatgaagc cataccaaac gacgagcgtg 8040

acaccacgat gcctgtagca atggcaacaa ccttgcgtaa actattaact ggcgaactac 8100

ttactctagc ttcccggcaa cagttgatag actggatgga ggcggataaa gttgcaggac 8160

cacttctgcg ctcggccctt ccggctggct ggtttattgc tgataaatct ggagccggtg 8220

agcgtgggtc tcgcggtatc attgcagcac tggggccaga tggtaagccc tcccgtatcg 8280

tagttatcta cacgacgggg agtcaggcaa ctatggatga acgaaataga cagatcgctg 8340

agataggtgc ctcactgatt aagcattggt aaccgattct aggtgcattg gcgcagaaaa 8400

aaatgcctga tgcgacgctg cgcgtcttat actcccacat atgccagatt cagcaacgga 8460

tacggcttcc ccaacttgcc cacttccata cgtgtcctcc ttaccagaaa tttatcctta 8520

agatcccgaa tcgtttaaac 8540

<210> 1001
<211> 4607
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 1001
ttggccactc cctctctgcg cgctcgctcg ctcactgagg ccgggcgacc aaaggtcgcc   60

cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc gagcgcgcag agagggagtg   120

gccaactcca tcactagggg ttcctagatc ttgccaacat accataaacc tcccattctg   180

ctaatgccca gcctaagttg gggagaccac tccagattcc aagatgtaca gtttgctttg   240

ctgggccttt ttcccatgcc tgcctttact ctgccagagt tatattgctg gggttttgaa   300

gaagatccta ttaaataaaa gaataagcag tattattaag tagccctgca tttcaggttt   360

ccttgagtgg caggccaggc ctggccgtga acgttcactg aaatcatggc ctcttggcca   420

agattgatag cttgtgcctg tccctgagtc ccagtccatc acgagcagct ggtttctaag   480

atgctatttc ccgtataaag catgagaccg tgacttgcca gccccacaga gccccgccct   540

tgtccatcac tggcatctgg actccagcct gggttggggc aaagagggaa atgagatcat   600

gtcctaaccc tgatcctctt gtcccacaga tatccagaac cctgaccctg cggctccggt   660

gcccgtcagt gggcagagcg cacatcgccc acagtccccg agaagttggg gggaggggtc   720

ggcaattgaa ccggtgccta gagaaggtgg cgcggggtaa actgggaaag tgatgtcgtg   780

tactggctcc gcctttttcc cgagggtggg ggagaaccgt atataagtgc agtagtcgcc   840

gtgaacgttc tttttcgcaa cgggtttgcc gccagaacac aggtaagtgc cgtgtgtggt   900

tcccgcgggc ctggcctctt tacgggttat ggcccttgcg tgccttgaat tacttccacg   960

cccctggctg cagtacgtga ttcttgatcc cgagcttcgg gttggaagtg ggtgggagag   1020

ttcgaggcct tgcgcttaag gagccccttc gcctcgtgct tgagttgagg cctggcttgg   1080

gcgctggggc cgccgcgtgc gaatctggtg gcaccttcgc gcctgtctcg ctgctttcga   1140

taagtctcta gccatttaaa atttttgatg acctgctgcg acgctttttt tctggcaaga   1200

tagtcttgta aatgcgggcc aagatgtgca cactggtatt tcggtttttg gggccgcggg 1260

cggcgacggg gcccgtgcgt cccagcgcac atgttcggcg aggcggggcc tgcgagcgcg 1320

gccaccgaga atcggacggg ggtagtctca agctggccgg cctgctctgg tgcctggcct 1380

cgcgccgccg tgtatcgccc cgccctgggc ggcaaggctg gcccggtcgg caccagttgc 1440

gtgagcggaa agatggccgc ttcccggccc tgctgcaggg agctcaaaat ggaggacgcg 1500

gcgctcggga gagcgggcgg gtgagtcacc cacacaaagg aaaagggcct ttccgtcctc 1560

agccgtcgct tcatgtgact ccacggagta ccgggcgccg tccaggcacc tcgattagtt 1620

ctcgagcttt tggagtacgt cgtctttagg ttggggggag gggttttatg cgatggagtt 1680

tccccacact gagtgggtgg agactgaagt taggccagct tggcacttga tgtaattctc 1740

cttggaattt gccctttttg agtttggatc ttggttcatt ctcaagcctc agacagtggt 1800

tcaaagtttt tttcttccat ttcaggtgtc gtgatgcggc cgccaccatg ggatcttgga 1860

cactgtgttg cgtgtccctg tgcatcctgg tggccaagca cacagatgcc ggcgtgatcc 1920

agtctcctag acacgaagtg accgagatgg gccaagaagt gaccctgcgc tgcaagccta 1980

tcagcggcca cgattacctg ttctggtaca gacagaccat gatgagaggc ctggaactgc 2040

tgatctactt caacaacaac gtgcccatcg acgacagcgg catgcccgag gatagattca 2100

gcgccaagat gcccaacgcc agcttcagca ccctgaagat ccagcctagc gagcccagag 2160

atagcgccgt gtacttctgc gccagcagaa agacaggcgg ctacagcaat cagccccagc 2220

actttggaga tggcacccgg ctgagcatcc tggaagatct gaagaacgtg ttcccacctg 2280

aggtggccgt gttcgagcct tctgaggccg agatcagcca cacacagaaa gccacactcg 2340

tgtgtctggc caccggcttc tatcccgatc acgtggaact gtcttggtgg gtcaacggca 2400

aagaggtgca cagcggcgtc agcaccgatc ctcagcctct gaaagagcag cccgctctga 2460

acgacagcag atactgcctg agcagcagac tgagagtgtc cgccaccttc tggcagaacc 2520

ccagaaacca cttcagatgc caggtgcagt tctacggcct gagcgagaac gatgagtgga 2580

cccaggatag agccaagcct gtgacacaga tcgtgtctgc cgaagcctgg ggcagagccg 2640

attgtggctt taccagcgag agctaccagc agggcgtgct gtctgccaca atcctgtacg 2700

agatcctgct gggcaaagcc actctgtacg ccgtgctggt gtctgccctg gtgctgatgg 2760

ccatggtcaa gcggaaggat agcaggggcg gctccggtgc cacaaacttc tccctgctca 2820

agcaggccgg agatgtggaa gagaaccctg gccctatgga aaccctgctg aaggtgctga 2880

gcggcacact gctgtggcag ctgacatggg tccgatctca gcagcctgtg cagtctcctc 2940

aggccgtgat tctgagagaa ggcgaggacg ccgtgatcaa ctgcagcagc tctaaggccc 3000

tgtacagcgt gcactggtac agacagaagc acggcgaggc ccctgtgttc ctgatgatcc 3060

tgctgaaagg cggcgagcag aagggccacg agaagatcag cgccagcttc aacgagaaga 3120

agcagcagtc cagcctgtac ctgacagcca gccagctgag ctacagcggc acctactttt 3180

gtggcaccgc ctggatcaac gactacaagc tgtctttcgg agccggcacc acagtgacag 3240

tgcgggccaa tattcagaac cccgatcctg ccgtgtacca gctgagagac agcaagagca 3300

gcgacaagag cgtgtgcctg ttcaccgact tcgacagcca gaccaacgtg tcccagagca 3360

aggacagcga cgtgtacatc accgataaga ctgtgctgga catgcggagc atggacttca 3420

agagcaacag cgccgtggcc tggtccaaca agagcgattt cgcctgcgcc aacgccttca 3480

acaacagcat tatccccgag gacacattct tcccaagtcc tgagagcagc tgcgacgtga 3540

agctggtgga aaagagcttc gagacagaca ccaacctgaa cttccagaac ctgagcgtga 3600

tcggcttcag aatcctgctg ctcaaggtgg ccggcttcaa cctgctgatg accctgagac 3660

tgtggtccag ctaacctcga ctgtgccttc tagttgccag ccatctgttg tttgcccctc 3720

ccccgtgcct tccttgaccc tggaaggtgc cactcccact gtcctttcct aataaaatga 3780

ggaaattgca tcgcattgtc tgagtaggtg tcattctatt ctggggggtg gggtggggca 3840

ggacagcaag ggggaggatt gggaagacaa tagcaggcat gctggggatg cggtgggctc 3900

tatggcttct gaggcggaaa gaaccagctg gggctctagg gggtatcccc actagtcgtg 3960

taccagctga gagactctaa atccagtgac aagtctgtct gcctattcac cgattttgat 4020

tctcaaacaa atgtgtcaca aagtaaggat tctgatgtgt atatcacaga caaaactgtg 4080

ctagacatga ggtctatgga cttcaagagc aacagtgctg tggcctggag caacaaatct 4140

gactttgcat gtgcaaacgc cttcaacaac agcattattc cagaagacac cttcttcccc 4200

agcccaggta agggcagctt tggtgccttc gcaggctgtt tccttgcttc aggaatggcc   4260

aggttctgcc cagagctctg gtcaatgatg tctaaaactc ctctgattgg tggtctcggc   4320

cttatccatt gccaccaaaa ccctcttttt actaagaaac agtgagcctt gttctggcag   4380

tccagagaat gacacgggaa aaaagcagat gaagagaagg tggcaggaga gggcacgtgg   4440

cccagcctca gtctctagat ctaggaaccc ctagtgatgg agttggccac tccctctctg   4500

cgcgctcgct cgctcactga ggccgcccgg gcaaagcccg ggcgtcgggc gacctttggt   4560

cgcccggcct cagtgagcga gcgagcgcgc agagagggag tggccaa   4607

<210> 1002
<211> 91
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<222> (1)..(20)
<223> n is a, c, g, or u

<400> 1002
nnnnnnnnnn nnnnnnnnnn guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucacg aaagggcacc gagucggugc u   91

<210> 1003
<211> 91
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<220>
<221> misc_feature
<222> (1)..(20)
<223> n is a, c, g, or u

<400> 1003
nnnnnnnnnn nnnnnnnnnn guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucacg aaagggcacc gagucggugc u   91

<210> 1004

<400> 1004
000

<210> 1005
<211> 887
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 1005
gggaagcuca gaauaaacgc ucaacuuugg ccggaucugc caccaugacc aaccuguccg   60

acaucaucga gaaggagacc ggcaagcagc uggugaucca ggaguccauc cugaugcugc   120

ccgaggaggu ggaggaggug aucggcaaca agcccgaguc cgacauccug gugcacaccg   180

ccuacgacga guccaccgac gagaacguga ugcugcugac cuccgacgcc cccgaguaca   240

agcccugggc ccuggugauc caggacucca acggcgagaa caagaucaag augcuguccg   300

gcggcuccaa gcggaccgcc gacggcuccg aguucgaguc ccccaagaag aagcggaagg   360

uggagugaua gcuagcacca gccucaagaa cacccgaaug gagucucuaa gcuacauaau   420

accaacuuac acuuuacaaa auguuguccc ccaaaaugua gccauucgua ucugcuccua   480

auaaaaagaa aguuucuuca cauucucucg agaaaaaaaa aaaauggaaa aaaaaaaaac   540

ggaaaaaaaa aaaagguaaa aaaaaaaaau auaaaaaaaa aaaacauaaa aaaaaaaaac   600

gaaaaaaaaa aaacguaaaa aaaaaaaacu caaaaaaaaa aaagauaaaa aaaaaaaacc   660

uaaaaaaaaa aaauguaaaa aaaaaaaagg gaaaaaaaaa aaacgcaaaa aaaaaaaaca   720

caaaaaaaaa aaaugcaaaa aaaaaaaauc gaaaaaaaaa aaaucuaaaa aaaaaaaacg   780

aaaaaaaaaa aacccaaaaa aaaaaaagac aaaaaaaaaa aauagaaaaa aaaaaaaguu   840

aaaaaaaaaa aacugaaaaa aaaaaaauuu aaaaaaaaaa aaucuag   887

<210> 1006
<211> 70
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 1006
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucacg aaagggcacc   60

gagucggugc   70

<210> 1007
<211> 70
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 1007
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucacg aaagggcacc   60

gagucggugc   70

<210> 1008
<211> 70
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 1008
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucacg aaagggcacc   60

gagucggugc   70

<210> 1009
<211> 68
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 1009
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaac uuggcaccga   60

gucggugc   68

<210> 1010
<211> 68
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 1010
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaaa auggcaccga   60

gucggugc   68

<210> 1011
<211> 68
<212> RNA

<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 1011
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaaa auggcaccga   60

gucggugc   68

<210> 1012
<211> 68
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 1012
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaaa auggcaccga   60

gucggugc   68

<210> 1013
<211> 80
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature

<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 1013
guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaac uugaaaaagu   60

ggcaccgagu cggugcuuuu   80

<210> 1014
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<220>
<221> misc_feature
<222> (1)..(20)
<223> n is a, c, g, or u

<400> 1014
nnnnnnnnnn nnnnnnnnnn guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu   100

<210> 1015
<211> 91
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 1015
gcugcagcgc acggguacca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucacg aaagggcacc gagucggugc u   91

<210> 1016
<211> 91
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> misc_feature
<223> contains 2'-O-Me and PS modifications; see specification as filed
       for detailed description of substitutions and preferred
       embodiments

<400> 1016
gcugcagcgc acggguacca guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc   60

cguuaucacg aaagggcacc gagucggugc u   91