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BORGES et al.(10) Pub. No.: US 2025/0262301 A1
(43) Pub. Date: Aug. 21, 2025(54) METHODS OF INDUCING
ANTIBODY-DEPENDENT CELLULAR
CYTOTOXICITY (ADCC) USING MODIFIED
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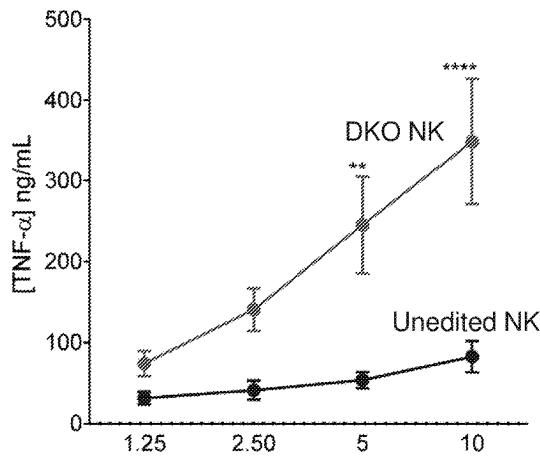
ABSTRACT

The present disclosure is directed to the use of modified NK cells for immunotherapy in combination with an antibody, or antigen-binding fragment thereof, to induce an enhanced antibody-dependent cellular cytotoxicity (ADCC) effect.

Specification includes a Sequence Listing.

SK-OV-3

(6 donors, 6 independent experiments)



■ Unedited NK
■ DKO NK

SK-OV-3

(6 donors, 6 independent experiments)

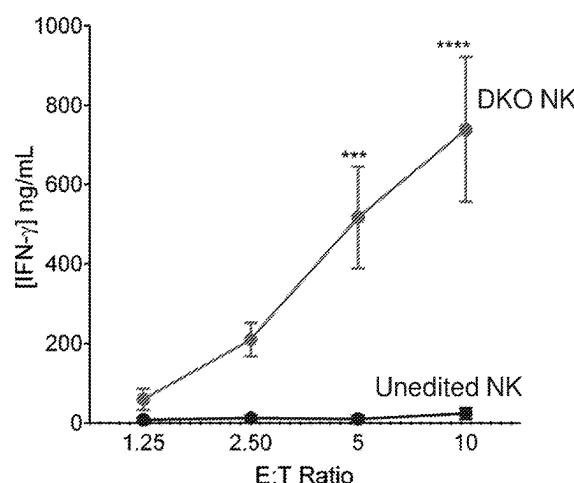


Fig. 1A

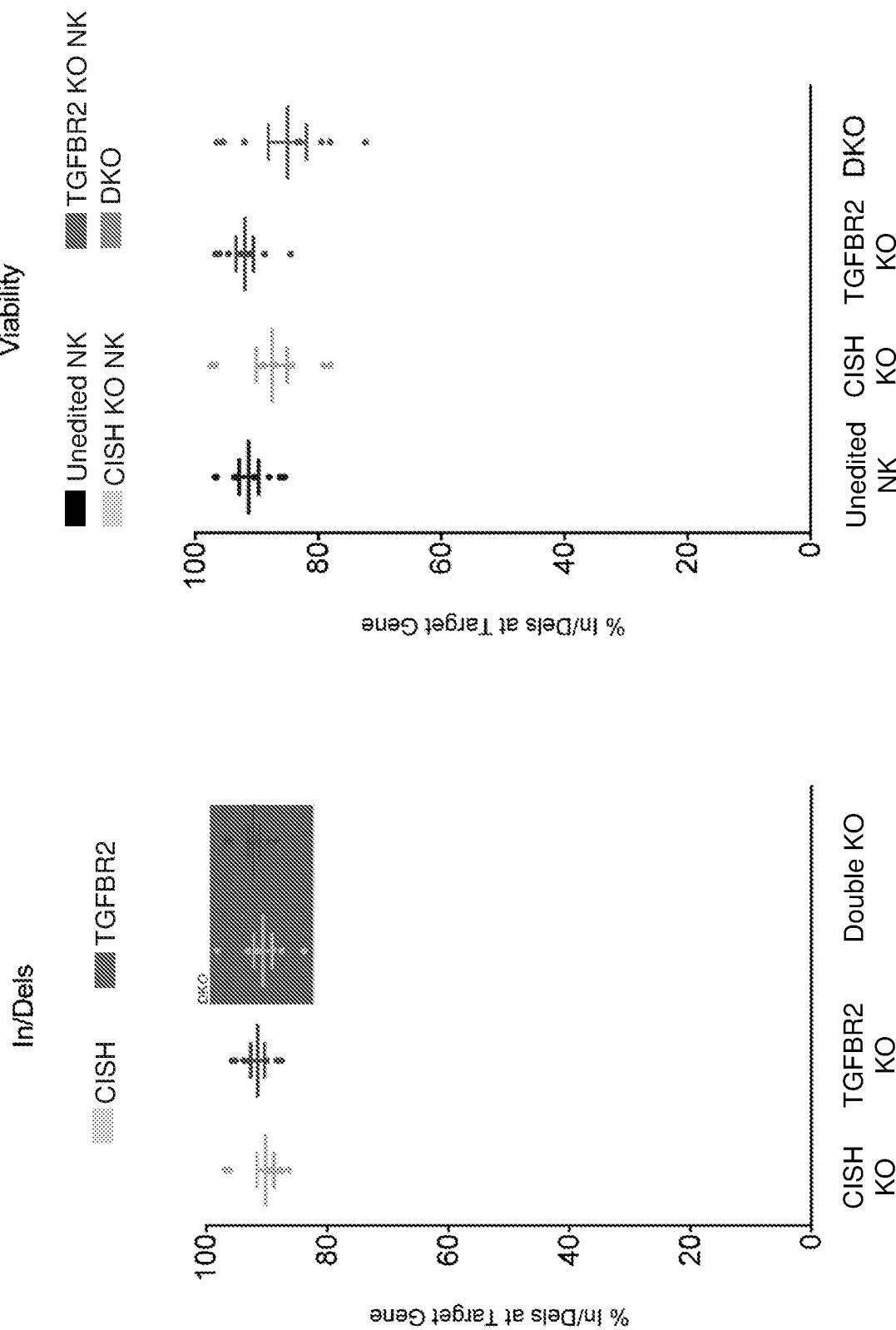


Fig. 1B

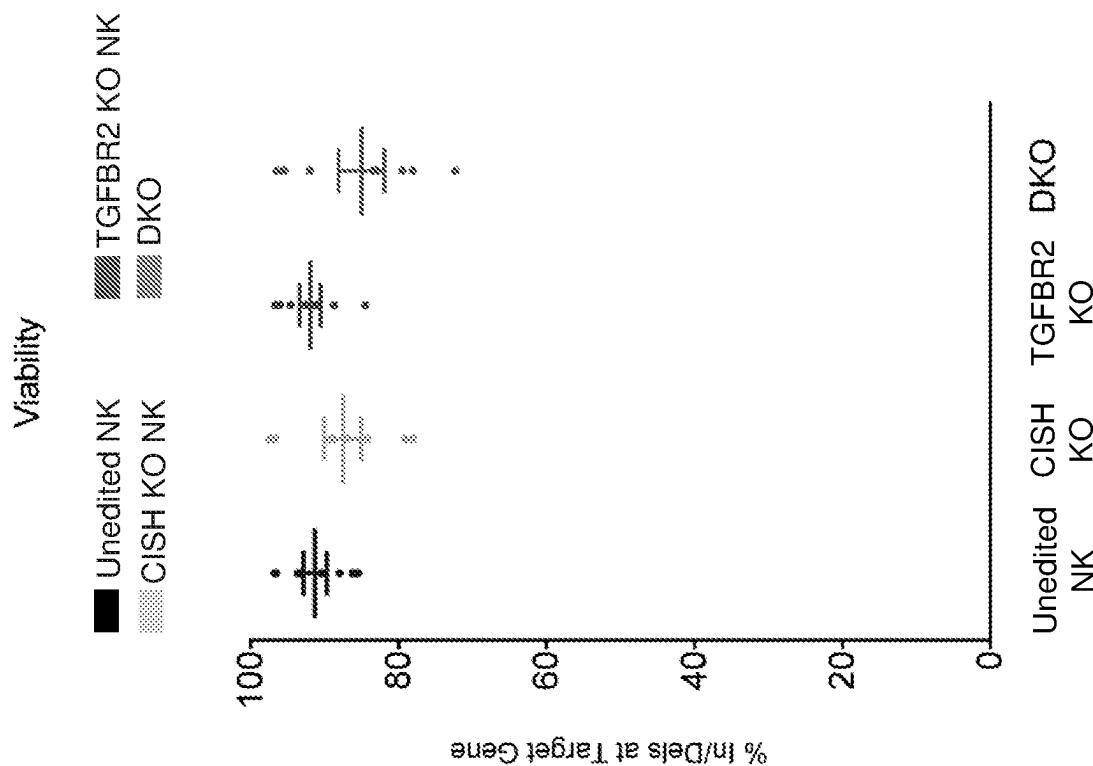


Fig. 2A

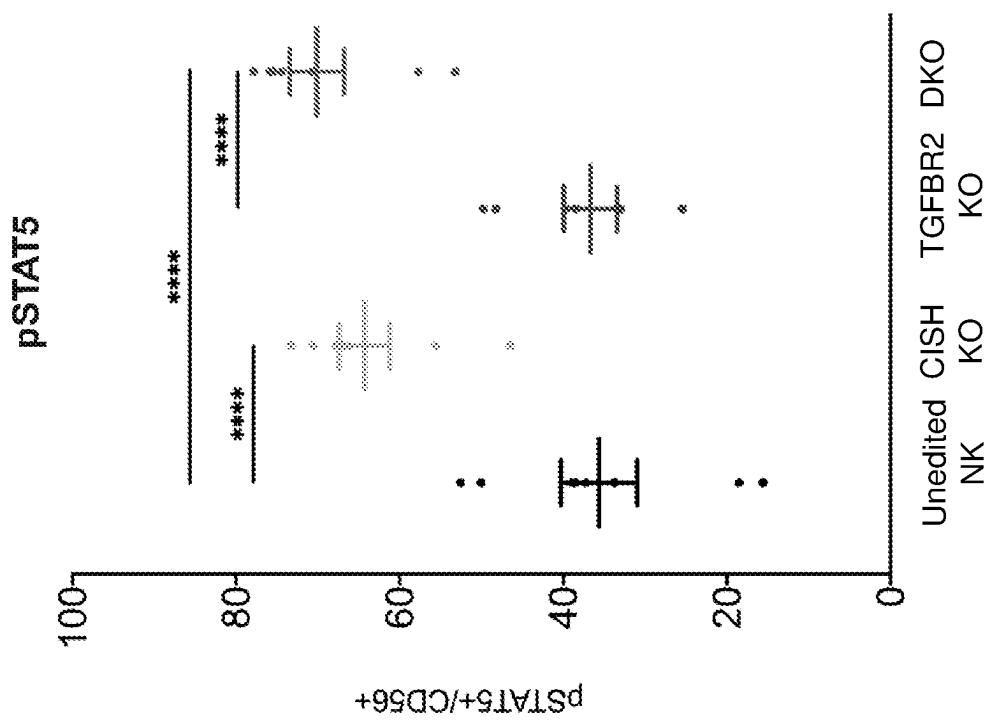


Fig. 2B

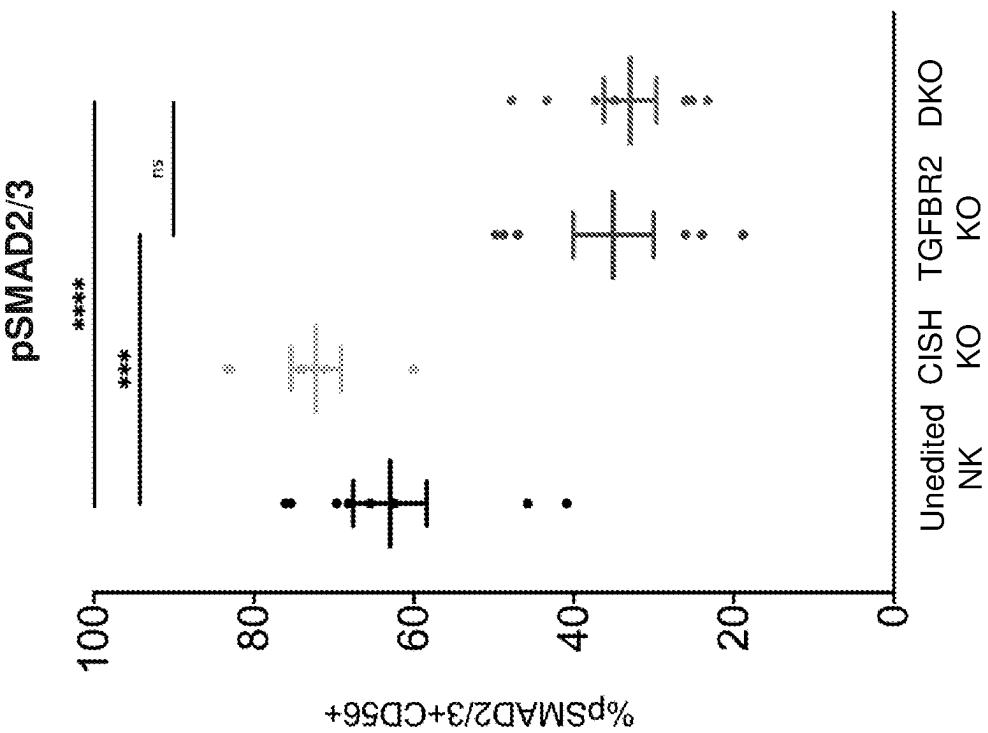


Fig. 3A
SK-OV-3
(6 donors, 6 independent experiments)

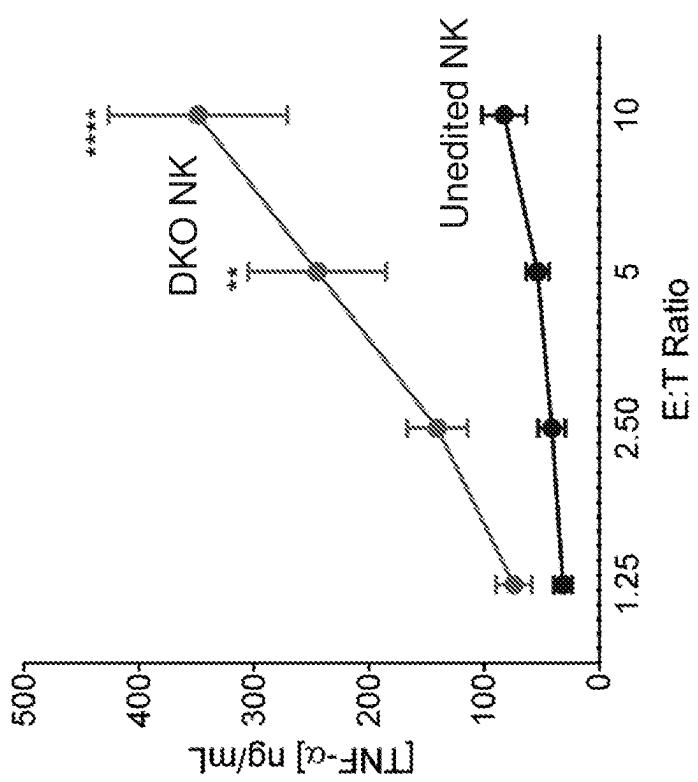


Fig. 3B
SK-OV-3
(6 donors, 6 independent experiments)

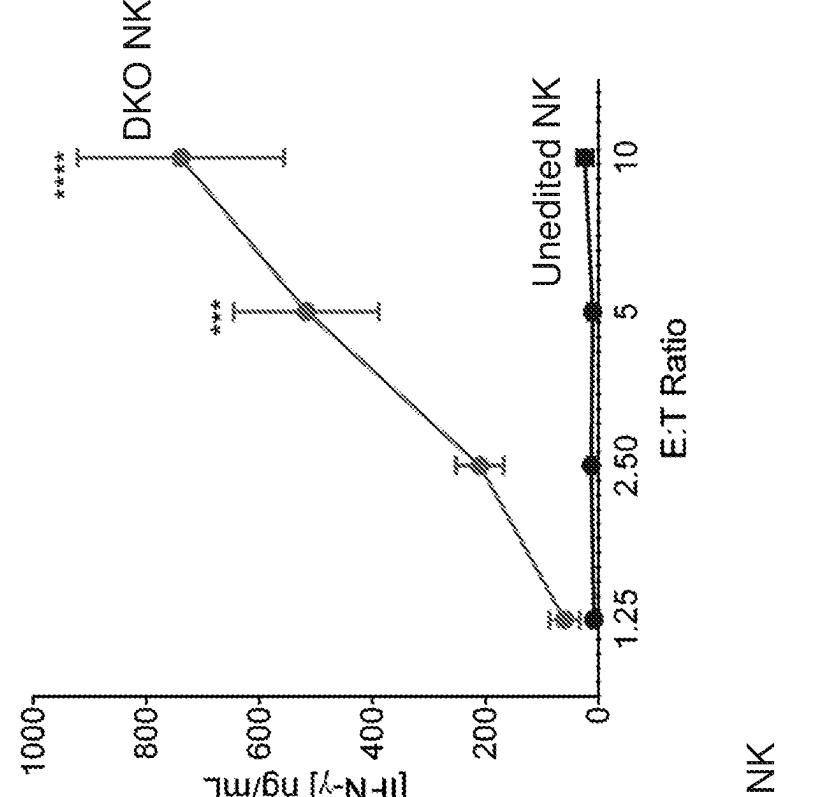


Fig. 3C
PC-3
(10 donors, 5 independent experiments)

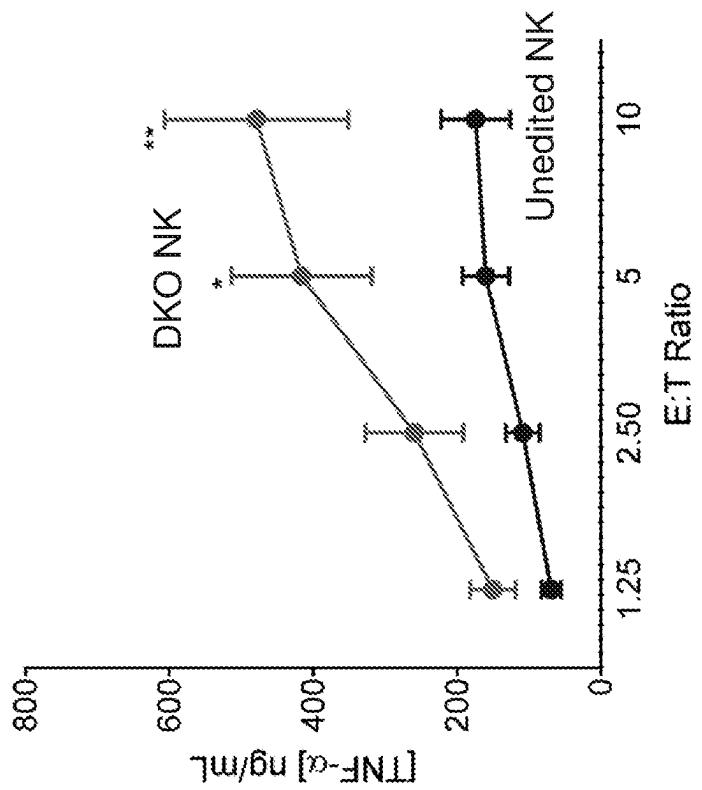
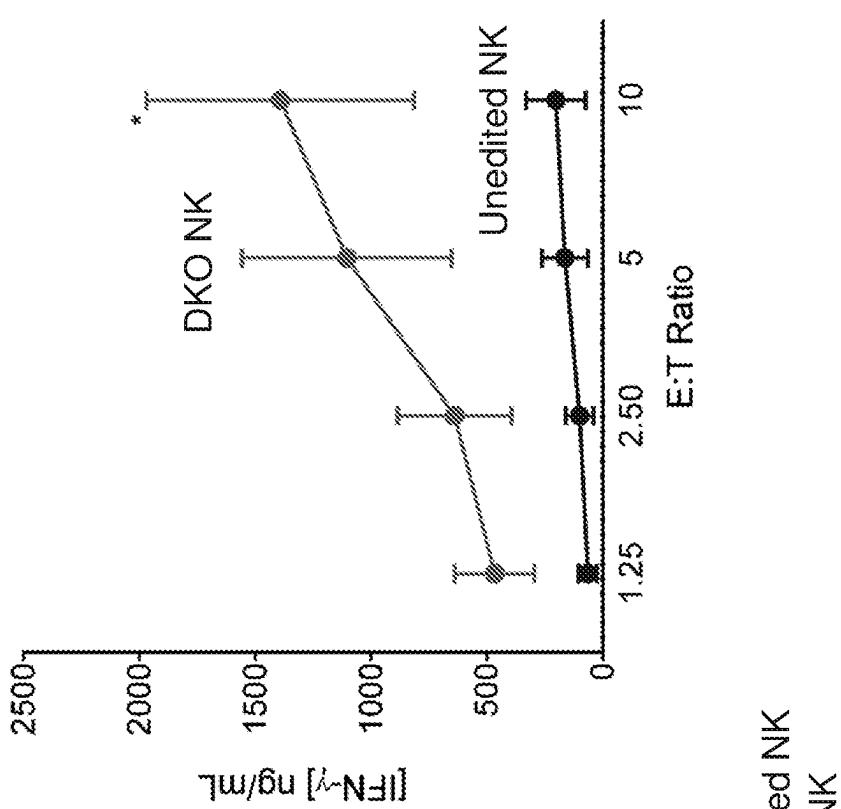


Fig. 3D
PC-3
(10 donors, 5 independent experiments)



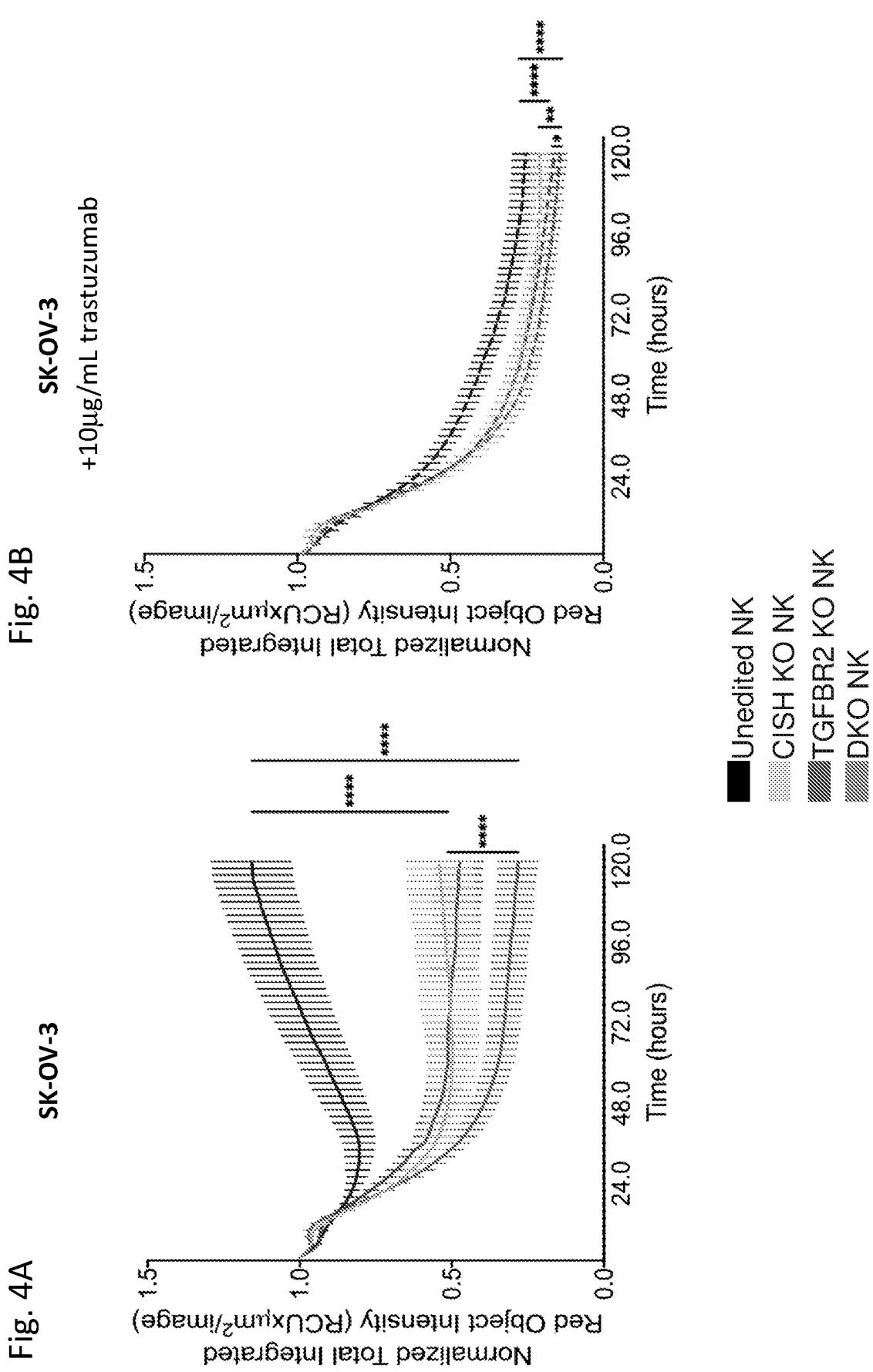


Fig. 4C
SK-OV-3

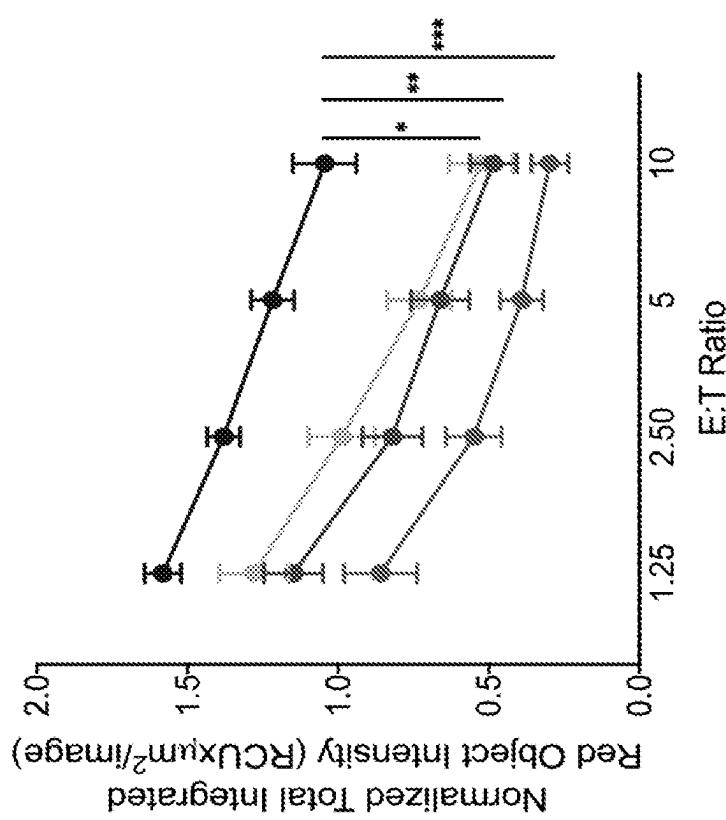


Fig. 4D
SK-OV-3

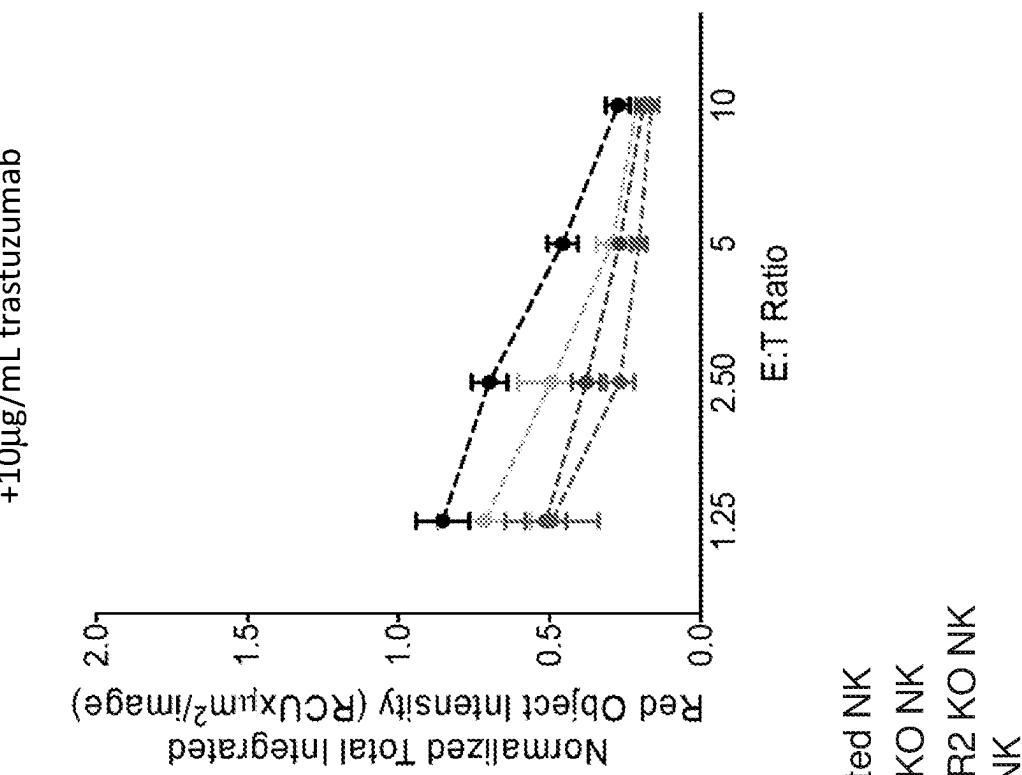


Fig. 5

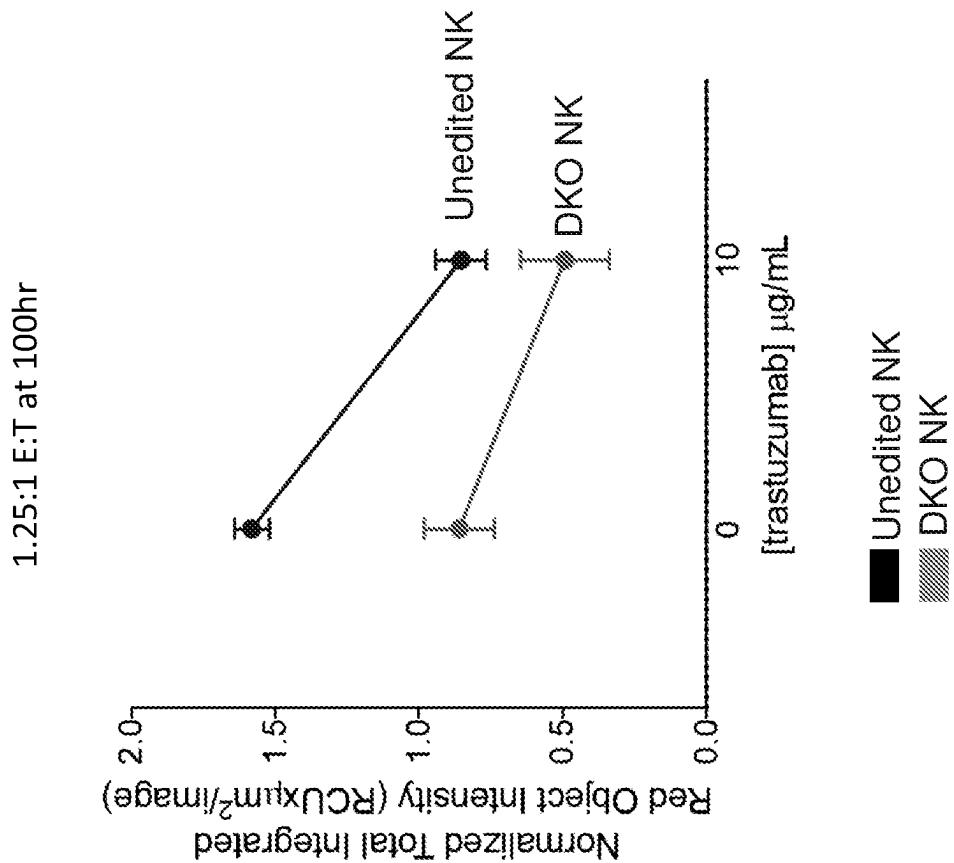


Fig. 6A

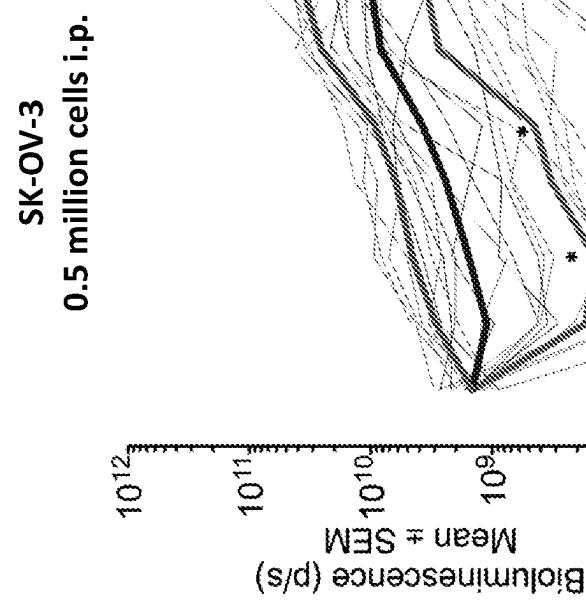


Fig. 6B

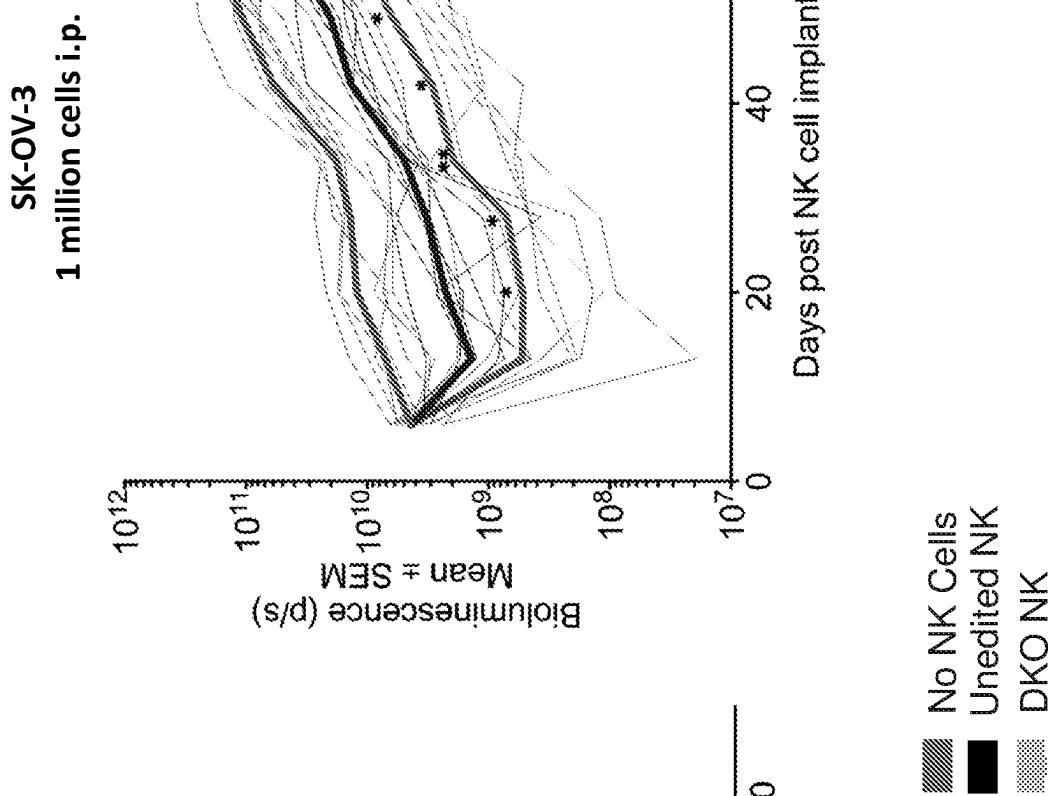


Fig. 6C

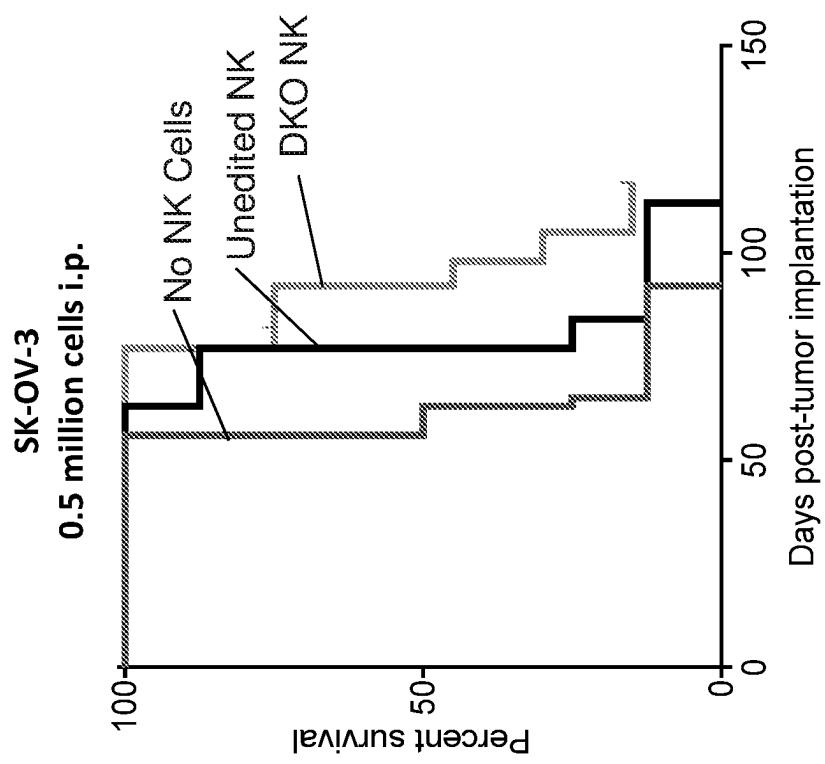


Fig. 6D

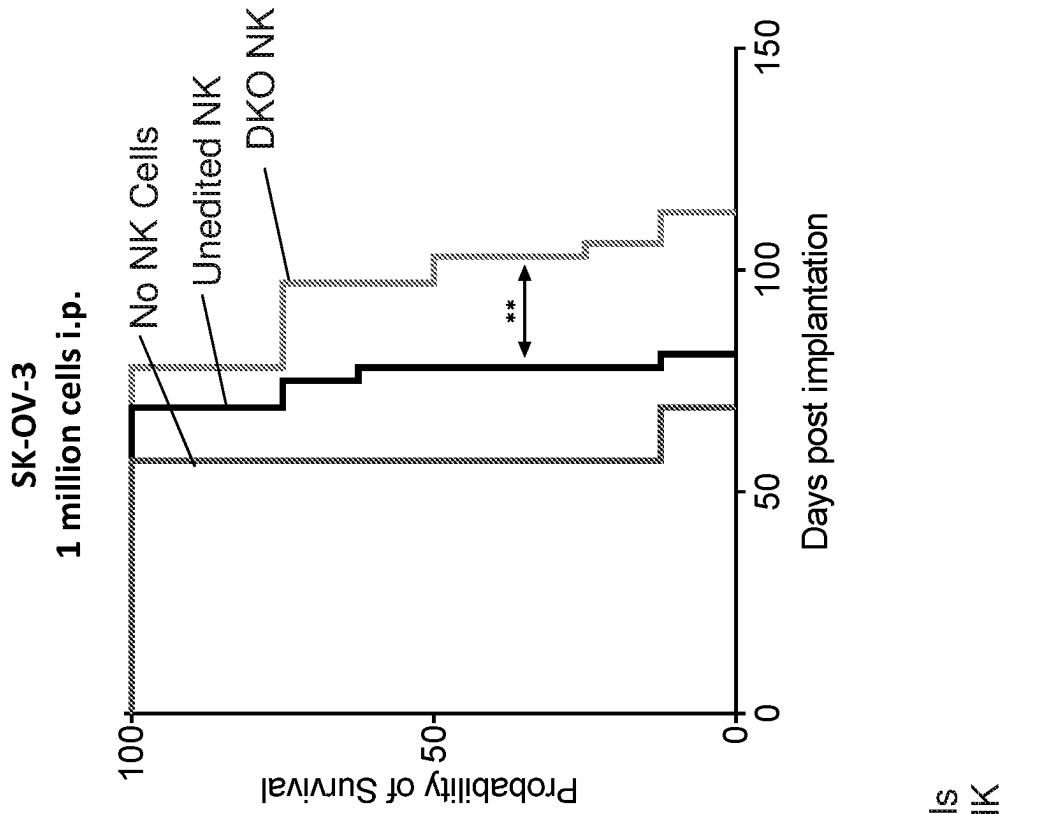


Fig. 7A

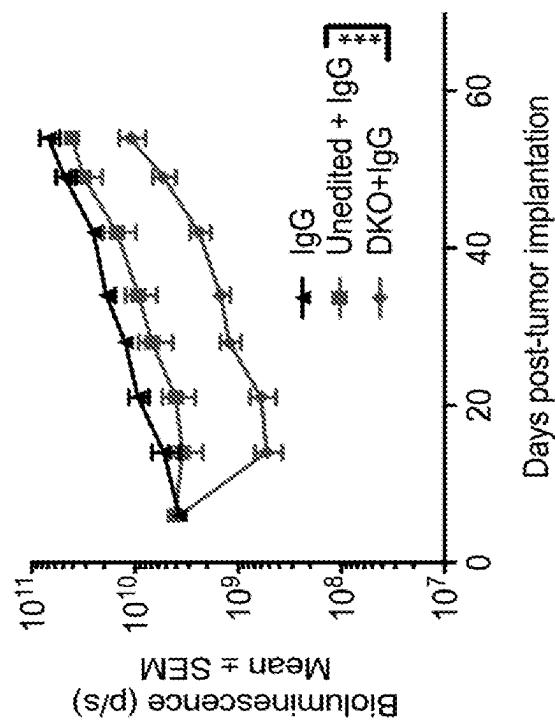


Fig. 7B

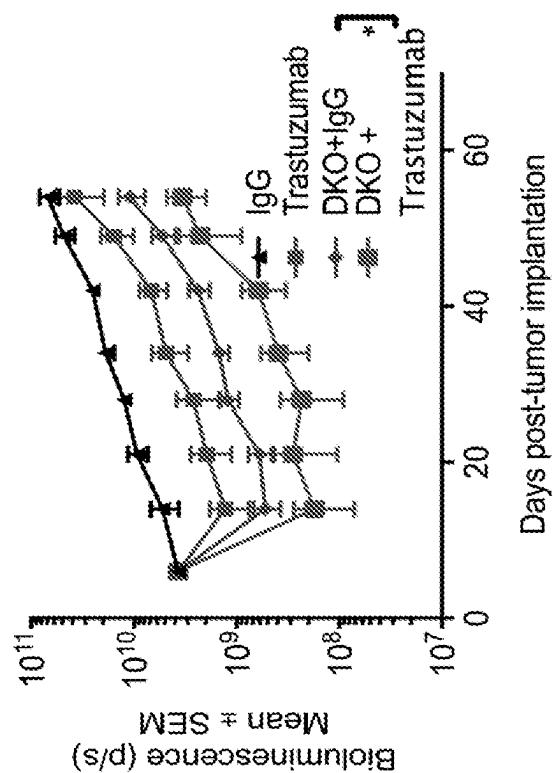


Fig. 7C

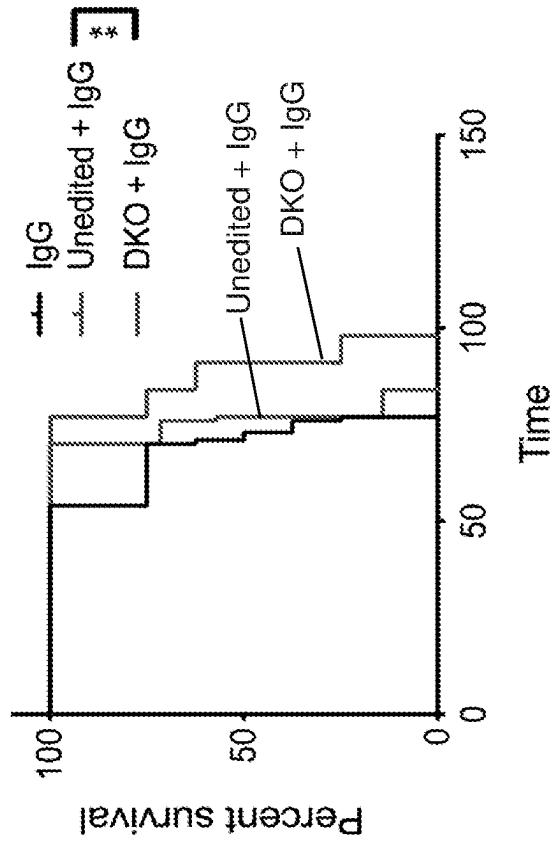


Fig. 7D

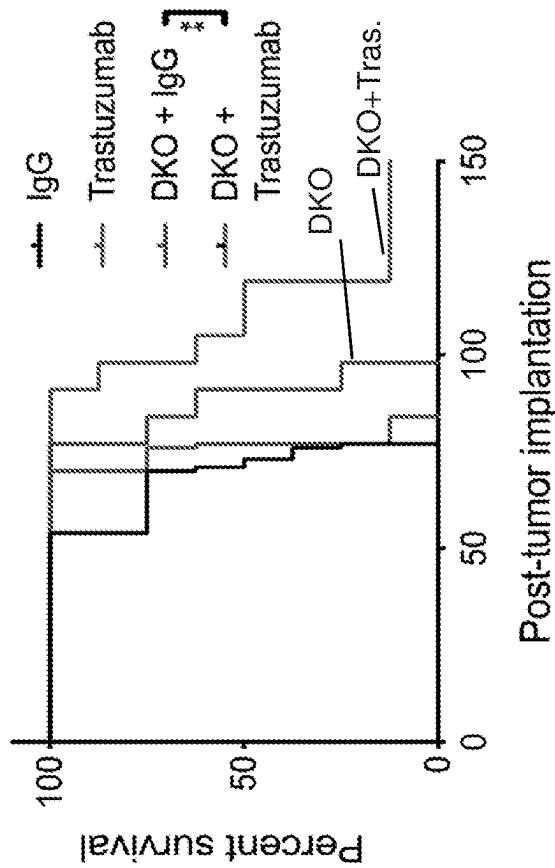


Fig. 8A

2D Heme Restim/Serial Killing Assay

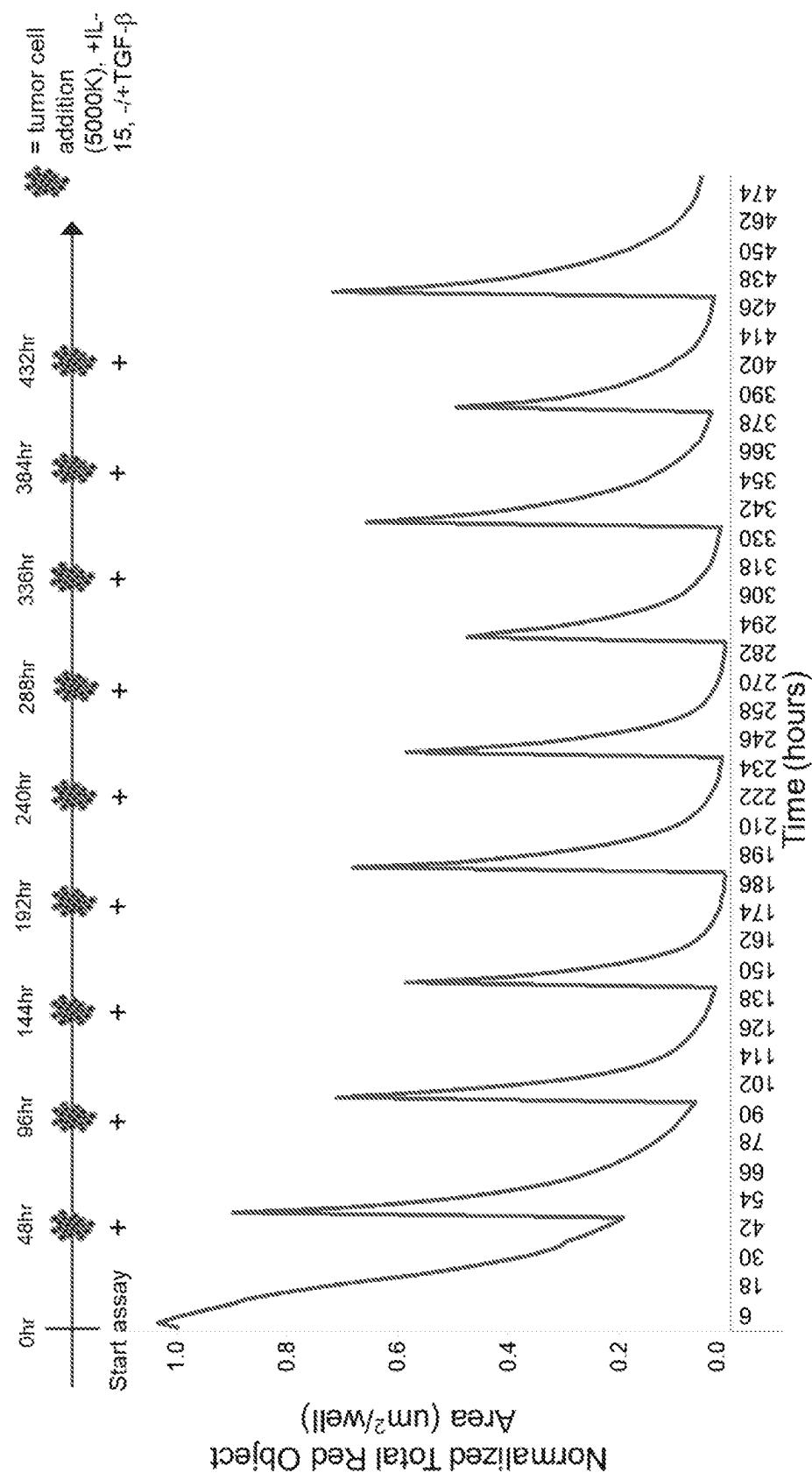


Fig. 8B

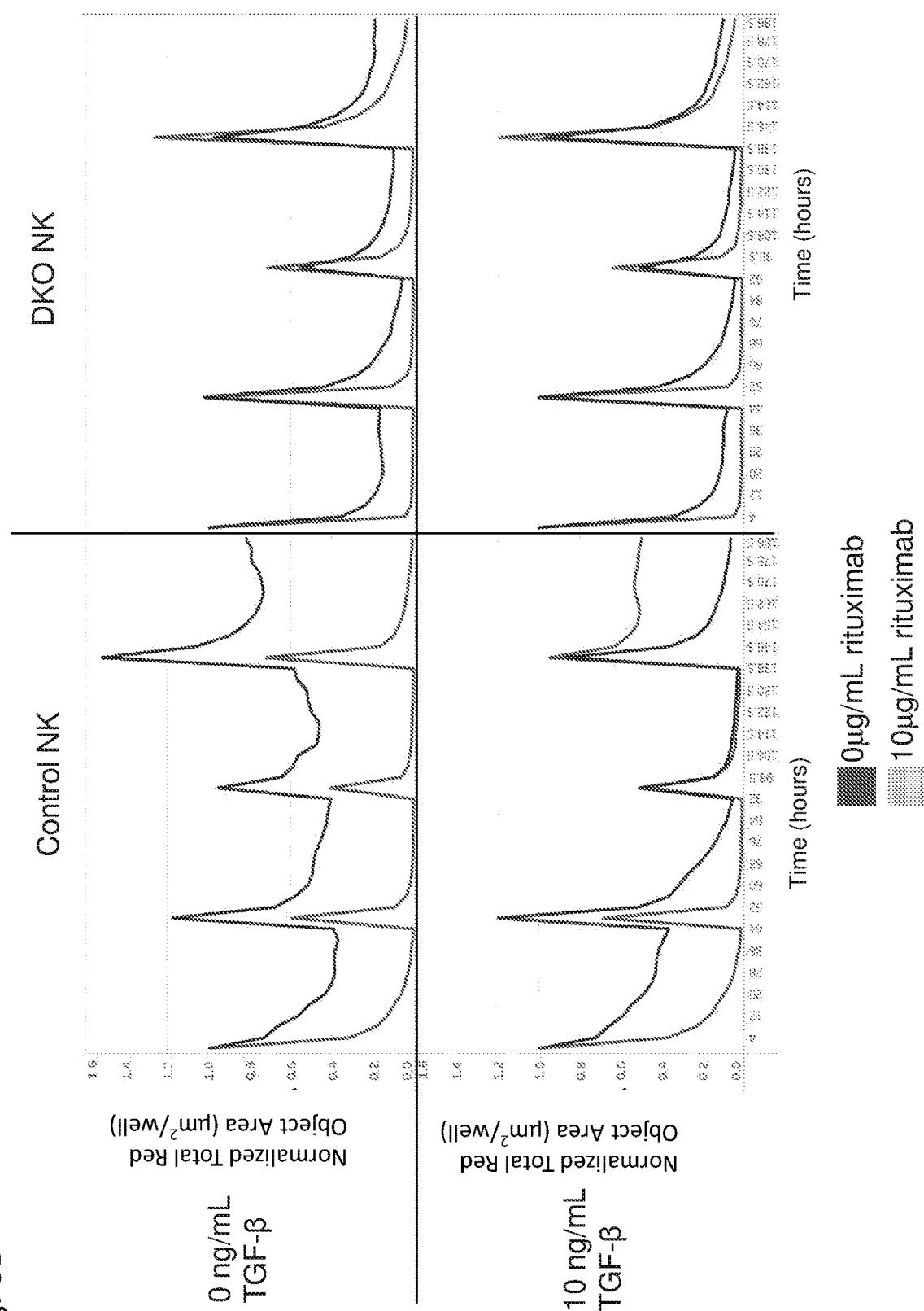


FIG. 9A

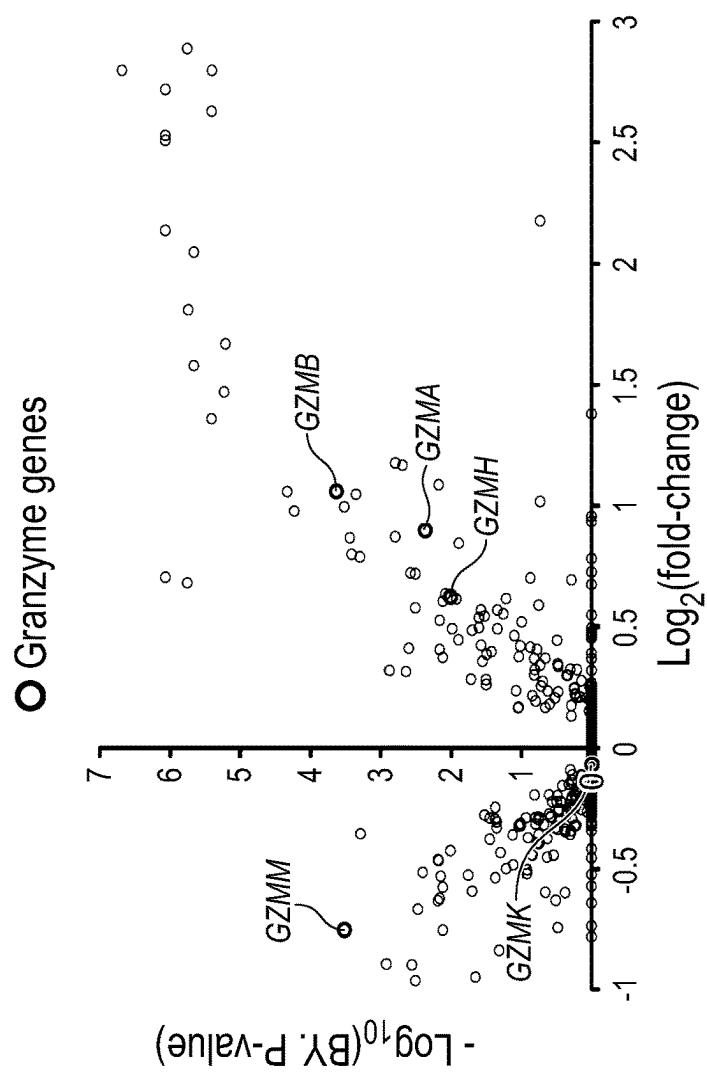


FIG. 9B

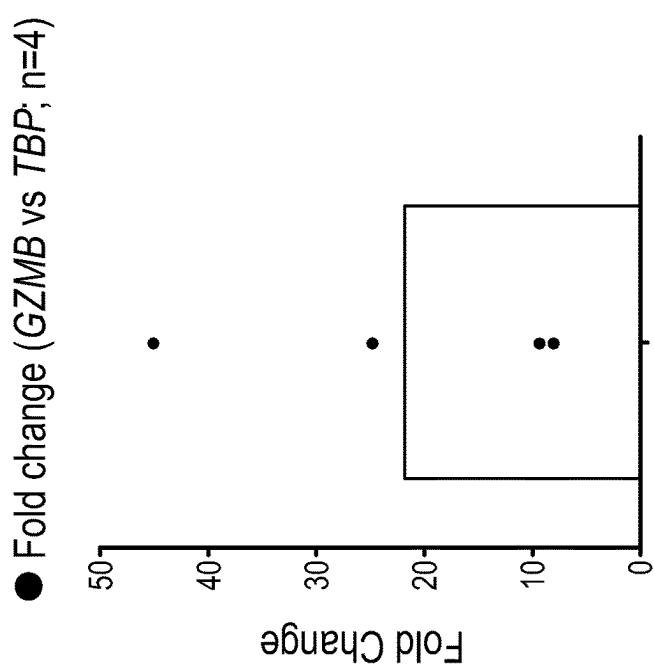


Fig. 9C

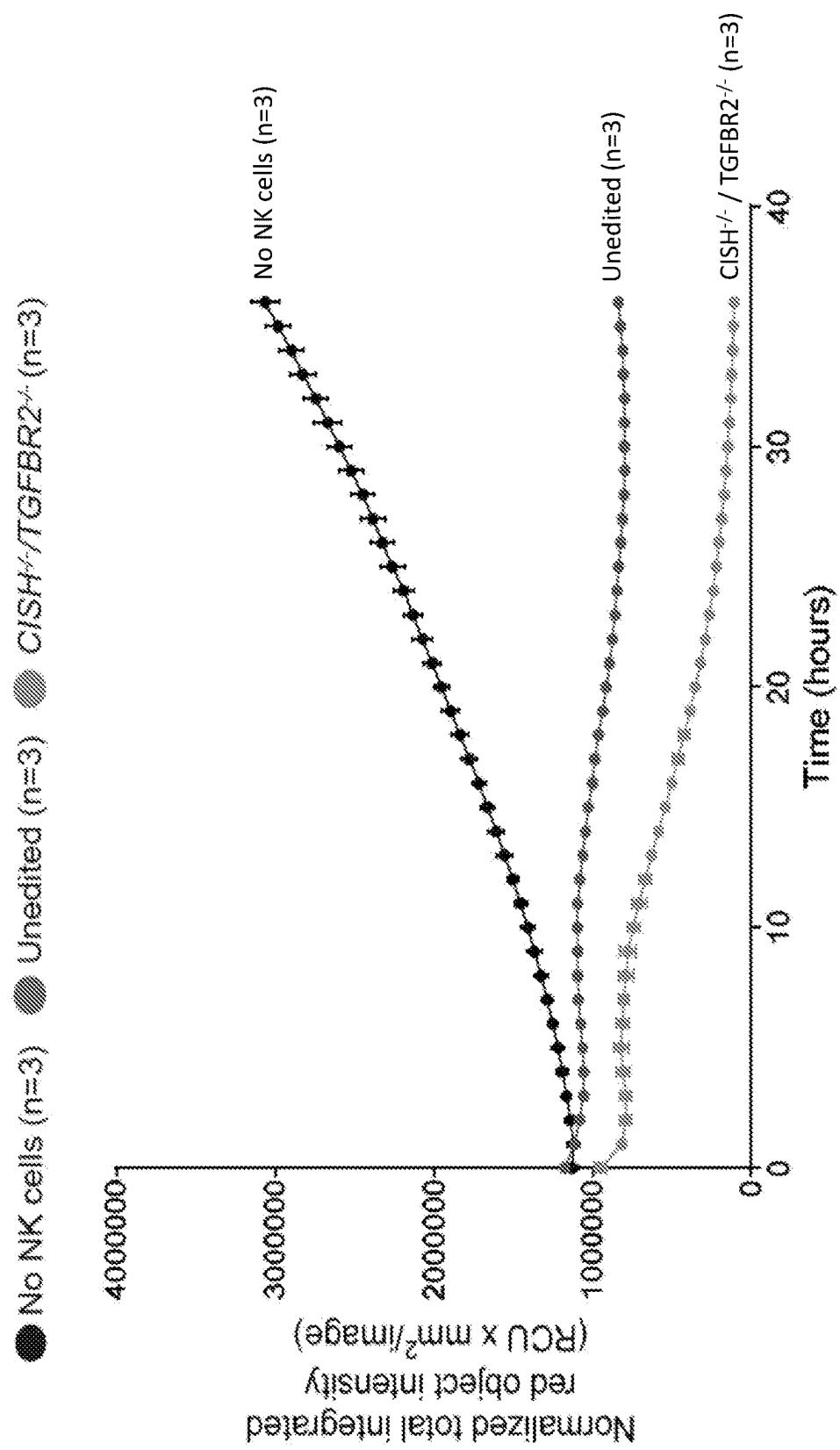


FIG. 9D

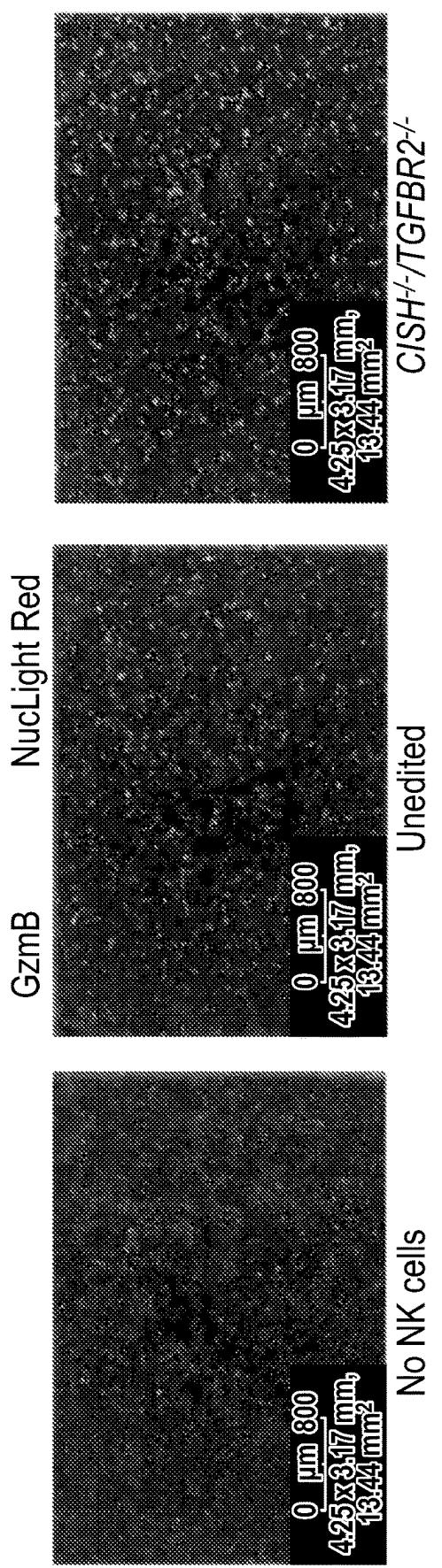


Fig. 9E

● No NK cells (n=3) ● Unedited (n=3) ● CIS $H^{-/-}$ /TGFBR2 $^{+/-}$ (n=3)

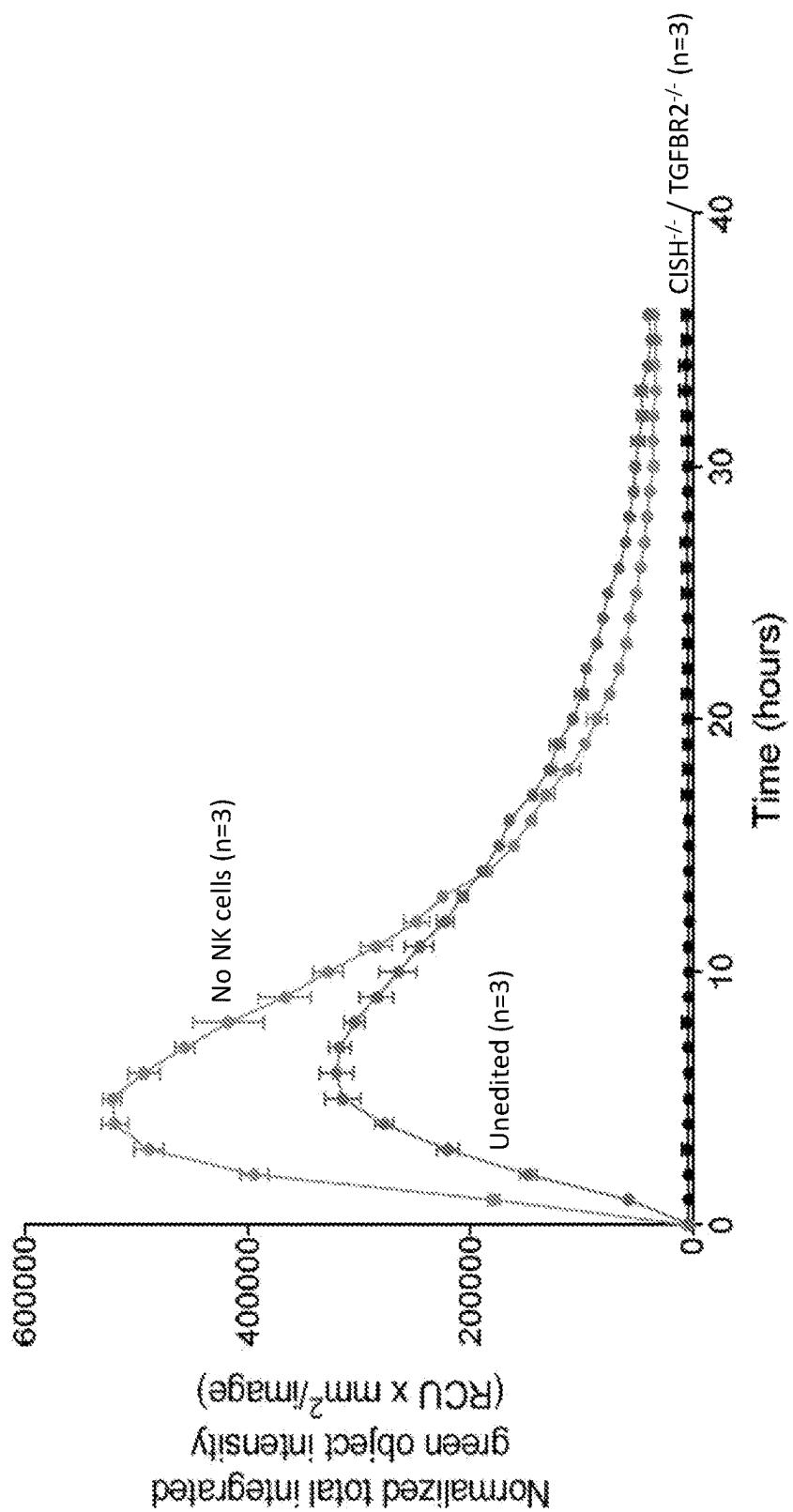


FIG. 10A

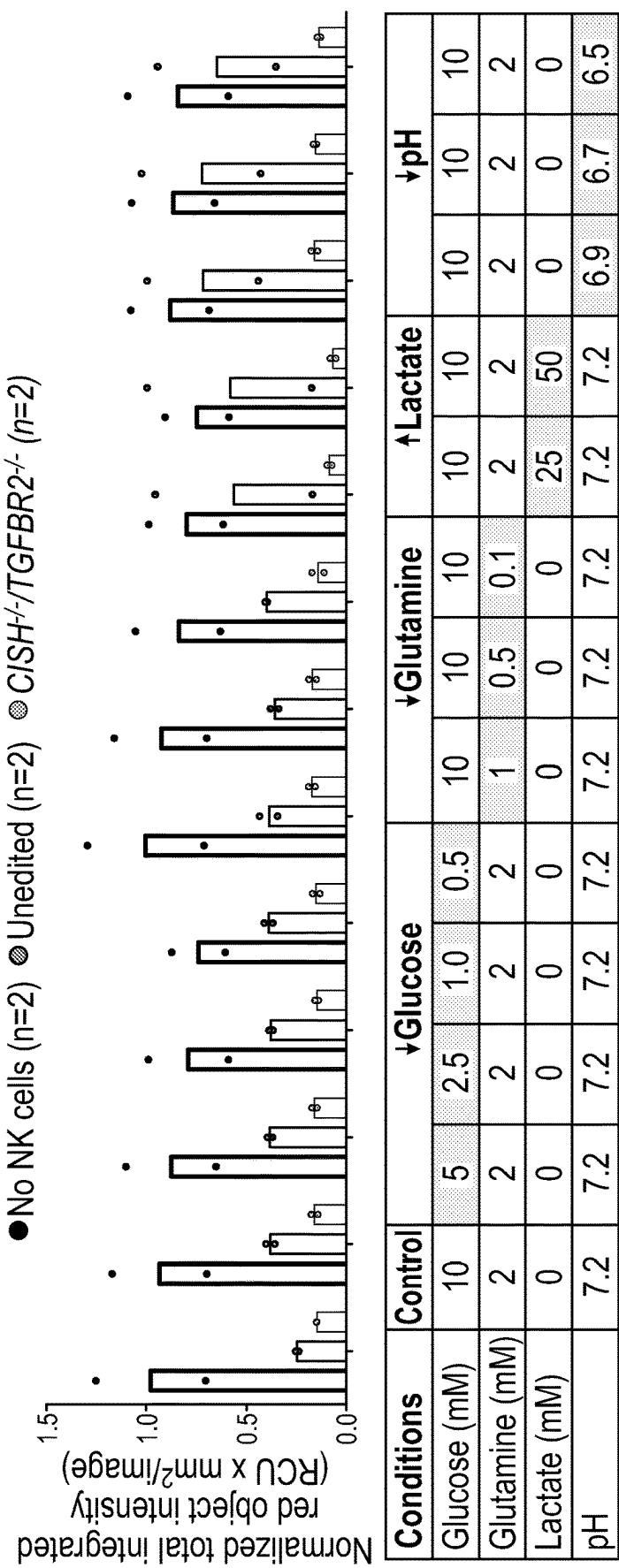
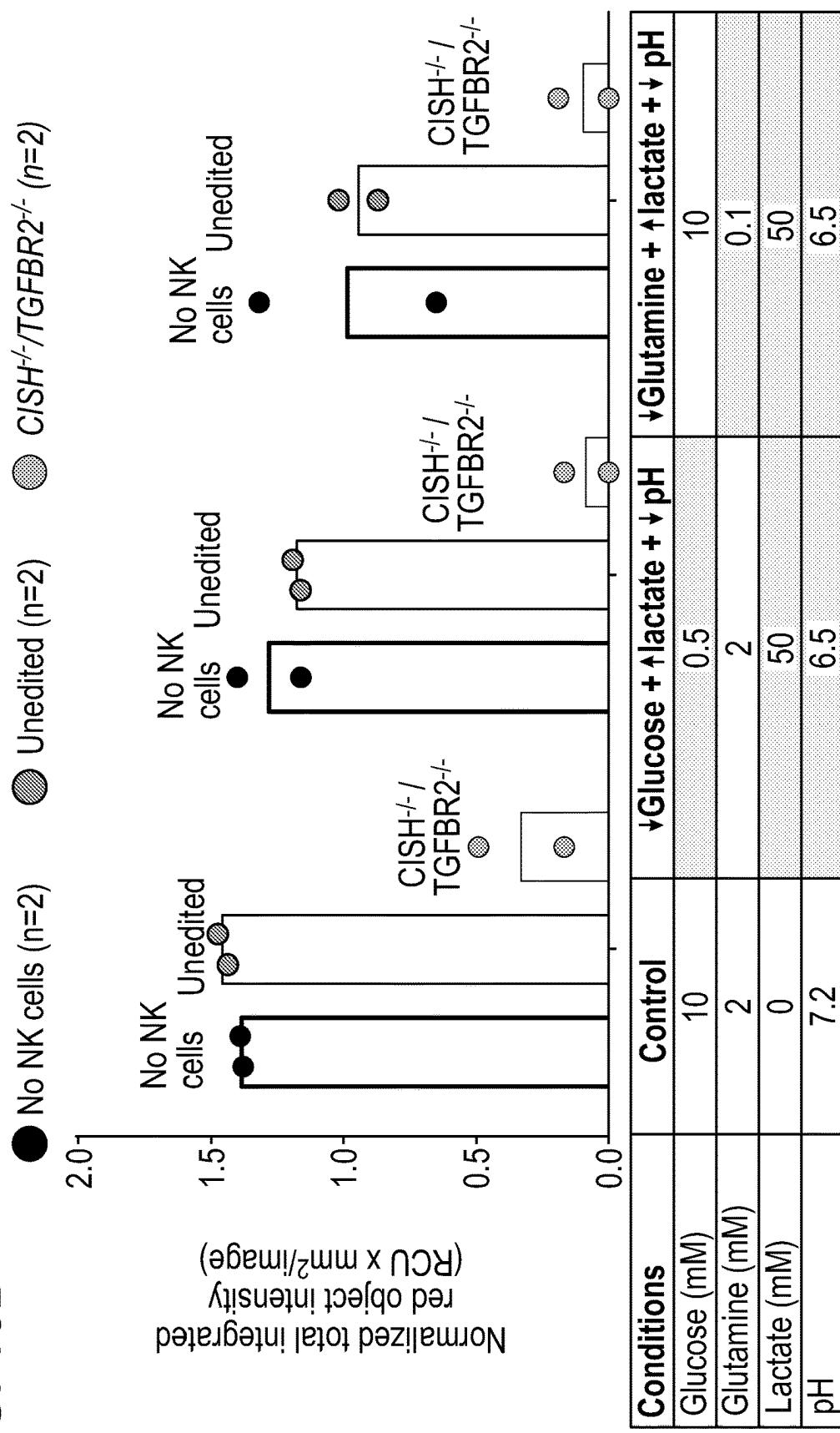
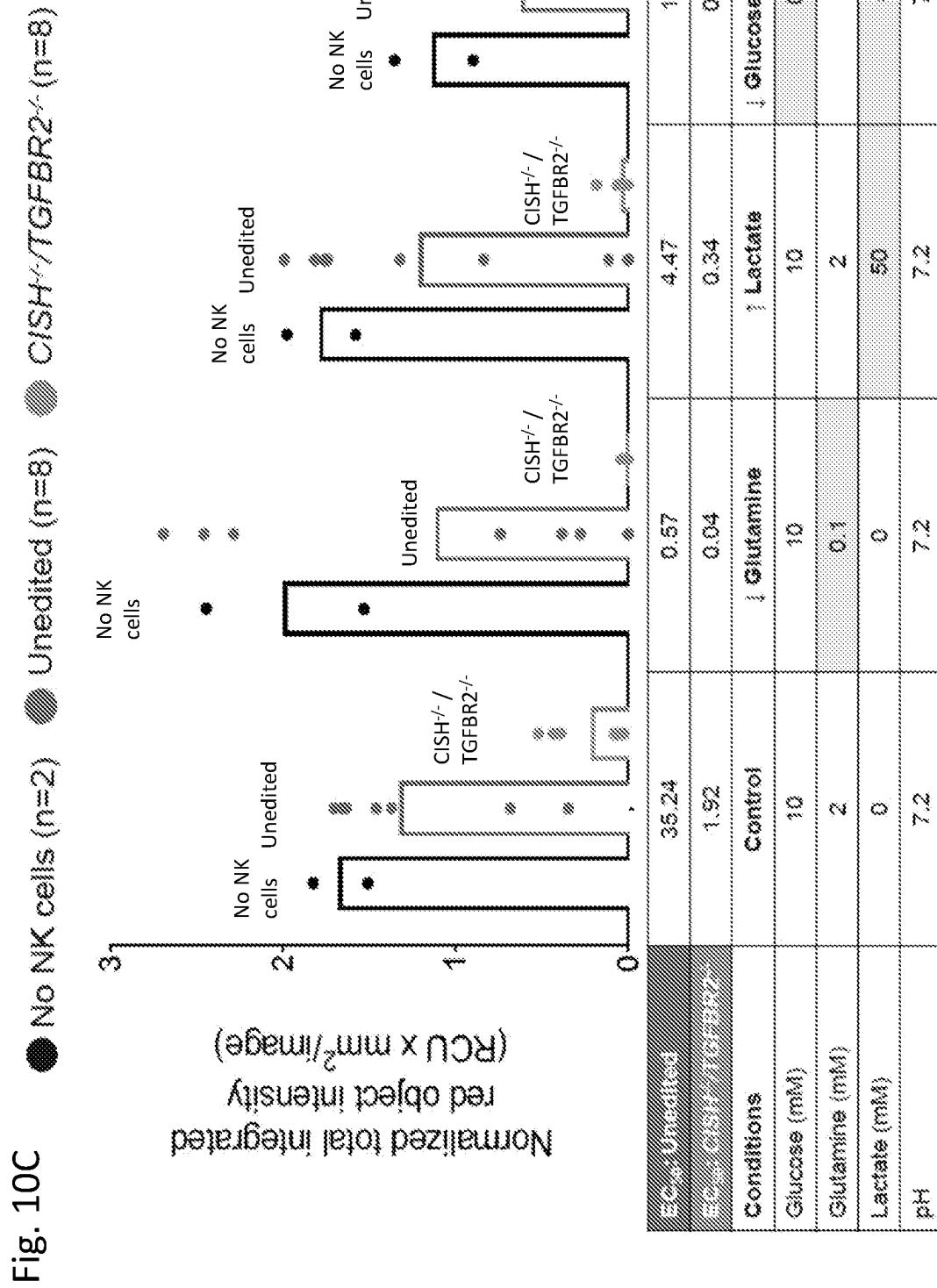
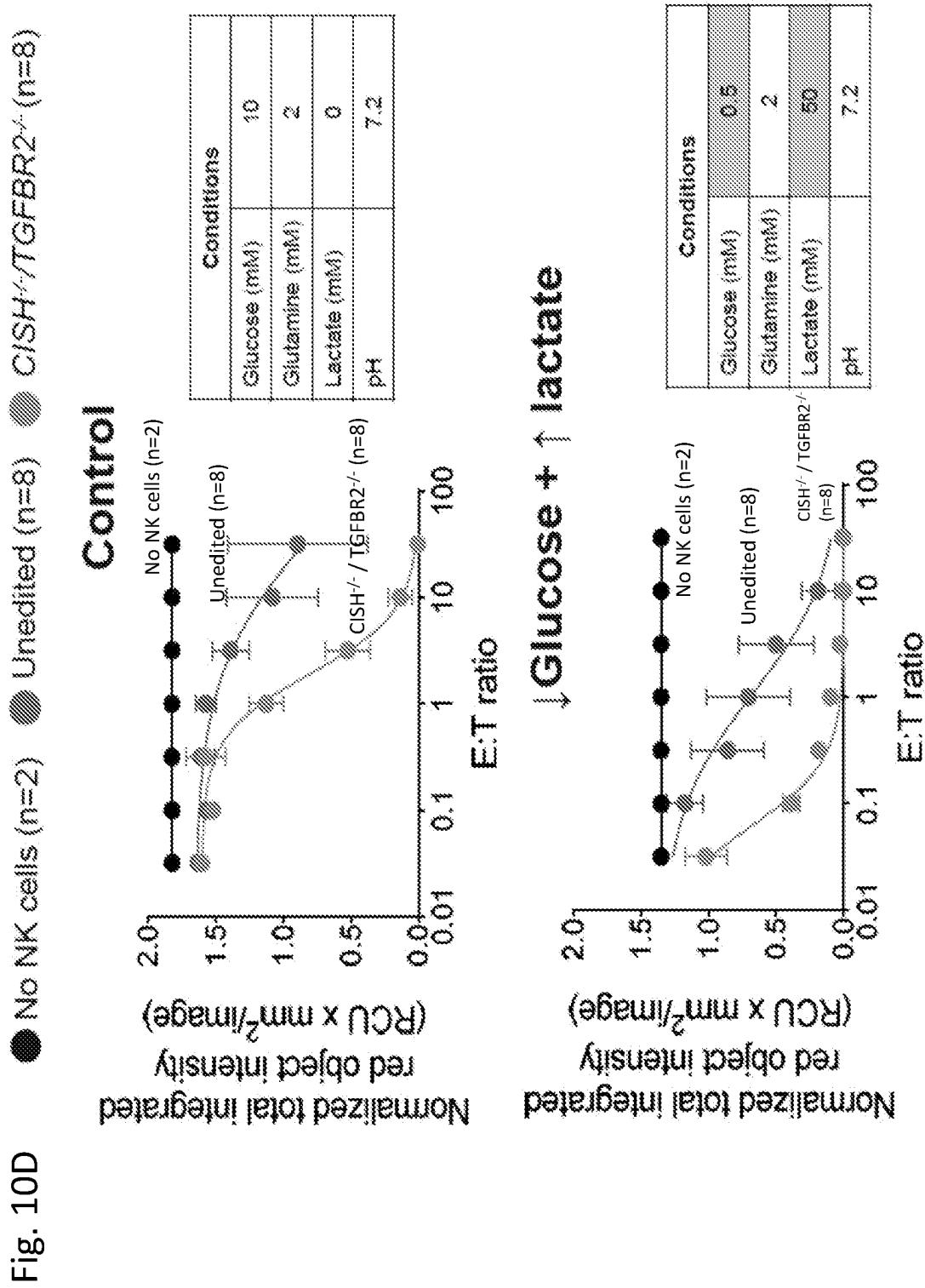


FIG. 10B







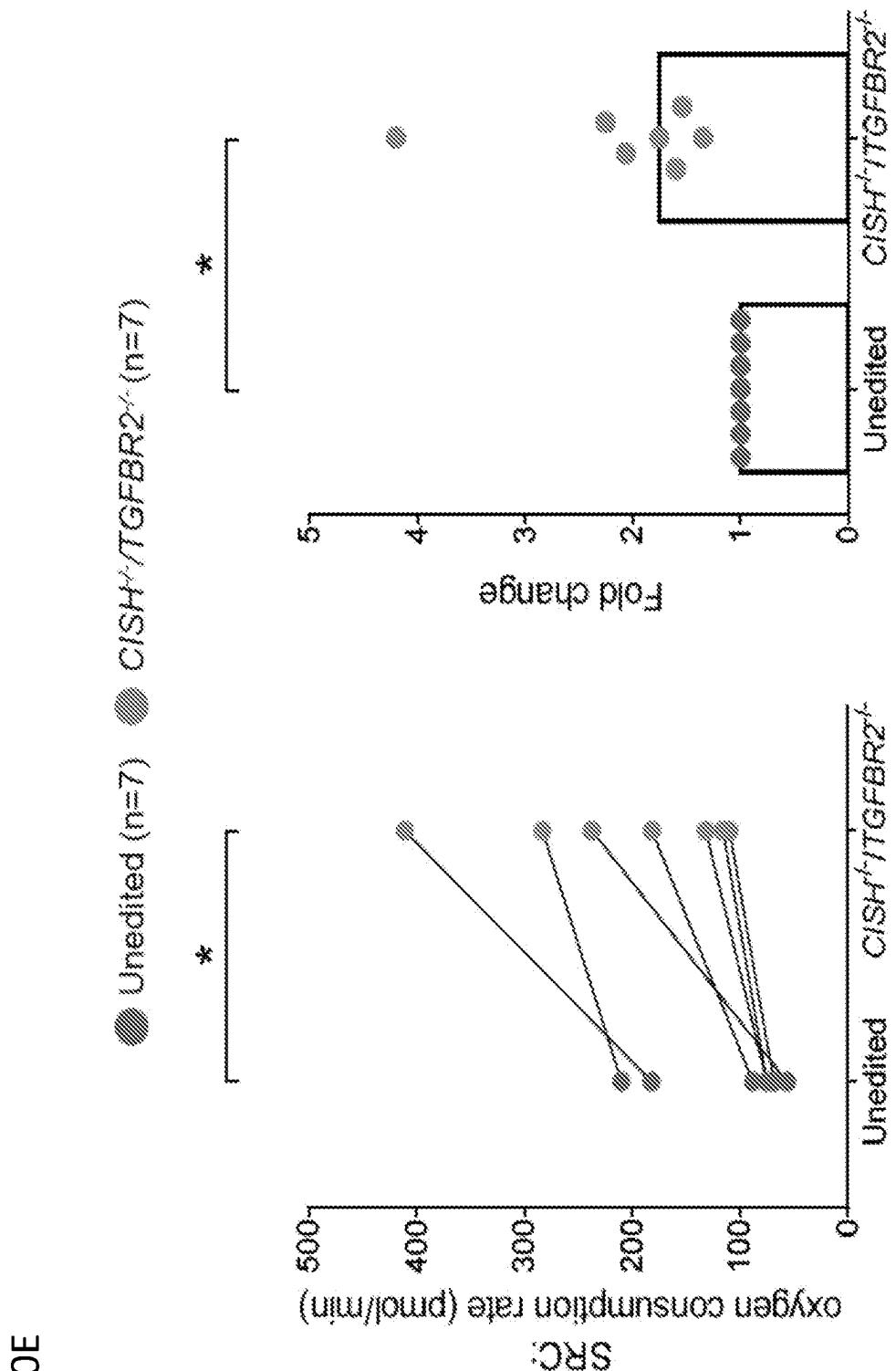


Fig. 10E

Fig. 11A

**Increased cytotoxicity
in the absence of TGF- β**

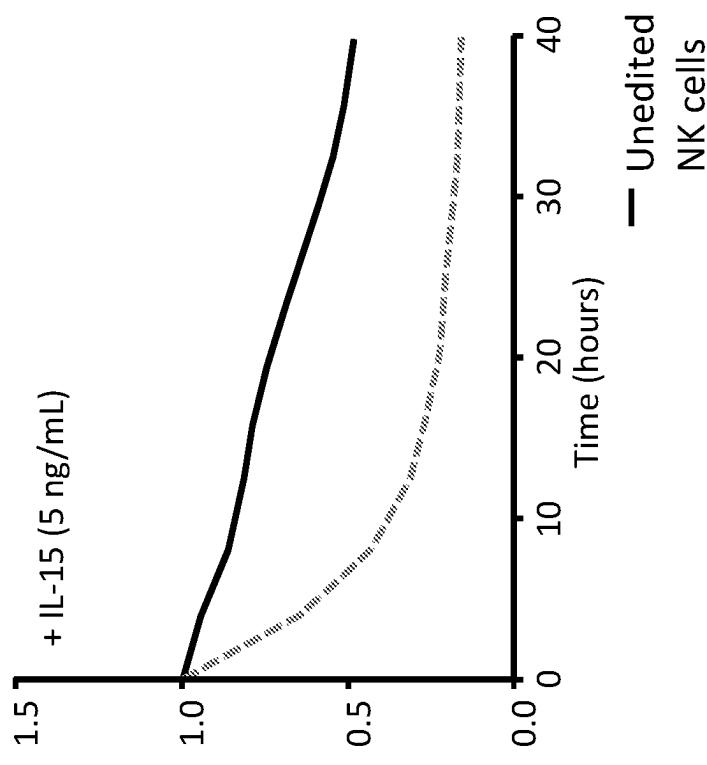
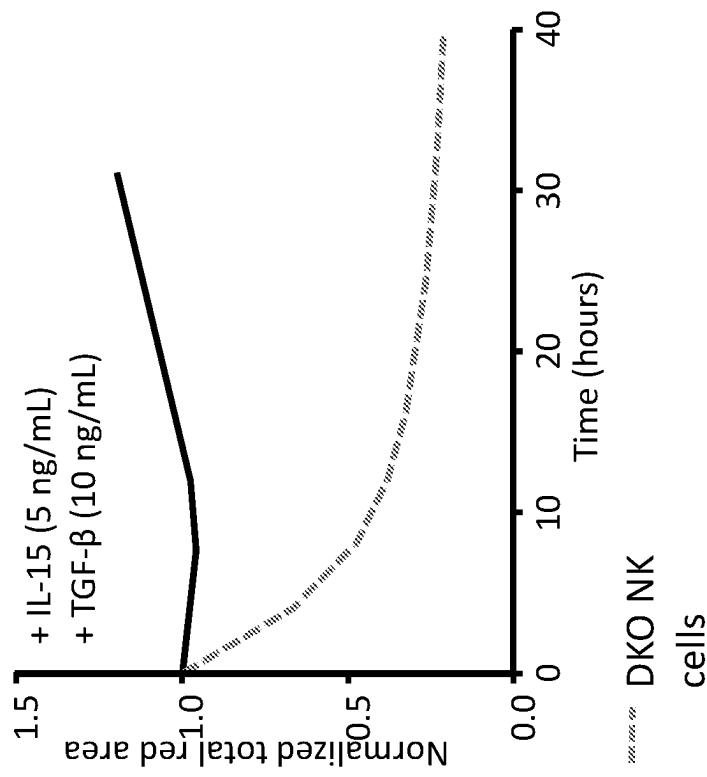


Fig. 11B

**Increased cytotoxicity
in the presence of TGF- β**



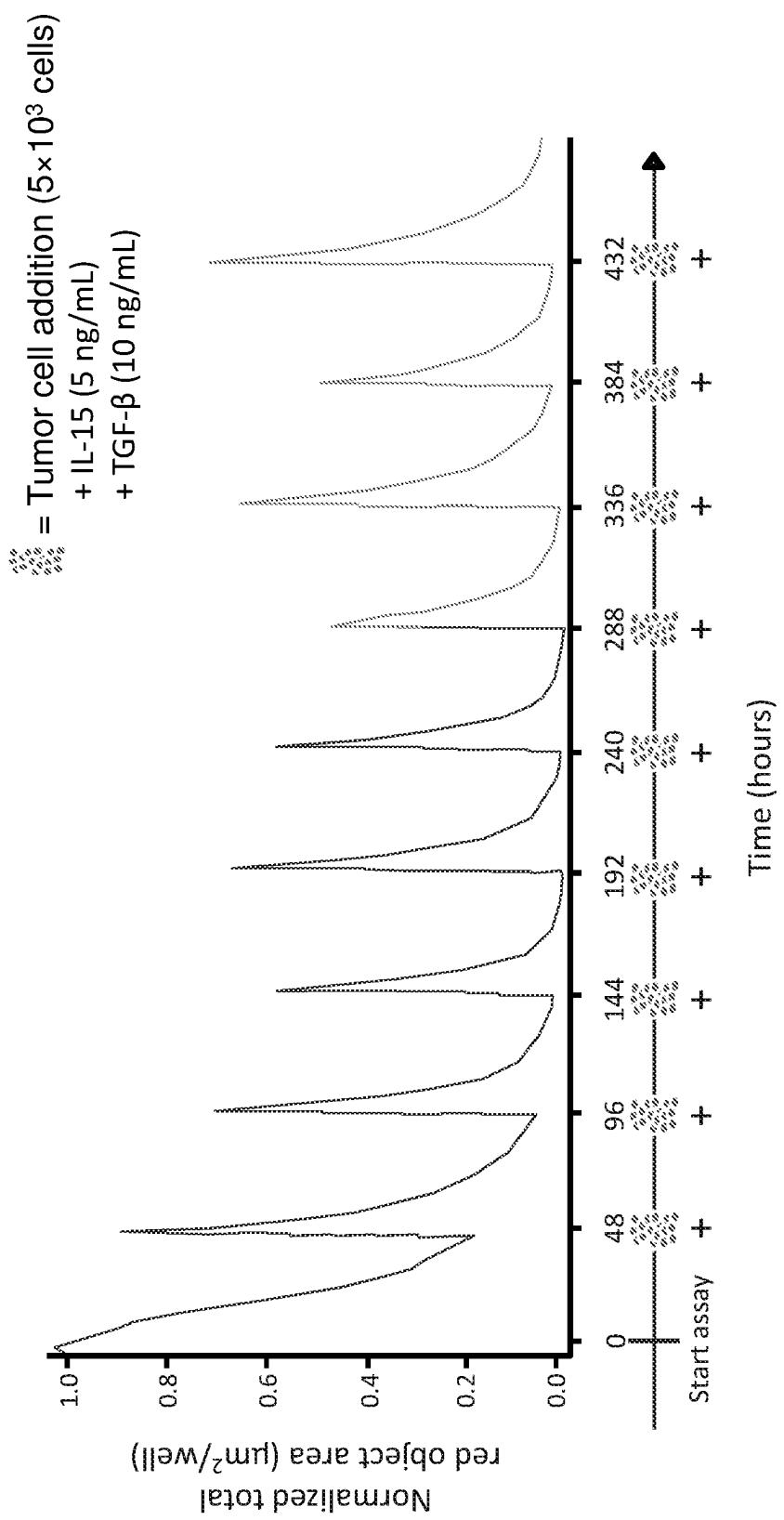


Fig. 12

Fig. 13

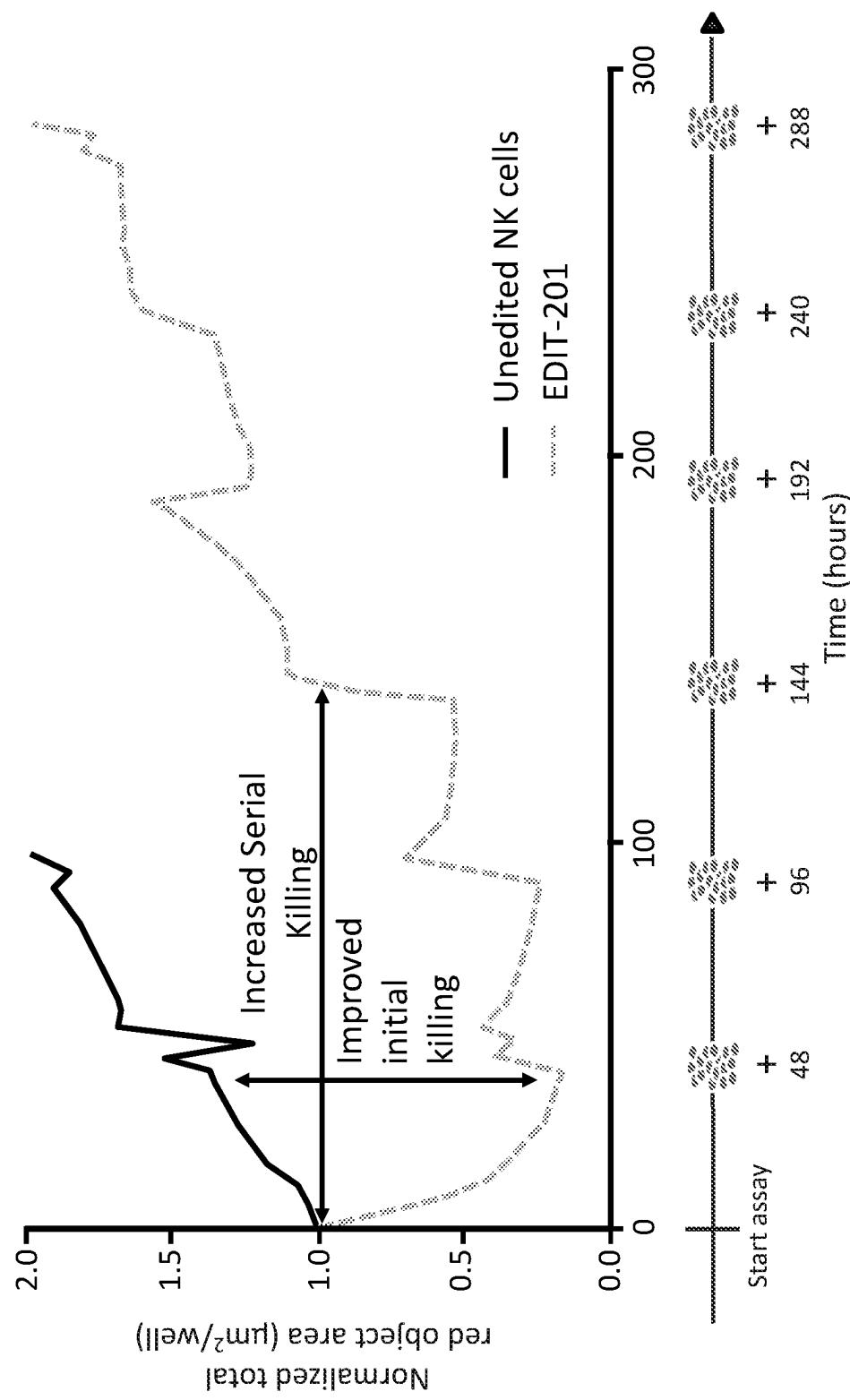


Fig. 14

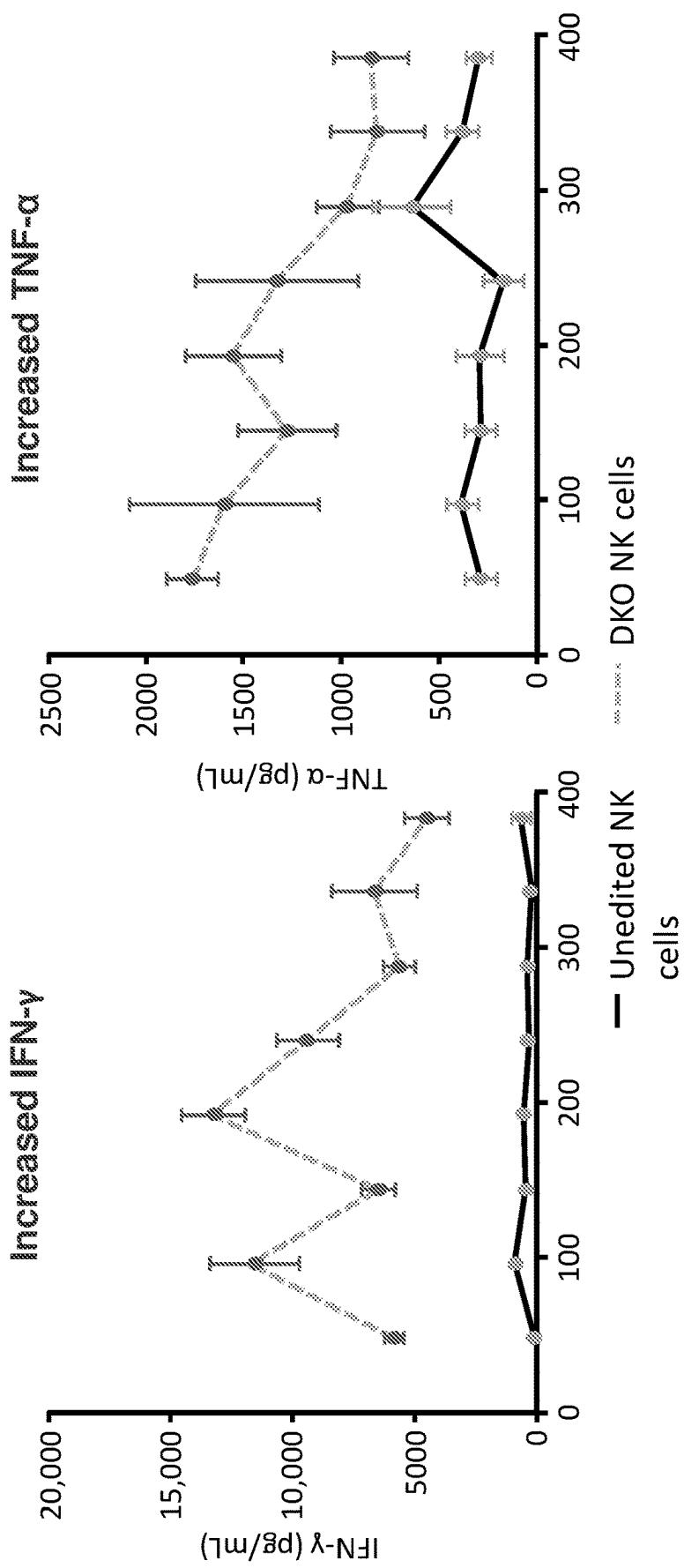


Fig. 15A

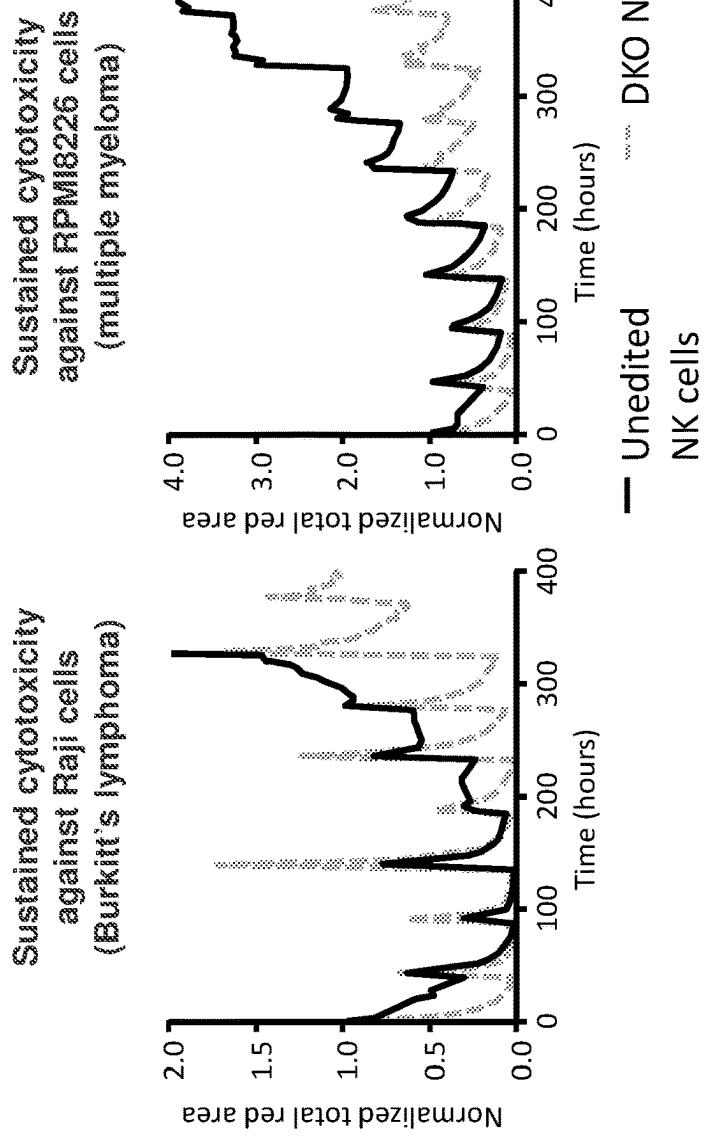


Fig. 15B

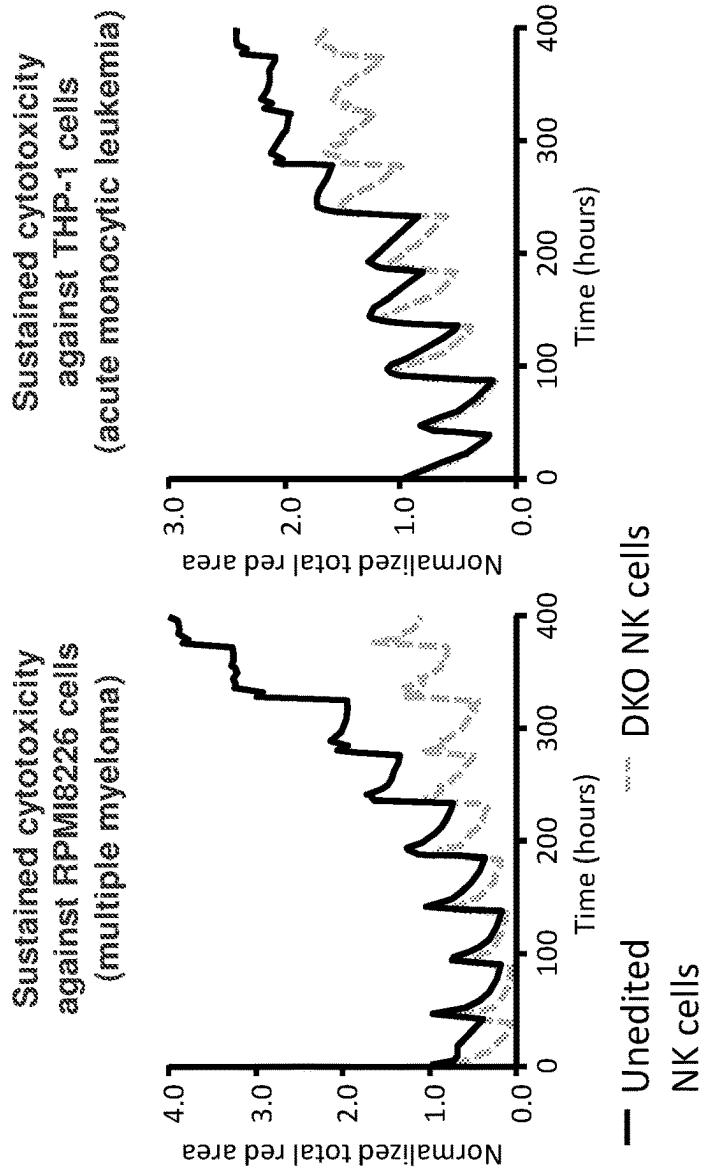
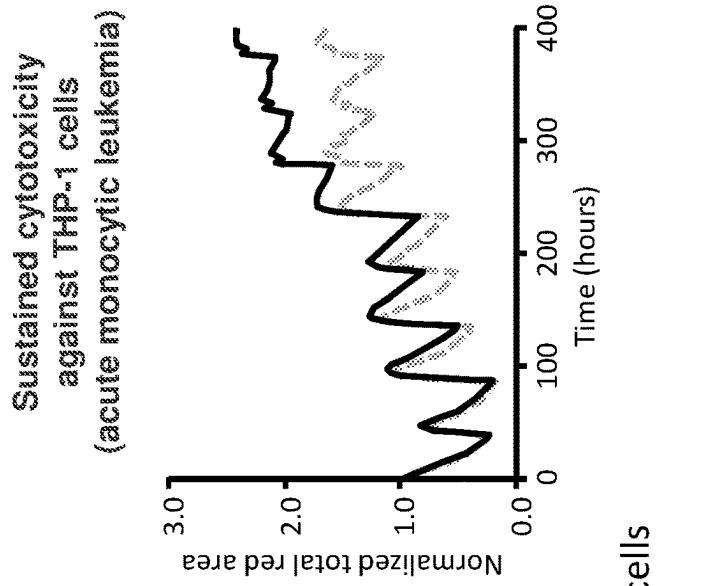


Fig. 15C



**METHODS OF INDUCING
ANTIBODY-DEPENDENT CELLULAR
CYTOTOXICITY (ADCC) USING MODIFIED
NATURAL KILLER (NK) CELLS**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

[0001] This application is a U.S. National Stage Application under 35 U.S.C. § 371 of International Patent Application No. PCT/US2021/056554, filed Oct. 26, 2021, which claims the benefit of U.S. Provisional Application No. 63/105,464, filed on Oct. 26, 2020; U.S. Provisional Application No. 63/115,112, filed on Nov. 18, 2020; and U.S. Provisional Application No. 63/165,786, filed on Mar. 25, 2021, the entire contents of each of which are expressly incorporated herein by reference.

SEQUENCE LISTING

[0002] This application incorporates by reference in its entirety the Computer Readable Form (CRF) of a Substitute Sequence Listing in ASCII text format submitted via Patent Center. The Substitute Sequence Listing text file submitted via Patent Center is entitled “14735-027-999_SUB_SEQ_LISTING.txt,” was created on Nov. 16, 2023, and is 415,811 bytes in size.

BACKGROUND

[0003] NK cells are useful for immunotherapy approaches, for example, in the context of immunooncology. NK cells are a type of cytotoxic innate lymphocyte. NK cells play an important role in tumor immunity, and the cytotoxic activity of NK cells is tightly regulated by a networks of activating and inhibitory pathways (see, e.g., Bald, T., Krummel, M. F., Smyth, M. J. et al. (2020) *Nat Immunol* 21, 835-847; and Huntington, N. D., Cursons, J. & Rautela, J. (2020) *Nat Rev Cancer* 20, 437-454; incorporated in their entireties herein by reference).

[0004] The use of naturally occurring or modified NK cells in immunotherapy approaches, e.g., via autologous or allogeneic NK cell transfer, has been reported, and while some success has been achieved, such approaches are typically characterized by a suboptimal NK cell response. In the context of immune-oncology, it is believed that this suboptimal response is, at least in part, to tumors harnessing NK cell inhibitory pathways to suppress cytotoxic NK cell activity, limit NK cell invasion, and/or inhibit NK cell proliferation and survival. Thus, application of NK cells in the therapy of solid tumors has seen limited success to date.

[0005] Initial work has been performed in trying to focus NK cell response on specific cells, e.g., by expressing a chimeric antigen receptor in NK cells that targets the NK cells to tumor cells, or by modulating activating or inhibitory NK cell pathways to achieve a stronger and/or more sustained NK cell response. See, e.g., Liu et al. (2020) *New England J. Medicine* 382(6):545-553; incorporated in its entirety herein by reference.

[0006] In pursuit of an off-the shelf allogeneic NK cell therapy, an induced pluripotent stem cell line has been developed in which cells express an enhanced version of CD16 (hnCD16), and NK cells have been derived from this iPSC line. See, e.g., Li et al., *Cell Stem Cell*. 2018 Aug. 2; 23(2):181-192.e5; incorporated in its entirety herein by reference.

[0007] However, to date all of these approaches have seen limited success. Therefore, there remains a need for the development of better therapeutic approaches for immunotherapy.

SUMMARY

[0008] The present disclosure provides modified NK cells (or other lymphocytes) that are useful in NK cell therapy, e.g., in the context of immunotherapeutic approaches, particularly in combination with a therapeutic antibody, or antigen-binding portion thereof, to generate striking antibody-dependent cellular cytotoxicity (ADCC) effects, thereby surprisingly increasing the effectiveness of the modified NK cells in killing target cells, e.g. cancer cells. ADCC is a mechanism of cell-mediated immune defense, where an immune effector cell actively lyses a target cell after its membrane-surface antigens have been bound by specific antibodies. To participate in ADCC, the immune effector cells must express Fc-gamma receptors (FcγR) to be able to recognize the Fc region of the antibodies that bind to the target cells. Most immune effector cells have both activating and inhibitory FcγR. An advantage of using NK cells to target cancer cells via ADCC is that, unlike other effector cells, NK cells only have activating FcγRs (e.g., FcγR IIIa, also known as CD16a, and FcγR IIc, also known as CD32c) and are believed to be the most important effectors of ADCC in humans. Thus, the use of the modified NK cells disclosed herein and antibodies targeting cancer cell-specific antigens to elicit ADCC provides novel and surprisingly effective immunotherapies.

[0009] In some embodiments, the modified NK cells provided herein can serve as an off-the-shelf clinical solution for patients having, or having been diagnosed with, a hyperproliferative disease, such as, for example, a cancer. In some embodiments, the modified NK cells exhibit an enhanced survival, proliferation, NK cell response level, NK cell response duration, resistance against reduction of NK cell functional persistence, and/or target recognition as compared to non-modified NK cells. For example, the modified NK cells provided herein may comprise genomic edits that result in a loss-of-function in TGF beta receptor 2 (TGF-betaR2) and/or a loss-of-function of CISH. In some embodiments, the modified NK cells comprise genomic edits that result in a loss-of-function of TGFbetaR2. In some embodiments, the modified NK cells comprise genomic edits that result in a loss-of-function of CISH. In some embodiments, the modified NK cells comprise genomic edits that result in a loss-of-function of TGFbetaR2 and a loss-of-function of CISH. In some embodiments, the modified NK cells consist of genomic edits that result in a loss-of-function of TGF-betaR2. In some embodiments, the modified NK cells consist of genomic edits that result in a loss-of-function of CISH. In some embodiments, the modified NK cells consist of genomic edits that result in a loss-of-function of TGF-betaR2 and a loss-of-function of CISH. Other modified NK cells that may be useful in the methods described herein are described in WO2020/168300, published on 17 Sep. 2020, the entire contents of which are expressly incorporated by reference herein.

[0010] In some embodiments, the modified NK cells provided herein may comprise genomic edits that result in: expression of a chimeric antigen receptor (CAR) of interest, e.g., a CAR targeting mesothelin, EGFR, HER2 and/or MICA/B; expression of a CD16 variant, e.g., a non-naturally

occurring CD16 variant such as, for example, hnCD16 (see, e.g., Zhu et al., Blood 2017, 130:4452, the contents of which are incorporated herein in their entirety by reference); expression of an IL15/IL15RA fusion; a loss-of-function in TGF beta receptor 2 (TGFbetaR2); and/or expression of a dominant-negative variant of TGFbetaR2; a loss-of-function of ADORA2A; a loss-of-function of B2M; expression of HLA-G; a loss-of-function of a CIITA; a loss-of-function of a PD1; a loss-of-function of TIGIT; and/or a loss-of-function of CISH; or any combination of two or more thereof in the modified NK cell. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of TGFbetaR2 and a loss-of-function of CISH. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of TGFbetaR2 and a loss-of-function of TIGIT. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of TGFbetaR2 and a loss-of-function of ADORA2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of TGFbetaR2 and a loss-of-function of NKG2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of CISH and a loss-of-function of TIGIT. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of CISH and a loss-of-function of ADORA2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of CISH and a loss-of-function of NKG2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of TIGIT and a loss-of-function of ADORA2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of TIGIT and a loss-of-function of NKG2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of ADORA2A and a loss-of-function of NKG2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of TGFbetaR2, a loss-of-function of CISH, and a loss-of-function of TIGIT. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of TGFbetaR2, a loss-of-function of CISH, and a loss-of-function of ADORA2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of TGFbetaR2, a loss-of-function of CISH, and a loss-of-function of NKG2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of TGFbetaR2, a loss-of-function of TIGIT, and a loss-of-function of ADORA2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of TGFbetaR2, a loss-of-function of ADORA2A, and a loss-of-function of NKG2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of CISH, a loss-of-function of TIGIT, and a loss-of-function of ADORA2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of CISH, a loss-of-function of TIGIT, and a loss-of-function of NKG2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of CISH, a loss-of-function of ADORA2A, and a loss-of-function of NKG2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of CISH, a loss-of-function of ADORA2A, and a loss-of-function of NKG2A. In one embodiment, the modified NK cell comprises genomic edits that result in a loss-of-function of CISH, a loss-of-function of ADORA2A, and a loss-of-function of NKG2A.

that result in a loss-of-function of TIGIT, a loss-of-function of ADORA2A, and a loss-of-function of NKG2A.

[0011] In some embodiments, the modified NK cells provided herein may comprise genomic edits that result in: expression of an exogenous a CD16 variant, e.g., hnCD16, expression of an exogenous IL15/IL15RA fusion, expression of an exogenous HLA-G, expression of an exogenous DN-TGFbetaR2, a loss of function in TGFbetaR2, a loss of function in B2M, a loss of function of PD1, a loss of function of TIGIT, and/or a loss of function of ADORA2A.

[0012] In some embodiments, the modified NK cells provided herein may comprise genomic edits that result in: expression of an exogenous a CD16 variant, e.g., hnCD16, expression of an exogenous IL15/IL15RA fusion, expression of an exogenous HLA-G, expression of an exogenous DN-TGFbetaR2, expression of a soluble MICA and/or MICB, a loss of function in TGFbetaR2, a loss of function in B2M, a loss of function of PD1, a loss of function of TIGIT, and/or a loss of function of ADORA2A.

[0013] In some embodiments, the modified NK cells provided herein may comprise genomic edits that result in: expression of an exogenous a CD16 variant, e.g., hnCD16, expression of an exogenous IL15/IL15RA fusion, expression of an exogenous HLA-G, expression of an exogenous DN-TGFbetaR2, expression of a soluble MICA and/or MICB, expression of an exogenous IL-12, expression of an exogenous IL-18, a loss of function in TGFbetaR2, a loss of function in B2M, a loss of function of PD1, a loss of function of TIGIT, and/or a loss of function of ADORA2A.

[0014] In some embodiments, the modified NK cells provided herein may comprise genomic edits that result in: expression of an exogenous a CD16 variant, e.g., hnCD16, expression of an exogenous IL15/IL15RA fusion, expression of an exogenous HLA-G, expression of an exogenous DN-TGFbetaR2, expression of an exogenous IL-12, expression of an exogenous IL-18, a loss of function in TGFbetaR2, a loss of function in B2M, a loss of function of PD1, a loss of function of TIGIT, and/or a loss of function of ADORA2A.

[0015] In some embodiments, the disclosure features a modified NK cell, wherein the modified NK cell does not express endogenous CD3, CD4, and/or CD8; and expresses at least one endogenous gene encoding: (i) CD56 (NCAM), CD49, and/or CD45; (ii) NK cell receptor (cluster of differentiation 16 (CD16)); (iii) natural killer group-2 member D (NKG2D); (iv) CD69; (v) a natural cytotoxicity receptor; or any combination of two or more thereof, wherein the modified NK cell further: (1) comprises at least one exogenous nucleic acid construct encoding: (i) a chimeric antigen receptor (CAR); (ii) a non-naturally occurring variant of immunoglobulin gamma Fc region receptor III (FcγRIII, CD16); (iii) interleukin 15 (IL-15); (iv) IL-15 receptor (IL-15R), or a variant thereof; (v) interleukin 12 (IL-12); (vi) interleukin-12 receptor (IL-12R), or a variant thereof, (vii) human leukocyte antigen G (HLA-G); (viii) human leukocyte antigen E (HLA-E); (ix) a nucleic acid sequence encoding leukocyte surface antigen cluster of differentiation CD47 (CD47); or any combination of two or more thereof; and/or (2) exhibits a loss of function of at least one of: (i) transforming growth factor beta receptor 2 (TGFβR2); (ii) adenosine A2a receptor (ADORA2A); (iii) T cell immunoreceptor with Ig and ITIM domains (TIGIT); (iv) β-2 microgobulin (B2M); (v) programmed cell death protein 1 (PD-1); (vi) cytokine inducible SH2 containing protein

(CISH); (vii) class II, major histocompatibility complex, transactivator (CIITA); (viii) natural killer cell receptor NKG2A (natural killer group 2A); (ix) two or more HLA class II histocompatibility antigen alpha chain genes, and/or two or more HLA class II histocompatibility antigen beta chain genes; (x) cluster of differentiation 32B (CD32B, FCGR2B); (xi) T cell receptor alpha constant (TRAC); or any combination of two or more thereof. In one embodiment, the modified NK cell exhibits a loss of function of TGF β R2 and a loss-of-function of CISH. In one embodiment, the modified NK cell exhibits a loss-of-function of TGFbetaR2 and a loss-of-function of TIGIT. In one embodiment, the modified NK cell exhibits a loss-of-function of TGFbetaR2 and a loss-of-function of ADORA2A. In one embodiment, the modified NK cell exhibits a loss-of-function of TGFbetaR2 and a loss-of-function of NKG2A. In one embodiment, the modified NK cell exhibits a loss-of-function of CISH and a loss-of-function of TIGIT. In one embodiment, the modified NK cell exhibits a loss-of-function of CISH and a loss-of-function of ADORA2A. In one embodiment, the modified NK cell exhibits a loss-of-function of CISH and a loss-of-function of NKG2A. In one embodiment, the modified NK cell exhibits a loss-of-function of TIGIT and a loss-of-function of ADORA2A. In one embodiment, the modified NK cell exhibits a loss-of-function of TIGIT and a loss-of-function of NKG2A. In one embodiment, the modified NK cell exhibits a loss-of-function of ADORA2A and a loss-of-function of NKG2A. In one embodiment, the modified NK cell exhibits a loss-of-function of TGFbetaR2, a loss-of-function of CISH, and a loss-of-function of TIGIT. In one embodiment, the modified NK cell exhibits a loss-of-function of TGFbetaR2, a loss-of-function of CISH, and a loss-of-function of ADORA2A. In one embodiment, the modified NK cell exhibits a loss-of-function of TGFbetaR2, a loss-of-function of CISH, and a loss-of-function of NKG2A. In one embodiment, the modified NK cell exhibits a loss-of-function of TGFbetaR2, a loss-of-function of TIGIT, and a loss-of-function of ADORA2A. In one embodiment, the modified NK cell exhibits a loss-of-function of TGFbetaR2, a loss-of-function of TIGIT, and a loss-of-function of NKG2A. In one embodiment, the modified NK cell exhibits a loss-of-function of CISH, a loss-of-function of TIGIT, and a loss-of-function of NKG2A. In one embodiment, the modified NK cell exhibits a loss-of-function of ADORA2A, and a loss-of-function of NKG2A. In one embodiment, the modified NK cell exhibits a loss-of-function of TIGIT, a loss-of-function of ADORA2A, and a loss-of-function of NKG2A.

[0016] In one embodiment, the modified NK cell does not express endogenous CD3, CD4, and/or CD8; and expresses at least one endogenous gene encoding: (i) CD56 (NCAM), CD49, and/or CD45; (ii) NK cell receptor (cluster of differentiation 16 (CD16)); (iii) natural killer group-2 member D (NKG2D); (iv) CD69; (v) a natural cytotoxicity receptor; or any combination of two or more thereof; wherein the modified NK cell further: (1) comprises at least one exogenous nucleic acid construct encoding: (i) a chimeric antigen receptor (CAR); (ii) a non-naturally occurring variant of

immunoglobulin gamma Fc region receptor III (Fc γ RIII, CD16); (iii) interleukin 15 (IL-15); (iv) IL-15 receptor (IL-15R), or a variant thereof; (v) interleukin 12 (IL-12); (vi) interleukin-12 receptor (IL-12R), or a variant thereof; (vii) human leukocyte antigen G (HLA-G); (viii) human leukocyte antigen E (HLA-E); (ix) a nucleic acid sequence encoding leukocyte surface antigen cluster of differentiation CD47 (CD47); or any combination of two or more thereof; and/or (2) exhibits a loss of function of transforming growth factor beta receptor 2 (TGF β R2), cytokine inducible SH2 containing protein (CISH), or a combination thereof.

[0017] In some embodiments, the modified NK cells comprise genomic edits that result in: expression of a CD16 variant, e.g., a non-naturally occurring CD16 variant such as, for example, hncD16 (see, e.g., Zhu et al., Blood 2017, 130:4452, the contents of which are incorporated herein in their entirety by reference); expression of an IL15/IL15RA fusion; a loss-of-function in TGF beta receptor 2 (TGF-betaR2); and a loss-of-function of CISH.

[0018] In another aspect, disclosed herein is a method of treating cancer in a subject, the method comprising administering to the subject a modified natural killer (NK) cell and a molecule comprising an Fc domain that binds cancer cells, e.g., an antibody, or an antigen-binding portion thereof, wherein the modified NK cell exhibits a loss of function of transforming growth factor beta receptor 2 (TGF β R2) and cytokine inducible SH2 containing protein (CISH), wherein the administering induces ADCC of a cancer cell in the subject, thereby treating the cancer in the subject.

[0019] In one aspect, disclosed herein is a method of inducing antibody-dependent cell-mediated cytotoxicity (ADCC) of a cancer cell, the method comprising contacting the cancer cell with a modified natural killer (NK) cell and a molecule comprising an Fc domain that binds cancer cells, e.g., an antibody, or antigen-binding portion thereof, wherein the modified NK cell exhibits a loss of function of transforming growth factor beta receptor 2 (TGF β R2) and cytokine inducible SH2 containing protein (CISH), thereby inducing ADCC of the cancer cell. In one embodiment, the contact is *in vivo* in a subject.

[0020] In one embodiment, the administration increases ADCC or enhances ADCC. In one embodiment, the administration increases ADCC by at least about 10%, at least about 15%, 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 6-fold, at least about 7-fold, at least about 8-fold, at least about 9-fold, or at least about 10-fold as compared to ADCC of a cancer cell using an unmodified NK cell and the antibody.

[0021] In another embodiment, the administering decreases tumor volume in the subject by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% after administering. In one embodiment, the administration decreases tumor

volume in the subject at the values listed above at least about 5 days, 7 days, 10 days, 14 days, 21 days, 30 days, 1 month, 40 days, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, one year after administering.

[0022] In one embodiment, the administering increases the survival time of the subject. In one embodiment, the survival time of the subject is increased by at least about two-fold, about three-fold, about four-fold, or about five-fold as compared to a subject, e.g., comparator subject, who has not been administered the modified NK cell and the antibody; by at least about two-fold, about three-fold, about four-fold, or about five-fold as compared to a subject, e.g., comparator subject, who has been administered the antibody alone; and/or by at least about 50% about 75%, about 100%, about 150%, about two-fold, about three-fold, about four-fold, or about five-fold as compared to a subject, e.g., comparator subject, who has been administered the modified NK cell alone. In one embodiment, the comparator subject is a subject with the same type of cancer cell as the subject. In one embodiment, the comparator subject is a subject with the same type of cancer cell as the subject and a comparable tumor burden as the subject. In one embodiment, the survival time of the comparator subject is an average survival time calculated from a population of subjects having the same type of cancer cell, and/or the same stage of cancer, and/or the same amount of tumor burden as the subject.

[0023] In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in a subject.

[0024] In one embodiment, the administration increases a level of TNF α by at least about two fold, at least about three-fold, at least about four-fold, or at least about five-fold as compared to a control level expression of TNF α . In one embodiment, the control level of TNF α is a level of TNF α produced by an unmodified NK cell under the same conditions. In another embodiment, the control level of TNF α is a reference level of TNF α . In one embodiment, the modified NK cell comprises an increase in level of TNF α by at least about two fold as compared to a control level expression of TNF α , wherein the control level of TNF α is a level of TNF α produced by an unmodified NK cell under the same conditions. In one embodiment, the modified NK cell comprises an increase in level of TNF α by at least about three fold as compared to the control level expression of TNF α .

[0025] In one embodiment, the administration increases a level of IFN γ by at least about two fold, at least about three-fold, at least about four-fold, or at least about five-fold as compared to a control level expression of IFN γ . In one embodiment, the control level of IFN γ is a level of IFN γ produced by an unmodified NK cell under the same conditions. In another embodiment, the control level of IFN γ is a reference level of IFN γ . In one embodiment, the modified NK cell comprises an increase in level of IFN γ by at least about two fold as compared to a control level expression of IFN γ , wherein the control level of IFN γ is a level of IFN γ produced by an unmodified NK cell under the same conditions. In one embodiment, the modified NK cell comprises an increase in level of IFN γ by at least about three fold as compared to the control level expression of IFN γ .

[0026] In one embodiment, the administration decreases normalized total integrated red object intensity in a tumor spheroid assay by at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at

least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or 100% as compared to a control level of normalized total integrated red object intensity, wherein the control level of normalized total integrated red object intensity is a level of normalized total integrated red object intensity produced using an unmodified NK cell under the same conditions. In one embodiment, the modified NK cell comprises a decrease in normalized total integrated red object intensity in a tumor spheroid assay by at least about 20% as compared to a control level of normalized total integrated red object intensity. In one embodiment, the control level of normalized total integrated red object intensity is a level of normalized total integrated red object intensity produced using an unmodified NK cell under the same conditions. In one embodiment, the modified NK cell comprises a decrease in normalized total integrated red object intensity in the tumor spheroid assay by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 75%, or about 100% as compared to the control level of normalized total integrated red object intensity.

[0027] In one embodiment, the administration increases a level of a cytolytic granule produced by the modified NK cell by at least about two fold, at least about three fold, at least about four fold, at least about five fold, at least about ten fold, or at least about twenty fold as compared to a control level expression of the cytolytic granule. In one embodiment, the control level of cytolytic granule is a level of cytolytic granule produced by an unmodified NK cell under the same conditions. In another embodiment, the control level of a cytolytic granule is a reference level of cytolytic granule. In one embodiment, the cytolytic granule is selected from the group consisting of GZMB, GZMA and GZMH. In one embodiment, the modified NK cell comprises an increase in level of a cytolytic granule by at least about two fold as compared to a control level expression of the cytolytic granule. In one embodiment, the cytolytic granule is selected from the group consisting of GZMB, GZMA and GZMH. In one embodiment, the control level of cytolytic granule is a level of cytolytic granule produced by an unmodified NK cell under the same conditions. In one embodiment, the modified NK cell comprises an increase in level of the cytolytic granule by at least about three fold as compared to the control level expression of the cytolytic granule.

[0028] In one embodiment, the administration increases a level of a cytolytic granule produced by the modified NK cell by at least about one hour, at least about two hours, at least about three hours, at least about four hours, or at least about five hours earlier as compared to a control level expression of the cytolytic granule. In one embodiment, the control level of cytolytic granule is a level of cytolytic granule produced by an unmodified NK cell under the same conditions. For example, the administration increases the level of the cytolytic granule produced by the modified NK cell by at least about one hour, at least about two hours, at least about three hours, at least about four hours, or at least about five hours earlier as compared to an observed increase in the level of the cytolytic granule produced by the unmodified NK cell under the same conditions. In another embodiment, the control level of a cytolytic granule is a reference

level of cytolytic granule. In one embodiment, the cytolytic granule is selected from the group consisting of GZMB, GZMA and GZMH.

[0029] In one embodiment, the administration increases a production rate of a cytolytic granule by the modified NK cell by at least about two fold, at least about three fold, at least about four fold, or at least about five fold as compared to a control production rate of the cytolytic granule. In one embodiment, the control production rate of cytolytic granule is a production rate of cytolytic granule by an unmodified NK cell under the same conditions. In another embodiment, the control production rate of a cytolytic granule is a reference production rate of cytolytic granule. In one embodiment, the cytolytic granule is selected from the group consisting of GZMB, GZMA and GZMH. In one embodiment, the modified NK cell comprises an increase in production rate of a cytolytic granule by at least about two fold as compared to a control production rate of the cytolytic granule. In one embodiment, the cytolytic granule is selected from the group consisting of GZMB, GZMA and GZMH. In one embodiment, the control production rate of cytolytic granule is a production rate of cytolytic granule by an unmodified NK cell under the same conditions. In one embodiment, the modified NK cell comprises an increase in production rate of the cytolytic granule by at least about three fold as compared to the control production rate of the cytolytic granule.

[0030] In one embodiment, the administration increases a level of CD107a in the modified NK cells by at least about two fold, at least about three fold, at least about four fold, or at least about five fold as compared to a control level expression of CD107a. In one embodiment, the control level of CD107a is a level of CD107a in an unmodified NK cell under the same conditions. In another embodiment, the control level of CD107a is a reference level of CD107a. In one embodiment, the modified NK cell comprises an increase in level of CD107a by at least about two fold as compared to a control level expression of CD107a. In one embodiment, the control level of CD107a is a level of CD107a in an unmodified NK cell under the same conditions. In one embodiment, the modified NK cell comprises an increase in level of CD107a by at least about three fold as compared to the control level expression of CD107a.

[0031] In one embodiment, the cytotoxicity activity of the modified NK cell under a nutrient-depriving condition is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or 100% higher as compared to a control level of cytotoxicity activity, wherein the control level of cytotoxicity activity is a cytotoxicity level of an unmodified NK cell under the same conditions. In one embodiment, the modified NK cell comprises an increase in cytotoxicity activity under a nutrient-depriving condition by at least about 20% as compared to a control level of cytotoxicity activity. In one embodiment, the control level of cytotoxicity activity is a cytotoxicity level of an unmodified NK cell under the same conditions. In one embodiment, the modified NK cell comprises an increase in cytotoxicity activity under the nutrient-depriving condition by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at

least about 60%, at least about 75% or about 100% as compared to the control level of cytotoxicity activity.

[0032] In one embodiment, the spare respiratory capacity of the modified NK cell is at least 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or 100% higher as compared to a control level of spare respiratory capacity, wherein the control level of spare respiratory capacity is a level of spare respiratory capacity of an unmodified NK cell under the same conditions. In one embodiment, the modified NK cell comprises an increase in spare respiratory capacity by at least 20% as compared to a control level of spare respiratory capacity. In one embodiment, the control level of spare respiratory capacity is a level of spare respiratory capacity of an unmodified NK cell under the same conditions. In one embodiment, the modified NK cell comprises an increase in spare respiratory capacity by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 75% or about 100% as compared to the control level of spare respiratory capacity.

[0033] In one embodiment, the molecule comprising an Fc domain that binds cancer cells, e.g., antibody, or antigen-binding portion thereof, binds epidermal growth factor receptor (EGFR), HER2, or CD20. In one embodiment, the antibody is cetuximab, trastuzumab, or rituximab, or an antigen-binding portion thereof.

[0034] In one embodiment, the modified NK cell is administered concurrently with the antibody. In one embodiment, the antibody is administered prior to the modified NK cell. In one embodiment, the antibody is administered 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, or 2 weeks prior to the modified NK cell. In one embodiment, the modified NK cell is administered prior to the antibody. In one embodiment, the modified NK cell is administered 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, or 2 weeks prior to the antibody. In another embodiment, the modified NK cell is administered once, and the antibody is administered at least two, three, four, or five times. In another embodiment, the modified NK cell is administered at least one, two, three, four or five times, and the antibody is administered at least one, two, three, four or five times, either concurrently or sequentially.

[0035] In one embodiment, the cancer cell is a head and neck cancer cell, breast cancer cell, colorectal cancer cell, gastric cancer cell, renal cell carcinoma (RCC) cell, or non-small cell lung cancer (NSCLC) cell, solid tumor cell, bladder cancer cell, hepatocellular carcinoma cell, prostate cancer cell, ovarian/uterine cancer cell, pancreatic cancer cell, mesothelioma cell, melanoma cell, glioblastoma cell, cervical cancer cell, oral cavity cancer cell, cancer of the pharynx, thyroid cancer cell, gallbladder cancer cell, soft tissue sarcoma, or a hematological cancer cell. In one embodiment, the cancer cell is a head and neck cancer cell.

[0036] In one embodiment, the modified NK cell has been modified using CRISPR prior to the administering. In one embodiment, the modified NK cell has been modified using a RNA guided nuclease and at least one guide RNA (gRNA). In one embodiment, the RNA guided nuclease comprises a sequence of SEQ ID NO: 1142, SEQ ID NO:1143, SEQ ID

NO: 1144, SEQ ID NO: 1145, SEQ ID NO: 1146, SEQ ID NO: 1147, SEQ ID NO: 1148, SEQ ID NO: 1149, or SEQ ID NO: 1150. In one embodiment, the RNA guided nuclease comprises a sequence of SEQ ID NO: 1146. In one embodiment, the gRNA targets a DNA sequence of any one of SEQ ID NOS: 769-875 or 1174. In one embodiment the gRNA targets a DNA sequence of any one of SEQ ID NOS: 540-768 or 1173. In one embodiment, the gRNA comprises a sequence of SEQ ID NO: 1164 or SEQ ID NO: 1170, and/or SEQ ID NO: 1166 or SEQ ID NO: 1172. In one embodiment, the modified NK cell was generated from a NK cell, e.g., a mature NK, or a stem cell. In one embodiment, the stem cell is an induced pluripotent stem cell (iPS) cell, a hematopoietic stem cell (HSC), or an embryonic stem cell. In one embodiment, the NK cell is an iNK cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] FIGS. 1A and 1B depict that robust single and double-gene editing of TGFBR2 and CISH was achieved in NK cells. 72 hours after CRISPR-EngCas12a editing for each KO combination, editing at CISH and TGFBR2 were assessed by NGS in FIG. 1A, and viability was assessed by AO/PI staining in FIG. 1B. Data were obtained from three unique NK cell donors, representative of a minimum of five independent experiments.

[0038] FIGS. 2A and 2B depict that knockout (KO) of CISH and TGFBR2 by CRISPR-EngCas12a increased phosphorylation of STAT5 (pSTAT5) upon IL-15 stimulation and reduced phosphorylation of SMAD2/3 (pSMAD2/3) upon TGF- β stimulation. NK cells were cytokine-starved for 18 hours, 72 hours after CRISPR-EngCas12a editing, followed by re-stimulation for 120 min with IL-15 (FIG. 2A) or IL-15 and TGF- β (FIG. 2B), and analyzed by phosphoflow cytometry assay. Data are representative of four unique NK cell donors in two independent experiments. Statistical difference is the result of 1-way ANOVA analysis (*p<0.05; **p<0.01; ***p<0.001, ****p<0.0001).

[0039] FIGS. 3A, 3B, 3C, and 3D depict that double KO (DKO) of CISH/TGFBR2 in NK cells by CRISPR-EngCas12a editing increased inflammatory cytokine production after co-culturing with spheroids of ovarian cancer cell line SK-OV-3 (FIGS. 3A and 3B) and prostate cancer cell line PC-3 (FIGS. 3C and 3D) in comparison to unedited control NK cells. Supernatants were harvested at the conclusion of the spheroid assay (120 hrs) and analyzed for TNF- α and IFN- γ by AlphaLISA (+TGF- β conditions). Statistical difference is the result of 2-way ANOVA analysis (*p<0.05; **p<0.01; ***p<0.001, ****p<0.0001).

[0040] FIGS. 4A, 4B, 4C, and 4D depict that CRISPR-EngCas12a editing enhanced anti-tumor activity of NK cells against SK-OV-3 ovarian tumor compared with unedited control NK cells in the in vitro spheroid assay at different effector cell to target cell (E:T) ratios. FIGS. 4A and 4B depict the tumor spheroid analysis at 10:1 E:T ratio in the presence of 10 ng/ml TGF- β , without and with the addition of 10 μ g/mL trastuzumab, respectively, as analyzed across a minimum of 4 unique donors and 3 independent experiments. Red object intensity was measured every two hours for 5 days on an Incucyte imaging system. FIGS. 4C and 4D depict the tumor spheroid analysis at 1.25:1, 2.5:1, 5:1 and 10:1 E:T ratios in the presence of 10 ng/ml TGF- β , without and with the addition of 10 μ g/mL trastuzumab, respectively, as analyzed across a minimum of 4 unique donors and 3

independent experiments. Red object intensity is shown at 100 hours following NK cell addition.

[0041] FIG. 5 depicts amplified tumor killing by NK cells through antibody-dependent cellular cytotoxicity in vitro. At low E:T ratio of 1.25:1, the addition of 10 μ g/mL trastuzumab significantly increased killing of SK-OV-3 tumor spheroids by both unedited and CISH/TGFBR2 DKO NK cells, as analyzed across a minimum of 4 unique donors and 3 independent experiments.

[0042] FIGS. 6A, 6B, 6C, and 6D depict that CRISPR-EngCas12a-edited NK cells reduced SK-OV-3 ovarian tumor burden more effectively than unedited control NK cells, leading to an increased median survival time in an in vivo mouse model. NSG mice (n=8 per group in two independent experiments) were inoculated via intraperitoneal (i.p.) with 0.5 million (FIGS. 6A and 6C) or 1 million (FIGS. 6B and 6D) luciferase-expressing SK-OV-3 cells. Seven days later, the mice were administered 10 million unedited NK cells or 10 million DKO NK cells by i.p. infusion. Tumor burden measured by bioluminescence signal from SK-OV-3 cells are shown in FIGS. 6A and 6B, and overall survival of mice are shown in FIGS. 6C and 6D. Data are representative of two independent experiments. Statistical difference is the result of 2-way ANOVA (*p<0.05; **p<0.01; ***p<0.001) for bioluminescence and log rank test for overall survival.

[0043] FIGS. 7A, 7B, 7C and 7D depict that trastuzumab mediated antibody-dependent cellular toxicity in NK cell treatments of SK-OV-3 tumor bearing mice. NSG mice (n=8 per group) were inoculated via intraperitoneal (i.p.) with 0.5 million luciferase-expressing SK-OV-3 cells. On day 7, mice were treated with 2.5 mpk isotype, 2.5 mpk trastuzumab, 10 million unedited CD56+NK cells, 10 million DKO CD56+NK cells or the combination of DKO CD56+NK cells with trastuzumab. The average tumor volumes are shown as mean \pm SEM (****p<0.0001, **p<0.01, *p<0.05, 2-way analysis of variance) (FIGS. 7A and 7B). Kaplan-Meier survival curves shown for the treatment groups as indicated (*p<0.05; **p<0.01; Gehan-Wilcoxon test) (FIGS. 7C and 7D). FIGS. 7A and 7C show that the DKO NK cells are effective at controlling tumor growth and increased mouse lifespan. FIGS. 7B and 7D show that administration of trastuzumab further reduced SK-PV-3 ovarian tumor burden and extended lifespan of tumor-bearing mice in treatments with DKO NK cells.

[0044] FIGS. 8A and 8B depict that DKO NK cells demonstrate more robust serial killing of Raji tumor cells over a tested period of more than 7 days with multiple de novo additions of Raji tumor target cells relative to control NK cells, and that combination with rituximab improved killing by both control and DKO NK cells. FIG. 8A shows the experimental set up of the assay. 200 thousand NK cells were seeded in each well. 10 thousand Raji tumor cells were added to the NK cells at the beginning of the assay, and subsequently 5 thousand tumor cells and IL-15 were bolused into each well every 48 hours. Surviving tumor cells were quantified by normalized total red object area. FIG. 8B shows that DKO NK cells demonstrate increased killing of Raji tumor cells relative to control NK and that the addition of rituximab improved killing by both types of NK cells.

[0045] FIG. 9A depicts upregulation of granzyme transcripts, GZMB, GZLMA and GZMH in CISH^{-/-} NK cells as assessed by NanoString analysis.

[0046] FIG. 9B depicts that GZMB transcripts were upregulated 22-fold in CISH/TGFBR2 DKO NK cells as quantified by RT-qPCR. TBP (TATA box binding protein) was used as a reference transcript.

[0047] FIG. 9C depicts that CISH/TGFBR2 DKO NK cells demonstrated enhanced tumor cytotoxicity relative to unedited control NK cells. CISH/TGFBR2 DKO NK cells were co-cultured with SK-OV-3 tumor spheroids in the presence of 10 ng/mL TGF- β over a time period of 36 hours at a 5:1 effector tumor ratio. Error bars represent standard deviation.

[0048] FIG. 9D shows representative Incucyte images of SK-OV3::GzmB cells co-cultured with CISH/TGFBR2 DKO NK cells or unedited NK control cells for 4 hours. FIG. 9D depicts that CISH/TGFBR2 DKO NK cells released more GzmB than unedited control NK cells when co-cultured with SK-OV-3 tumor cells.

[0049] FIG. 9E depicts that CISH/TGFBR2 DKO NK cells demonstrated higher levels of GzmB granulation at earlier time points relative to unedited NK control cells.

[0050] FIG. 10A depicts that CISH/TGFBR2 DKO NK cells had enhanced cytotoxicity when compared to unedited control NK cells in unfavorable metabolic conditions in isolation. CISH/TGFBR2 DKO NK cells were co-cultured with SK-OV-3 tumor spheroids without TGF- β at a 10:1 effector tumor ratio.

[0051] FIG. 10B depicts that CISH/TGFBR2 DKO NK cells had enhanced cytotoxicity when compared to unedited control NK cells in multifactorially unfavorable metabolic conditions. The CISH/TGFBR2 DKO NK cells or the unedited control cells were co-cultured with SK-OV-3 tumor spheroids in the presence of 10 ng/mL TGF- β at a 5:1 effector tumor ratio.

[0052] FIG. 10C depicts that CISH/TGFBR2 DKO NK cells had enhanced cytotoxicity when compared to unedited control NK cells against tumor cells evolved to grow in unfavorable metabolic conditions. The CISH/TGFBR2 DKO NK cells or the unedited control cells were co-cultured with SK-OV-3 tumor spheroids that were selectively evolved to grow in unfavorable metabolic conditions in the presence of 10 ng/mL TGF- β at a 10:1 effector tumor ratio. EC50 was measured at 100 hours.

[0053] FIG. 10D depicts that CISH/TGFBR2 DKO NK cells had a greater cytotoxicity potential in unfavorable metabolic conditions than in control media compared to unedited control NK cells. The CISH/TGFBR2 DKO NK cells or the unedited control cells were co-cultured with SK-OV-3 tumor spheroids that were selectively evolved to grow in unfavorable metabolic conditions in the presence of 10 ng/mL TGF- β at 100 hours at various effector target ratios as indicated.

[0054] FIG. 10E depicts that CISH/TGFBR2 DKO NK cells exhibited significantly greater metabolic fitness (i.e., greater spare respiratory capacity (SRC)) than unedited control NK cells after overnight IL-15 starvation. *p<0.05.

[0055] FIGS. 11A and 11B depict that CISH/TGFBR2 DKO NK cells enhanced anti-tumor activity against Nalm6 cells in the presence of TGF- β , respectively, as analyzed across a minimum of 5 unique donors and 2 independent experiments. CISH/TGFBR2 DKO NK cells and unedited control NK cells were co-cultured with Nalm6 tumor cells at a 20:1 effector tumor ratio in the presence of 5 ng/mL IL-15, without and with the addition of 10 ng/mL TGF- β . Increased

cytotoxicity was observed in all conditions while a greater increase was observed when TGF- β was added in the cell culture.

[0056] FIG. 12 depicts that CISH/TGFBR2 DKO NK cells demonstrate robust serial killing against Nalm6 cells over a tested period up to 20 days with multiple additions of Nalm6 cells relative to control NK cells.

[0057] FIG. 13 depicts that CISH/TGFBR2 DKO NK cells continually killed Nalm6 tumor cells for more than 8 days, whereas unedited NK cells had limited serial killing effect. Data are representative of NK cells from 6 unique donors in 2 independent experiments.

[0058] FIG. 14 depicts that CISH/TGFBR2 DKO NK cells produced increased levels of inflammatory cytokines (IFN- γ and TNF- α) throughout the serial-killing assay in the presence of TGF- β relative to unedited control NK cells.

[0059] FIGS. 15A, 15B, and 15C depict that CISH/TGFBR2 DKO NK cells demonstrated sustained serial-killing activity against numerous other hematologic tumor cell lines, e.g., Raji (Burkitt's lymphoma) (FIG. 15A), RPM18226 (multiple myeloma) (FIG. 15B) and THP-1 cells (acute monocytic leukemia) (FIG. 15C), in the presence of TGF- β . Data are representative of NK cells from 5 unique donors in 5 independent experiments.

DETAILED DESCRIPTION

[0060] The present disclosure provides modified NK cells (or other lymphocytes) that are useful in NK cell therapy, e.g., in the context of immunotherapeutic approaches, in combination with a therapeutic antibody, or antigen-binding portion thereof, to generate striking antibody-dependent cellular cytotoxicity (ADCC) effects, thereby surprisingly increasing the effectiveness of the modified NK cells in killing target cells, e.g. cancer cells. ADCC is a mechanism of cell-mediated immune defense, where an immune effector cell actively lyses a target cell after its membrane-surface antigens have been bound by specific antibodies. To participate in ADCC, the immune effector cells must express Fc-gamma receptors (Fc γ R) to be able to recognize the Fc region of the antibodies that bind to the target cells. Most immune effector cells have both activating and inhibitory Fc γ R. An advantage of using NK cells to target cancer cells via ADCC is that, unlike other effector cells, NK cells only have activating Fc γ Rs (e.g., Fc γ R IIIa, also known as CD16a, and Fc γ R IIc, also known as CD32c) and are believed to be the most important effectors of ADCC in humans. Thus, the use of the modified NK cells disclosed herein and antibodies targeting cancer cell-specific antigens to elicit ADCC provides novel and surprisingly effective immunotherapies.

[0061] Some aspects of the present disclosure provide compositions, methods, and strategies for the generation of modified NK cells. In some embodiments, such modified NK cells are generated by editing the genome of NK cells, e.g., mature NK cells. In one embodiment, NK cells are obtained from a healthy donor, and then edited using the compositions and methods described herein to make modified NK cells. For example, NK cell expansion ex vivo is described at least in Myers and Miller, Exploring the NK cell platform for cancer immunotherapy, Nat Rev Clin Oncol (2020), <https://doi.org/10.1038/s41571-020-0426-7>, the entire contents of which are expressly incorporated herein by reference.

[0062] In other embodiments, modified NK cells are generated by editing the genome of a cell from which an NK cell is derived, either *in vitro* or *in vivo*. In some embodiments, the cell from which an NK cell is derived is a stem cell, for example, a hematopoietic stem cell (HSC), or a pluripotent stem cells, such as, e.g., an embryonic stem cell (ES cell) or an induced pluripotent stem cell (iPS cell). For example, in some embodiments, modified NK cells are generated by editing the genome of an ES cell, an iPS cell, or a hematopoietic stem cell, and subsequently differentiating the edited stem cell into an NK cell. In some embodiments, where the generation of modified NK cells involves differentiation of the modified NK cell from an iPS cell, the editing of the genome may take place at any suitable time during the generation, maintenance, or differentiation of the iPS cell. For example, where a donor cell is reprogrammed into an iPS cell, the donor cell, e.g., a somatic cell such as, for example, a fibroblast cell or a T lymphocyte, may be subjected to the gene editing approaches described herein before reprogramming to an iPS cell, during the reprogramming procedure, or after the donor cell has been reprogrammed to an iPS cell.

[0063] NK cells derived from iPS cells are also referred to herein as iNK cells. In some embodiments, the present disclosure provides compositions, methods, and strategies for generating iNK cells that have been derived from developmentally mature cells, also referred to as somatic cells, such as, for example, fibroblasts or peripheral blood cells.

[0064] In some embodiments, the present disclosure provides compositions, methods, and strategies for generating iNK cells that have been derived from developmentally mature T cells (T cells that have undergone thymic selection). One hallmark of developmentally mature T cells is a rearranged T cell receptor locus. During T cell maturation, the TCR locus undergoes V(D)J rearrangements to generate complete V-domain exons. These rearrangements are retained throughout reprogramming of a T cells to an induced pluripotent stem (iPS) cell, and throughout differentiation of the resulting iPS cell to a somatic cell.

[0065] One advantage of using T cells for the generation of iPS cells is that T cells can be edited with relative ease, e.g., by CRISPR-based methods or other gene-editing methods.

[0066] Another advantage of using T cells for the generation of iPS cells is that the rearranged TCR locus allows for genetic tracking of individual cells and their daughter cells. If the reprogramming, expansion, culture, and/or differentiation strategies involved in the generation of NK cells a clonal expansion of a single cell, the rearranged TCR locus can be used as a genetic marker unambiguously identifying a cell and its daughter cells. This, in turn, allows for the characterization of a cell population as truly clonal, or for the identification of mixed populations, or contaminating cells in a clonal population.

[0067] A third advantage of using T cells in generating iNK cells carrying multiple edits is that certain karyotypic aberrations associated with chromosomal translocations are selected against in T cell culture. Such aberrations pose a concern when editing cells by CRISPR technology, and in particular when generating cells carrying multiple edits.

[0068] A fourth advantage of using T cell derived iPS cells as a starting point for the derivation of therapeutic lymphocytes is that it allows for the expression of a pre-screened TCR in the lymphocytes, e.g., via selecting the T cells for

binding activity against a specific antigen, e.g., a tumor antigen, reprogramming the selected T cells to iPS cells, and then deriving lymphocytes from these iPS cells that express the TCR (e.g., T cells). This strategy would also allow for activating the TCR in other cell types, e.g., by genetic or epigenetic strategies.

[0069] A fifth advantage of using T cell derived iPS cells as a starting point for iNK differentiation is that the T cells retain at least part of their “epigenetic memory” throughout the reprogramming process, and thus subsequent differentiation of the same or a closely related cell type, such as iNK cells will be more efficient and/or result in higher quality cell populations as compared to approaches using non-related cells, such as fibroblasts, as a starting point for iNK derivation.

Definitions and Abbreviations

[0070] Unless otherwise specified, each of the following terms have the meaning set forth in this section.

[0071] The indefinite articles “a” and “an” refer to at least one of the associated noun, and are used interchangeably with the terms “at least one” and “one or more.”

[0072] The conjunctions “or” and “and/or” are used interchangeably as non-exclusive disjunctions.

[0073] “Subject” means a human or non-human animal. A human subject can be any age (e.g., an infant, child, young adult, or adult), and may suffer from a disease, or may be in need of alteration of a gene or a combination of specific genes. Alternatively, the subject may be an animal, which term includes, but is not limited to, a mammal, and, more particularly, a non-human primate, a rodent (e.g., a mouse, rat, hamster, etc.), a rabbit, a guinea pig, a dog, a cat, and so on. In certain embodiments of this disclosure, the subject is livestock, e.g., a cow, a horse, a sheep, or a goat. In certain embodiments, the subject is poultry.

[0074] The terms “treatment,” “treat,” and “treating,” refer to a clinical intervention aimed to reverse, alleviate, delay the onset of, or inhibit the progress, and/or prevent or delay the recurrence of a disease or disorder, or one or more symptoms thereof, as described herein. Treatment, e.g., in the form of a modified NK cell or a population of modified NK cells as described herein, may be administered to a subject after one or more symptoms have developed and/or after a disease has been diagnosed. Treatment may be administered in the absence of symptoms, e.g., to prevent or delay onset of a symptom or inhibit onset or progression of a disease. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[0075] “Prevent,” “preventing,” and “prevention” refer to the prevention of a disease in a mammal, e.g., in a human, including (a) avoiding or precluding the disease; (b) affecting the predisposition toward the disease; or (c) preventing or delaying the onset of at least one symptom of the disease.

[0076] The terms “polynucleotide”, “nucleotide sequence”, “nucleic acid”, “nucleic acid molecule”, “nucleic acid sequence”, and “oligonucleotide” refer to a series of nucleotide bases (also called “nucleotides”) in DNA and RNA, and mean any chain of two or more nucleotides. The polynucleotides, nucleotide sequences, nucleic acids etc. can be chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. They can be

modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, its hybridization parameters, etc. A nucleotide sequence typically carries genetic information, including, but not limited to, the information used by cellular machinery to make proteins and enzymes. These terms include double- or single-stranded genomic DNA, RNA, any synthetic and genetically manipulated polynucleotide, and both sense and antisense polynucleotides. These terms also include nucleic acids containing modified bases.

[0077] Conventional IUPAC notation is used in nucleotide sequences presented herein, as shown in Table 1, below (see also Cornish-Bowden A, Nucleic Acids Res. 1985 May 10; 13(9):3021-30, incorporated by reference herein). It should be noted, however, that "T" denotes "Thymine or Uracil" in those instances where a sequence may be encoded by either DNA or RNA, for example in gRNA targeting domains.

TABLE 1

IUPAC nucleic acid notation	
Character	Base
A	Adenine
T	Thymine or Uracil
G	Guanine
C	Cytosine
U	Uracil
K	G or T/U
M	A or C
R	A or G
Y	C or T/U
S	C or G
W	A or T/U
B	C, G or T/U
V	A, C or G
H	A, C or T/U
D	A, G or T/U
N	A, C, G or T/U

[0078] The terms "protein," "peptide" and "polypeptide" are used interchangeably to refer to a sequential chain of amino acids linked together via peptide bonds. The terms

include individual proteins, groups or complexes of proteins that associate together, as well as fragments or portions, variants, derivatives and analogs of such proteins. Peptide sequences are presented herein using conventional notation, beginning with the amino or N-terminus on the left, and proceeding to the carboxyl or C-terminus on the right. Standard one-letter or three-letter abbreviations can be used. [0079] The term "variant" refers to an entity such as a polypeptide, polynucleotide or small molecule that shows significant structural identity with a reference entity but differs structurally from the reference entity in the presence or level of one or more chemical moieties as compared with the reference entity. In many embodiments, a variant also differs functionally from its reference entity. In general, whether a particular entity is properly considered to be a "variant" of a reference entity is based on its degree of structural identity with the reference entity.

[0080] The term "endogenous," as used herein in the context of nucleic acids (e.g., genes, protein-encoding genomic regions, promoters), refers to a native nucleic acid or protein in its natural location, e.g., within the genome of a cell. In contrast, the term "exogenous," as used herein in the context of nucleic acids, e.g., expression constructs, cDNAs, indels, and nucleic acid vectors, refers to nucleic acids that have artificially been introduced into the genome of a cell using, for example, gene-editing or genetic engineering techniques, e.g., CRISPR-based editing techniques.

[0081] The terms "RNA-guided nuclease" and "RNA-guided nuclease molecule" are used interexchangably herein. In some embodiments, the RNA-guided nuclease is a RNA-guided DNA endonuclease enzyme. In some embodiments, the RNA-guided nuclease is a CRISPR nuclease. Non-limiting examples of RNA-guided nucleases are listed in Table 2 below, and the methods and compositions disclosed herein can use any combination of RNA-guided nucleases disclosed herein, or known to those of ordinary skill in the art. Those of ordinary skill in the art will be aware of additional nucleases and nuclease variants suitable for use in the context of the present disclosure, and it will be understood that the present disclosure is not limited in this respect.

TABLE2

RNA-Guided Nucleases			
Nuclease	Length (a.a.)	PAM	Reference
SpCas9	1368	NGG	Cong et al., <i>Science</i> . 2013; 339(6121): 819-23
SaCas9	1053	NNGRRT	Ran et al., <i>Nature</i> . 2015; 520(7546): 186-91.
(KKH) SaCas9	1067	NNNNRRT	Kleininstiver et al., <i>Nat Biotechnol</i> . 2015; 33(12): 1293-1298
AsCpf1 (AsCas12a)	1353	TTTV	Zetsche et al., <i>Nat Biotechnol</i> . 2017; 35(1): 31-34.
LbCpf1 (LbCas 12a)	1274	TTTV	Zetsche et al., <i>Cell</i> . 2015; 163(3): 759-71.
CasX	980	TTC	Burstein et al., <i>Nature</i> . 2017; 542(7640): 237-241.
CasY	1200	TA	Burstein et al., <i>Nature</i> . 2017; 542(7640): 237-241.
Cas12hi	870	RTR	Yan et al., <i>Science</i> . 2019; 363(6422): 88-91.
Cas12ii	1093	TTN	Yan et al., <i>Science</i> . 2019; 363(6422): 88-91.

TABLE2-continued

RNA-Guided Nucleases			
Nuclease	Length (a.a.)	PAM	Reference
Cas12c1	unknown	TG	Yan et al., <i>Science</i> . 2019; 363(6422): 88-91.
Cas12c2	unknown	TN	Yan et al., <i>Science</i> . 2019; 363(6422): 88-91.
eSpCas9	1423	NGG	Chen et al., <i>Nature</i> . 2017; 550(7676): 407-410.
Cas9-HF1	1367	NGG	Chen et al., <i>Nature</i> . 2017; 550(7676): 407-410.
HypaCas9	1404	NGG	Chen et al., <i>Nature</i> . 2017; 550(7676): 407-410.
dCas9-Pok1	1623	NGG	U.S. Pat. No. 9,322,037
Sniper-Cas9	1389	NGG	Lee et al., <i>Nat Commun</i> . 2018; 9(1): 3048.
xCas9	1786	NGG, NG, Wang et al., GAA, GAT	Plant Biotechnol J. 2018; pbi.13053.
AaCas 12b	1129	TTN	Teng et al. <i>Cell Discov</i> . 2018; 4:63.
evoCas9	1423	NGG	Casini et al., <i>Nat Biotechnol</i> . 2018; 36(3): 265-271.
SpCas9-NG	1423	NG	Nishimasu et al., <i>Science</i> . 2018; 361(6408): 1259-1262.
VRQR	1368	NGA	Li et al., <i>The CRISPR Journal</i> , 2018; 01:01
VRER	1372	NGCG	Kleinstiver et al., <i>Nature</i> . 2016; 529(7587): 490-5.
NmeCas9	1082	NNNNGAT	Amrani et al., <i>Genome Biol</i> . 2018; 19(1): 214. T
CjCas9	984	NNNNRYA C	Kim et al., <i>Nat Commun</i> . 2017; 8: 14500.
BhCas12b	1108	ATTN	Strecker et al., <i>Nat Commun</i> . 2019 Jan. 22; 10(1): 212.
BhCas12b V4	1108	ATTN	Strecker et al., <i>Nat Commun</i> . 2019 Jan. 22; 10(1): 212.
CasΦ			Pausch et al., <i>Science</i> 2020; 369(6501): 333-337.

[0082] Additional suitable RNA-guided nucleases, e.g., Cas9 and Cas12 nucleases, will be apparent to the skilled artisan in view of the present disclosure, and the disclosure is not limited by the exemplary suitable nucleases provided herein. In some embodiment, a suitable nuclease is a Cas9 or Cpf1 (Cas12a) nuclease. In some embodiments, the disclosure also embraces nuclease variants, e.g., Cas9 or Cpf1 nuclease variants. A nuclease variant refers to a nuclease comprising an amino acid sequence characterized by one or more amino acid substitutions, deletions, or additions as compared to the wild type amino acid sequence of the nuclease. Suitable nucleases and nuclease variants may also include purification tags (e.g., polyhistidine tags) and signaling peptides, e.g., comprising or consisting of a nuclear localization signal sequence. Some non-limiting examples of suitable nucleases and nuclease variants are described in more detail elsewhere herein, and also include those described in PCT application PCT/US2019/22374, filed Mar. 14, 2019, and entitled “Systems and Methods for the Treatment of Hemoglobinopathies,” the entire contents of which are incorporated herein by reference.

[0083] In some embodiments, the RNA-guided nuclease is an *Acidaminococcus* sp. Cpf1 variant (AsCpf1 variant).

Suitable Cpf1 nuclease variants, including suitable AsCpf1 variants will be known or apparent to those of ordinary skill in the art based on the present disclosure, and include, but are not limited to, the Cpf1 variants disclosed herein or otherwise known in the art. For example, in some embodiments, the RNA-guided nuclease is an *Acidaminococcus* sp. Cpf1 RR variant (AsCpf1-RR). In another embodiment, the RNA-guided nuclease is a Cpf1 RVR variant. For example, suitable Cpf1 variants include those having an M537R substitution, an H800A substitution, and/or an F870L substitution, or any combination thereof (numbering scheme according to AsCpf1 wild-type sequence). In some embodiments, the RNA-guided nuclease is an *Acidaminococcus* sp. Cpf1 variant (AsCpf1 variant) having an M537R substitution, an H800A substitution, and an F870L substitution (numbering scheme according to AsCpf1 wild-type sequence).

[0084] The term “hematopoietic stem cell,” or “definitive hematopoietic stem cell” as used herein, refers to CD34+ stem cells capable of giving rise to both mature myeloid and lymphoid cell types including T cells, natural killer cells and B cells.

[0085] As used herein, the terms “reprogramming” or “dedifferentiation” or “increasing cell potency” or “increas-

ing developmental potency” refers to a method of increasing the potency of a cell or dedifferentiating the cell to a less differentiated state. For example, a cell that has an increased cell potency has more developmental plasticity (i.e., can differentiate into more cell types) compared to the same cell in the non-reprogrammed state. In other words, a reprogrammed cell is one that is in a less differentiated state than the same cell in a non-reprogrammed state. In some embodiments, the term “reprogramming” refers to de-differentiating a somatic cell, or a multipotent stem cell, into a pluripotent stem cell, also referred to as an induced pluripotent stem cell, or iPS cell. Suitable methods for the generation of iPS cells from somatic or multipotent stem cells are well known to those of skill in the art.

[0086] As used herein, the term “differentiation” is the process by which an unspecialized (“uncommitted”) or less specialized cell acquires the features of a specialized cell such as, for example, a blood cell or a muscle cell. A differentiated or differentiation-induced cell is one that has taken on a more specialized (“committed”) position within the lineage of a cell. For example, an iPS cell can be differentiated into various more differentiated cell types, for example, a neural or a hematopoietic stem cell, a lymphocyte, a cardiomyocyte, and other cell types, upon treatment with suitable differentiation factors in the cell culture medium. Suitable methods, differentiation factors, and cell culture media for the differentiation of pluri- and multipotent cell types into more differentiated cell types are well known to those of skill in the art. The term “committed”, when applied to the process of differentiation, refers to a cell that has proceeded in the differentiation pathway to a point where, under normal circumstances, it will continue to differentiate into a specific cell type or subset of cell types, and cannot, under normal circumstances, differentiate into a different cell type or revert to a less differentiated cell type.

[0087] As used herein, the terms “differentiation marker,” “differentiation marker gene,” or “differentiation gene,” refers to genes or proteins whose expression are indicative of cell differentiation occurring within a cell, such as a pluripotent cell. Differentiation marker genes include, but are not limited to, the following genes: CD34, CD4, CD8, CD3, CD56 (NCAM), CD49, CD45; NK cell receptor (cluster of differentiation 16 (CD16)), natural killer group-2 member D (NKG2D), CD69, NKp30, NKp44, NKp46, CD158b, FOXA2, FGF5, SOX17, XIST, NODAL, COL3A1, OTX2, DUSP6, EOMES, NR2F2, NROB1, CXCR4, CYP2B6, GAT A3, GATA4, ERBB4, GATA6, HOXC6, INHA, SMAD6, RORA, NIPBL, TNFSF11, CDH11, ZIC4, GAL, SOX3, PITX2, APOA2, CXCL5, CER1, FOXQ1, MLL5, DPP10, GSC, PCDH10, CTCFL, PCDH20, TSHZ1, MEGF10, MYC, DKK1, BMP2, LEFTY2, HES1, CDX2, GNAS, EGR1, COL3A1, TCF4, HEPH, KDR, TOX, FOXA1, LCK, PCDH7, CD1D FOXG1, LEFTY1, TUJ1, T gene (Brachyury), ZIC1, GATA1, GATA2, HDAC4, HDAC5, HDAC7, HDAC9, NOTCH1, NOTCH2, NOTCH4, PAX5, RBPJ, RUNX1, STAT1 and STAT3.

[0088] As used herein, the term “differentiation marker gene profile,” or “differentiation gene profile,” “differentiation gene expression profile,” “differentiation gene expression signature,” “differentiation gene expression panel,” “differentiation gene panel,” or “differentiation gene signature” refers to the expression or levels of expression of a plurality of differentiation marker genes.

[0089] As used herein in the context of cellular developmental potential, the term “potency” or “developmental potency” refers to the sum of all developmental options accessible to the cell (i.e., the developmental potency). The continuum of cell potency includes, but is not limited to, totipotent cells, pluripotent cells, multipotent cells, oligopotent cells, unipotent cells, and terminally differentiated cells.

[0090] As used herein, the term “pluripotent” refers to the ability of a cell to form all lineages of the body or soma (i.e., the embryo proper). For example, embryonic stem cells are a type of pluripotent stem cells that are able to form cells from each of the three germs layers, the ectoderm, the mesoderm, and the endoderm. Pluripotency is a continuum of developmental potencies ranging from the incompletely or partially pluripotent cell (e.g., an epiblast stem cell or EpiSC), which is unable to give rise to a complete organism to the more primitive, more pluripotent cell, which is able to give rise to a complete organism (e.g., an embryonic stem cell or an induced pluripotent stem cell).

[0091] As used herein, the term “induced pluripotent stem cell” or, iPS cell refers to a stem cell obtained from a differentiated somatic, e.g., adult, neonatal, or fetal cell by a process referred to as reprogramming into cells capable of differentiating into tissues of all three germ or dermal layers: mesoderm, endoderm, and ectoderm. IPS cells are not found in nature.

[0092] As used herein, the term “embryonic stem cell” refers to pluripotent stem cells derived from the inner cell mass of the embryonic blastocyst. Embryonic stem cells are pluripotent and give rise during development to all derivatives of the three primary germ layers: ectoderm, endoderm and mesoderm. They do not contribute to the extra-embryonic membranes or the placenta, i.e., are not totipotent.

[0093] As used herein, the term “multipotent stem cell” refers to a cell that has the developmental potential to differentiate into cells of one or more germ layers (ectoderm, mesoderm and endoderm), but not all three. Thus, a multipotent cell can also be termed a “partially differentiated cell.” Multipotent cells are well known in the art, and examples of multipotent cells include adult stem cells, such as for example, hematopoietic stem cells and neural stem cells. “Multipotent” indicates that a cell may form many types of cells in a given lineage, but not cells of other lineages. For example, a multipotent hematopoietic cell can form the many different types of blood cells (red, white, platelets, etc.), but it cannot form neurons. Accordingly, the term “multipotency” refers to a state of a cell with a degree of developmental potential that is less than totipotent and pluripotent.

[0094] Pluripotency can be determined, in part, by assessing pluripotency characteristics of the cells. Pluripotency characteristics include, but are not limited to: (i) pluripotent stem cell morphology; (ii) the potential for unlimited self-renewal; (iii) expression of pluripotent stem cell markers including, but not limited to SSEA1 (mouse only), SSEA3/4, SSEA5, TRA1-60/81, TRA1-85, TRA2-54, GCTM-2, TG343, TG30, CD9, CD29, CD133/prominin, CD140a, CD56, CD73, CD90, CD105, OCT4, NANOG, SOX2, CD30 and/or CD50; (iv) ability to differentiate to all three somatic lineages (ectoderm, mesoderm and endoderm); (v) teratoma formation consisting of the three somatic lineages; and (vi) formation of embryoid bodies consisting of cells from the three somatic lineages.

[0095] As used herein, the term “pluripotent stem cell morphology” refers to the classical morphological features of an embryonic stem cell. Normal embryonic stem cell morphology is characterized by being round and small in shape, with a high nucleus-to-cytoplasm ratio, the notable presence of nucleoli, and typical intercell spacing.

[0096] As used herein, the term “nutrient-depriving condition” refers to unfavorable growth or metabolic conditions where either a lower level of nutrients or a lack of nutrients is observed. Nutrient deprivation is one of the hallmark conditions of the tumor microenvironment. The rapid growth of the tumor leads to the development of a hypoxic and nutrient deprived microenvironment within the core of the tumor mass due to an insufficient blood supply. In some embodiments, the nutrient-depriving condition comprises a decreasing concentration of nutrients for cell metabolism, e.g., glucose or glutamine. In some embodiments, the nutrient-depriving condition comprises a decreasing concentration of glucose, e.g., a concentration of glucose from about 10 mM, about 9 mM, about 8 mM, about 7 mM, about 6 mM, about 5 mM, about 4 mM, about 3 mM, about 2 mM or about 1 mM to a concentration of glucose less than about 1 mM, e.g., about 0.9 mM, about 0.8 mM, about 0.7 mM, about 0.6 mM, about 0.5 mM, about 0.4 mM, about 0.3 mM, about 0.2 mM or about 0.1 mM. In some embodiments, the nutrient-depriving condition comprises a decreasing concentration of glutamine, e.g., a concentration of glutamine from about 10 mM, about 9 mM, about 8 mM, about 7 mM, about 6 mM, about 5 mM, about 4 mM, about 3 mM, about 2 mM or about 1 mM to a concentration of glutamine less than about 1 mM, e.g., about 0.9 mM, about 0.8 mM, about 0.7 mM, about 0.6 mM, about 0.5 mM, about 0.4 mM, about 0.3 mM, about 0.2 mM or about 0.1 mM. In some embodiments, the nutrient-depriving condition comprises an increasing concentration of inhibitory metabolic, e.g., lactate, e.g., a concentration of lactate from about 0 mM, about 0.1 mM, about 0.2 mM, about 0.3 mM, about 0.4 mM, about 0.5 mM, about 0.6 mM, about 0.7 mM, about 0.8 mM, about 0.9 mM or about 1 mM to a concentration of lactate about 10 mM, about 15 mM, about 20 mM, about 25 mM, about 30 mM, about 35 mM, about 40 mM, about 45 mM or about 50 mM. In another embodiment, the nutrient-depriving condition comprises a decreasing pH, e.g., from a pH about 7.5, about 7.4, about 7.3, about 7.2, about 7.1 or about 7 to a pH about 6.9, about 6.8, about 6.7, about 6.6 or about 6.5.

[0097] As used herein, the term “spare respiratory capacity” refers to a functional parameter for evaluation of mitochondrial reserve. Spare respiratory capacity is the difference between basal ATP production and its maximal activity. When cells are subjected to stress, energy demand increases, with more ATP required to maintain cellular functions. A cell with a larger spare respiratory capacity can produce more ATP and overcome more stress.

Genome Editing Systems

[0098] The present disclosure relates to the generation of modified NK cells, e.g., NK cells the genome of which has been modified, or that are derived from a multipotent or pluripotent stem cell, e.g., an HSC, ES cell, or iPS cell, the genome of which has been modified. The NK cells and stem cells provided herein can be modified using any gene-editing technology known to those of ordinary skill in the art, including, for example, by using genome editing systems, e.g., CRISPR.

[0099] The term “genome editing system” refers to any system having RNA-guided DNA editing activity. Genome editing systems of the present disclosure include at least two components adapted from naturally occurring CRISPR systems: a guide RNA (gRNA) and an RNA-guided nuclease. These two components form a complex that is capable of associating with a specific nucleic acid sequence and editing the DNA in or around that nucleic acid sequence, for instance by making one or more of a single-strand break (an SSB or nick), a double-strand break (a DSB) and/or a point mutation.

[0100] Naturally occurring CRISPR systems are organized evolutionarily into two classes and five types (Makarova et al. Nat Rev Microbiol. 2011 June; 9(6): 467-477 (Makarova), incorporated by reference herein), and while genome editing systems of the present disclosure may adapt components of any type or class of naturally occurring CRISPR system, the embodiments presented herein are generally adapted from Class 2, and type II or V CRISPR systems. Class 2 systems, which encompass types II and V, are characterized by relatively large, multidomain RNA-guided nuclease proteins (e.g., Cas9 or Cpf1) and one or more guide RNAs (e.g., a crRNA and, optionally, a tracrRNA) that form ribonucleoprotein (RNP) complexes that associate with (i.e. target) and cleave specific loci complementary to a targeting (or spacer) sequence of the crRNA. Genome editing systems according to the present disclosure similarly target and edit cellular DNA sequences, but differ significantly from CRISPR systems occurring in nature. For example, the unimolecular guide RNAs described herein do not occur in nature, and both guide RNAs and RNA-guided nucleases according to this disclosure may incorporate any number of non-naturally occurring modifications.

[0101] Genome editing systems can be implemented (e.g. administered or delivered to a cell or a subject) in a variety of ways, and different implementations may be suitable for distinct applications. For instance, a genome editing system is implemented, in certain embodiments, as a protein/RNA complex (a ribonucleoprotein, or RNP), which can be included in a pharmaceutical composition that optionally includes a pharmaceutically acceptable carrier and/or an encapsulating agent, such as a lipid or polymer micro- or nano-particle, micelle, liposome, etc. In certain embodiments, a genome editing system is implemented as one or more nucleic acids encoding the RNA-guided nuclease and guide RNA components described above (optionally with one or more additional components); in certain embodiments, the genome editing system is implemented as one or more vectors comprising such nucleic acids, for instance a viral vector such as an adeno-associated virus; and in certain embodiments, the genome editing system is implemented as a combination of any of the foregoing. Additional or modified implementations that operate according to the principles set forth herein will be apparent to the skilled artisan and are within the scope of this disclosure.

[0102] It should be noted that the genome editing systems of the present disclosure can be targeted to a single specific nucleotide sequence, or may be targeted to—and capable of editing in parallel—two or more specific nucleotide sequences through the use of two or more guide RNAs. The use of multiple gRNAs is referred to as “multiplexing” throughout this disclosure, and can be employed to target multiple, unrelated target sequences of interest, or to form

multiple SSBs or DSBs within a single target domain and, in some cases, to generate specific edits within such target domain. For example, International Patent Publication No. WO 2015/138510 by Maeder et al. (Maeder), which is incorporated by reference herein, describes a genome editing system for correcting a point mutation (C.2991+1655A to G) in the human CEP290 gene that results in the creation of a cryptic splice site, which in turn reduces or eliminates the function of the gene. The genome editing system of Maeder utilizes two guide RNAs targeted to sequences on either side of (i.e. flanking) the point mutation, and forms DSBs that flank the mutation. This, in turn, promotes deletion of the intervening sequence, including the mutation, thereby eliminating the cryptic splice site and restoring normal gene function.

[0103] As another example, WO 2016/073990 by Cotta-Ramusino, et al. ("Cotta-Ramusino"), incorporated by reference herein, describes a genome editing system that utilizes two gRNAs in combination with a Cas9 nickase (a Cas9 that makes a single strand nick such as *S. pyogenes* D10A), an arrangement termed a "dual-nickase system." The dual-nickase system of Cotta-Ramusino is configured to make two nicks on opposite strands of a sequence of interest that are offset by one or more nucleotides, which nicks combine to create a double strand break having an overhang (5' in the case of Cotta-Ramusino, though 3' overhangs are also possible). The overhang, in turn, can facilitate homology directed repair events in some circumstances. And, as another example, WO 2015/070083 by Palestrant et al. ("Palestrant", incorporated by reference herein) describes a gRNA targeted to a nucleotide sequence encoding Cas9 (referred to as a "governing RNA"), which can be included in a genome editing system comprising one or more additional gRNAs to permit transient expression of a Cas9 that might otherwise be constitutively expressed, for example in some virally transduced cells. These multiplexing applications are intended to be exemplary, rather than limiting, and the skilled artisan will appreciate that other applications of multiplexing are generally compatible with the genome editing systems described here.

[0104] Genome editing systems can, in some instances, form double strand breaks that are repaired by cellular DNA double-strand break mechanisms such as NHEJ or HDR. These mechanisms are described throughout the literature, for example by Davis & Maizels, PNAS, 111(10):E924-932, Mar. 11, 2014 (Davis) (describing Alt-HDR); Frit et al. DNA Repair 17(2014) 81-97 (Frit) (describing Alt-NHEJ); and Iyama and Wilson III, DNA Repair (Amst.) 2013-August; 12(8): 620-636 (Iyama) (describing canonical HDR and NHEJ pathways generally).

[0105] Where genome editing systems operate by forming DSBs, such systems optionally include one or more components that promote or facilitate a particular mode of double-strand break repair or a particular repair outcome. For instance, Cotta-Ramusino also describes genome editing systems in which a single stranded oligonucleotide "donor template" is added; the donor template is incorporated into a target region of cellular DNA that is cleaved by the genome editing system, and can result in a change in the target sequence.

[0106] In certain embodiments, genome editing systems modify a target sequence, or modify expression of a gene in or near the target sequence, without causing single- or double-strand breaks. For example, a genome editing system

may include an RNA-guided nuclease fused to a functional domain that acts on DNA, thereby modifying the target sequence or its expression. As one example, an RNA-guided nuclease can be connected to (e.g. fused to) a cytidine deaminase functional domain, and may operate by generating targeted C-to-A substitutions. Exemplary nuclease/deaminase fusions are described in Komor et al. Nature 533, 420-424 (19 May 2016) ("Komor"), which is incorporated by reference. Alternatively, a genome editing system may utilize a cleavage-inactivated (i.e. a "dead") nuclease, such as a dead Cas9 (dCas9), and may operate by forming stable complexes on one or more targeted regions of cellular DNA, thereby interfering with functions involving the targeted region(s) including, without limitation, mRNA transcription, chromatin remodeling, etc.

Guide RNA (gRNA) Molecules

[0107] The terms "guide RNA" and "gRNA" refer to any nucleic acid that promotes the specific association (or "targeting") of an RNA-guided nuclease such as a Cas9 or a Cpf1 to a target sequence such as a genomic or episomal sequence in a cell. gRNAs can be unimolecular (comprising a single RNA molecule, and referred to alternatively as chimeric), or modular (comprising more than one, and typically two, separate RNA molecules, such as a crRNA and a tracrRNA, which are usually associated with one another, for instance by duplexing). gRNAs and their component parts are described throughout the literature, for instance in Briner et al. (Molecular Cell 56(2), 333-339, Oct. 23, 2014 (Briner), which is incorporated by reference), and in Cotta-Ramusino.

[0108] In bacteria and archaea, type II CRISPR systems generally comprise an RNA-guided nuclease protein such as Cas9, a CRISPR RNA (crRNA) that includes a 5' region that is complementary to a foreign sequence, and a trans-activating crRNA (tracrRNA) that includes a 5' region that is complementary to, and forms a duplex with, a 3' region of the crRNA. While not intending to be bound by any theory, it is thought that this duplex facilitates the formation of—and is necessary for the activity of—the Cas9/gRNA complex. As type II CRISPR systems were adapted for use in gene editing, it was discovered that the crRNA and tracrRNA could be joined into a single unimolecular or chimeric guide RNA, in one non-limiting example, by means of a four nucleotide (e.g. GAAA) "tetraloop" or "linker" sequence bridging complementary regions of the crRNA (at its 3' end) and the tracrRNA (at its 5' end). (Mali et al. Science. 2013 Feb. 15; 339(6121): 823-826 ("Mali"); Jiang et al. Nat Biotechnol. 2013 March; 31(3): 233-239 ("Jiang"); and Jinek et al., 2012 Science August 17; 337 (6096): 816-821 ("Jinek"), all of which are incorporated by reference herein.)

[0109] Guide RNAs, whether unimolecular or modular, include a "targeting domain" that is fully or partially complementary to a target domain within a target sequence, such as a DNA sequence in the genome of a cell where editing is desired. Targeting domains are referred to by various names in the literature, including without limitation "guide sequences" (Hsu et al., Nat Biotechnol. 2013 September; 31(9): 827-832, ("Hsu"), incorporated by reference herein), "complementarity regions" (Cotta-Ramusino), "spacers" (Briner) and generically as "crRNAs" (Jiang). Irrespective of the names they are given, targeting domains are typically 10-30 nucleotides in length, and in certain embodiments are 16-24 nucleotides in length (for instance,

16, 17, 18, 19, 20, 21, 22, 23 or 24 nucleotides in length), and are at or near the 5' terminus of in the case of a Cas9 gRNA, and at or near the 3' terminus in the case of a Cpf1 gRNA.

[0110] In addition to the targeting domains, gRNAs typically (but not necessarily, e.g., as discussed below) include a plurality of domains that may influence the formation or activity of gRNA/Cas9 complexes. For instance, as mentioned above, the duplexed structure formed by first and secondary complementarity domains of a gRNA (also referred to as a repeat:anti-repeat duplex) interacts with the recognition (REC) lobe of Cas9 and can mediate the formation of Cas9/gRNA complexes. (Nishimasu et al., Cell 156, 935-949, Feb. 27, 2014 (Nishimasu 2014) and Nishimasu et al., Cell 162, 1113-1126, Aug. 27, 2015 (Nishimasu 2015), both incorporated by reference herein). It should be noted that the first and/or second complementarity domains may contain one or more poly-A tracts, which can be recognized by RNA polymerases as a termination signal. The sequence of the first and second complementarity domains are, therefore, optionally modified to eliminate these tracts and promote the complete in vitro transcription of gRNAs, for instance through the use of A-G swaps as described in Briner, or A-U swaps. These and other similar modifications to the first and second complementarity domains are within the scope of the present disclosure.

[0111] Along with the first and second complementarity domains, Cas9 gRNAs typically include two or more additional duplexed regions that are involved in nuclease activity in vivo but not necessarily in vitro. (Nishimasu 2015). A first stem-loop one near the 3' portion of the second complementarity domain is referred to variously as the "proximal domain," (Cotta-Ramusino) "stem loop 1" (Nishimasu 2014 and 2015) and the "nexus" (Briner). One or more additional stem loop structures are generally present near the 3' end of the gRNA, with the number varying by species: *S. pyogenes* gRNAs typically include two 3' stem loops (for a total of four stem loop structures including the repeat:anti-repeat duplex), while *S. aureus* and other species have only one (for a total of three stem loop structures). A description of conserved stem loop structures (and gRNA structures more generally) organized by species is provided in Briner.

[0112] While the foregoing description has focused on gRNAs for use with Cas9, it should be appreciated that other RNA-guided nucleases have been (or may in the future be) discovered or invented which utilize gRNAs that differ in some ways from those described to this point. For instance, Cpf1 ("CRISPR from Prevotella and Francisella 1") is a recently discovered RNA-guided nuclease that does not require a tracrRNA to function. (Zetsche et al., 2015, Cell 163, 759-771 Oct. 22, 2015 (Zetsche I), incorporated by reference herein). A gRNA for use in a Cpf1 genome editing system generally includes a targeting domain and a complementarity domain (alternately referred to as a "handle"). It should also be noted that, in gRNAs for use with Cpf1, the targeting domain is usually present at or near the 3' end, rather than the 5' end as described above in connection with Cas9 gRNAs (the handle is at or near the 5' end of a Cpf1 gRNA).

[0113] Those of skill in the art will appreciate that, although structural differences may exist between gRNAs from different prokaryotic species, or between Cpf1 and Cas9 gRNAs, the principles by which gRNAs operate are generally consistent. Because of this consistency of opera-

tion, gRNAs can be defined, in broad terms, by their targeting domain sequences, and skilled artisans will appreciate that a given targeting domain sequence can be incorporated in any suitable gRNA, including a unimolecular or chimeric gRNA, or a gRNA that includes one or more chemical modifications and/or sequential modifications (substitutions, additional nucleotides, truncations, etc.). Thus, for economy of presentation in this disclosure, gRNAs may be described solely in terms of their targeting domain sequences.

[0114] More generally, skilled artisans will appreciate that some aspects of the present disclosure relate to systems, methods and compositions that can be implemented using multiple RNA-guided nucleases. For this reason, unless otherwise specified, the term gRNA should be understood to encompass any suitable gRNA that can be used with any RNA-guided nuclease, and not only those gRNAs that are compatible with a particular species of Cas9 or Cpf1. By way of illustration, the term gRNA can, in certain embodiments, include a gRNA for use with any RNA-guided nuclease occurring in a Class 2 CRISPR system, such as a type II or type V or CRISPR system, or an RNA-guided nuclease derived or adapted therefrom.

[0115] In some embodiments, the guide RNA used comprises a modification as compared to the standard gRNA scaffold. Such modifications may comprise, for example, chemical modifications of a part of the gRNA, e.g., of a nucleobase or backbone moiety. In some embodiments, such a modification may also include the presence of a DNA nucleotide within the gRNA, e.g., within or outside of the targeting domain. In some embodiments, the modification may include an extension of the gRNA scaffold, e.g., by addition of 1-100 nucleotides, including RNA and/or DNA nucleotides at the 3' or the 5' terminus of the guide RNA, e.g., at the terminus distal to the targeting domain.

[0116] Generally, gRNAs include the sugar group ribose, which is a 5-membered ring having an oxygen. Exemplary modified gRNAs can include, without limitation, replacement of the oxygen in ribose (e.g., with sulfur (S), selenium (Se), or alkylene, such as, e.g., methylene or ethylene); addition of a double bond (e.g., to replace ribose with cyclopentenyl or cyclohexenyl); ring contraction of ribose (e.g., to form a 4-membered ring of cyclobutane or oxetane); ring expansion of ribose (e.g., to form a 6- or 7-membered ring having an additional carbon or heteroatom, such as for example, anhydrohexitol, altritol, mannitol, cyclohexanyl, cyclohexenyl, and morpholino that also has a phosphoramidate backbone). Although the majority of sugar analog alterations are localized to the 2' position, other sites are amenable to modification, including the 4' position. In certain embodiments, a gRNA comprises a 4'-S, 4'-Se or a 4'-C-aminomethyl-2'-O-Me modification.

[0117] In certain embodiments, deaza nucleotides, e.g., 7-deaza-adenosine, can be incorporated into the gRNA. In certain embodiments, O- and N-alkylated nucleotides, e.g., N6-methyl adenosine, can be incorporated into the gRNA. In certain embodiments, one or more or all of the nucleotides in a gRNA are deoxynucleotides.

[0118] In certain embodiments, gRNAs as used herein may be modified or unmodified gRNAs. In certain embodiments, a gRNA may include one or more modifications. In certain embodiments, the one or more modifications may include a phosphorothioate linkage modification, a phosphorodithioate (PS2) linkage modification, a 2'-O-methyl

modification, or combinations thereof. In certain embodiments, the one or more modifications may be at the 5' end of the gRNA, at the 3' end of the gRNA, or combinations thereof.

[0119] In certain embodiments, a gRNA modification may comprise one or more phosphorodithioate (PS2) linkage modifications.

[0120] In some embodiments, a gRNA used herein includes one or more or a stretch of deoxyribonucleic acid (DNA) bases, also referred to herein as a "DNA extension." In some embodiments, a gRNA used herein includes a DNA extension at the 5' end of the gRNA, the 3' end of the gRNA, or a combination thereof. In certain embodiments, the DNA extension may be 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, 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, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 DNA bases long. For example, in certain embodiments, the DNA extension may be 1, 2, 3, 4, 5, 10, 15, 20, or 25 DNA bases long. In certain embodiments, the DNA extension may include one or more DNA bases selected from adenine (A), guanine (G), cytosine (C), or thymine (T). In certain embodiments, the DNA extension includes the same DNA bases. For example, the DNA extension may include a stretch of adenine (A) bases. In certain embodiments, the DNA extension may include a stretch of thymine (T) bases. In certain embodiments, the DNA extension includes a combination of different DNA bases. In certain embodiments, a DNA extension may comprise a sequence set forth in Table 3.

[0121] In certain embodiments, a gRNA used herein includes a DNA extension as well as one or more chemical modification, e.g., one or more phosphorothioate linkage modifications, one or more phosphorodithioate (PS2) linkage modifications, one or more 2'-O-methyl modifications, or combinations thereof. In certain embodiments, the one or more modifications may be at the 5' end of the gRNA, at the 3' end of the gRNA, or combinations thereof. In certain embodiments, a gRNA including a DNA extension may comprise a sequence set forth in Table 3 that includes a DNA extension. Without wishing to be bound by theory, it is contemplated that any DNA extension may be used herein, so long as it does not hybridize to the target nucleic acid being targeted by the gRNA. In some embodiments, a gRNA with a DNA extension exhibits an increase in editing at the target nucleic acid site relative to a gRNA which does not include such a DNA extension. In some embodiments, a gRNA with a DNA extension exhibits more effective delivery into NK cells and/or stem cells relative to a gRNA which does not include such an extension.

[0122] In some embodiments, a gRNA used herein includes one or more or a stretch of ribonucleic acid (RNA) bases, also referred to herein as an "RNA extension." In some embodiments, a gRNA used herein includes an RNA extension at the 5' end of the gRNA, the 3' end of the gRNA, or a combination thereof. In certain embodiments, the RNA extension may be 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, 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, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 RNA bases long. For example, in certain embodiments, the RNA extension may be 1, 2, 3, 4, 5, 10, 15, 20, or 25 RNA bases long. In certain embodiments, the RNA extension may include one or more RNA bases selected from adenine (rA), guanine (rG), cytosine (rC), or uracil (rU), in which the "r" represents RNA, 2'-hydroxy. In certain embodiments, the RNA extension includes the same RNA bases. For example, the RNA extension may include a stretch of adenine (rA) bases. In certain embodiments, the RNA extension includes a combination of different RNA bases. In certain embodiments, an RNA extension may comprise a sequence set forth in Table 3.

[0123] In certain embodiments, a gRNA used herein includes an RNA extension as well as one or more chemical modifications, e.g., one or more phosphorothioate linkage modifications, one or more phosphorodithioate (PS2) linkage modifications, one or more 2'-O-methyl modifications, or combinations thereof. In certain embodiments, the one or more modifications may be at the 5' end of the gRNA, at the 3' end of the gRNA, or combinations thereof. In certain embodiments, a gRNA including a RNA extension may comprise a sequence set forth in Table 3 that includes an RNA extension. gRNAs including an RNA extension at the 5' end of the gRNA may comprise a sequence disclosed herein. gRNAs including an RNA extension at the 3' end of the gRNA may comprise a sequence disclosed herein.

[0124] It is contemplated that gRNAs used herein may also include an RNA extension and a DNA extension. In certain embodiments, the RNA extension and DNA extension may both be at the 5' end of the gRNA, the 3' end of the gRNA, or a combination thereof. In certain embodiments, the RNA extension is at the 5' end of the gRNA and the DNA extension is at the 3' end of the gRNA. In certain embodiments, the RNA extension is at the 3' end of the gRNA and the DNA extension is at the 5' end of the gRNA.

[0125] In some embodiments, a gRNA which includes a modification, e.g., a DNA extension at the 5' end, and/or a chemical modification as disclosed herein, is complexed with a RNA-guided nuclease, e.g., an AsCpf1 nuclease, to form an RNP, which is then employed to edit a target cell, e.g., an NK cell.

[0126] Exemplary suitable 5' extensions for Cpf1 guide RNAs are provided in the table below:

TABLE3

gRNA 5' Extensions		5' modification
SEQ ID NO:	5' extension sequence	
	rCrUrUrUrU	+5 RNA
1	rArArGrArCrCrUrUrUrU	+10 RNA
2	rArUrGrUrGrUrUrUrUrGrUrCrArArArArGrArCrCrUrUrUrU	+25 RNA

TABLE3 -continued

gRNA 5' Extensions		
SEQ ID NO:	5' extension sequence	5' modification
3	rArGrGrCrCrArGrCrUrUrGrCrCrGrGrUrUrUrUrArGrUrCrGrUr+60 RNA GrCrUrGrCrUrUrCrArUrGrUrGrUrUrUrGrUrCrArArArGrAr CrCrUrUrUrU	
	CTTTT	+5 DNA
4	AAGACCTTTT	+10 DNA
5	ATGTGTTTGTCAAAAGACCTTT	+25 DNA
6	AGGCCAGCTTGCCGGTTTTAGTCGTGCTGCTCATGTGTT TTGTCAAAAGACCTTT	+60 DNA
7	TTTTGTCAAAAGACCTTT	+20 DNA
8	GCTTCATGTGTTTGTCAAAAGACCTTT	+30 DNA
9	GCCGGTTTTAGTCGTGCTGCTCATGTGTTTGTCAAAAG ACCTTT	+50 DNA
10	TAGTCGTGCTGCTTCATGTGTTTGTCAAAAGACCTTT	+40 DNA
11	C*C*GAAGTTTCTTCGGTTT	+20 DNA + 2xPS
12	T*T*TTCCGAAGTTTCTTCGGTTT	+25 DNA + 2xPS
13	A*A*CGCTTTTCCGAAGTTTCTTCGGTTT	+30 DNA + 2xPS
14	G*C*GTTGTTTCAACGCTTTCCGAAGTTTCTTCGGTTT	+41 DNA + 2xPS
15	G*G*CTCTTTGAAGCCTTTGCGTTGTTCAACGCTTT CCGAAGTTTCTTCGGTTT	+62 DNA + 2xPS
16	A*T*GTGTTTGTCAAAAGACCTTT	+25 DNA + 2xPS
17	AAAAAAAAAAAAAAAAAAAAAAA	+25 A
18	TTTTTTTTTTTTTTTTTTTT	+25 T
19	mA*mU*rGrUrGrUrUrUrUrGrUrCrArArArGrArCrUrUrUrU	+25 RNA + 2xPS
20	mA*mA*rA	PolyA RNA + 2xPS
21	mU*mU*rU	PolyU RNA + 2xPS

All bases are in upper case

Lowercase "r" represents RNA, 2'-hydroxy; bases not modified by an "r" are DNA

All bases are linked via standard phosphodiester bonds except as noted:

"*" represents phosphorothioate modification

"ps" represents phosphorothioate modification

[0127] Additional suitable gRNA modifications will be apparent to those of ordinary skill in the art based on the present disclosure. Suitable gRNA modifications include, for example, those described in PCT application PCT/US2018/054027, filed on Oct. 2, 2018, and entitled "MODIFIED CPF1 GUIDE RNA;" in PCT application PCT/US2015/000143, filed on Dec. 3, 2015, and entitled "GUIDE RNA WITH CHEMICAL MODIFICATIONS;" in PCT application PCT/US2016/026028, filed Apr. 5, 2016, and entitled "CHEMICALLY MODIFIED GUIDE RNAs FOR CRISPR/CAS-MEDIATED GENE REGULATION;" and in PCT application PCT/US2016/053344, filed on Sep. 23, 2016, and entitled "NUCLEASE-MEDIATED GENOME EDITING OF PRIMARY CELLS AND ENRICHMENT THEREOF;" the entire contents of each of which are incorporated herein by reference.

gRNA Design

[0128] Methods for selection and validation of target sequences as well as off-target analyses have been described previously, e.g., in Mali; Hsu; Fu et al., 2014 Nat biotechnol 32(3): 279-84, Heigwer et al., 2014 Nat methods 11(2):122-3; Bae et al. (2014) Bioinformatics 30(10): 1473-5; and Xiao A et al. (2014) Bioinformatics 30(8): 1180-1182. Each of these references is incorporated by reference herein. As a non-limiting example, gRNA design may involve the use of a software tool to optimize the choice of potential target sequences corresponding to a user's target sequence, e.g., to minimize total off-target activity across the genome. While off-target activity is not limited to cleavage, the cleavage efficiency at each off-target sequence can be predicted, e.g., using an experimentally-derived weighting scheme. These and other guide selection methods are described in detail in Maeder and Cotta-Ramusino.

[0129] In certain embodiments, one or more or all of the nucleotides in a gRNA are modified. Strategies for modifying a gRNA are described in WO2019/152519, published Aug. 8, 2019, the entire contents of which are expressly incorporated herein by reference.

[0130] Non-limiting examples of guide RNAs suitable for certain embodiments embraced by the present disclosure are provided herein, for example, in the Tables below. Those of ordinary skill in the art will be able to envision suitable guide RNA sequences for a specific nuclease, e.g., a Cas9 or Cpf-1 nuclease, from the disclosure of the targeting domain sequence, either as a DNA or RNA sequence. For example, a guide RNA comprising a targeting sequence consisting of RNA nucleotides would include the RNA sequence corresponding to the targeting domain sequence provided as a DNA sequence, and this contain uracil instead of thymidine nucleotides. For example, a guide RNA comprising a targeting domain sequence consisting of RNA nucleotides, and described by the DNA sequence TCTGCAGAAATGTTCCCCGT (SEQ ID NO:22) would have a targeting domain of the corresponding RNA sequence UCUGCAGAAAUGUUCCCCGU (SEQ ID NO:23). As will be apparent to the skilled artisan, such a targeting sequence would be linked to a suitable guide RNA scaffold, e.g., a crRNA scaffold sequence or a chimeric crRNA/tracerRNA scaffold sequence. Suitable gRNA scaffold sequences are known to those of ordinary skill in the art. For AsCpf1, for example, a suitable scaffold sequence comprises

the sequence UAAUUUCUACUCUUGUAGAU (SEQ ID NO:24), added to the 5'-terminus of the targeting domain. In the example above, this would result in a Cpf1 guide RNA of the sequence UAAUUUCUACUCUUGUAGAUUCUGCAGAAAUGUUCCCCGU (SEQ ID NO:25). Those of skill in the art would further understand how to modify such a guide RNA, e.g., by adding a DNA extension (e.g., in the example above, adding a 25-mer DNA extension as described herein would result, for example, in a guide RNA of the sequence ATGTGTTTTGTCAAAAGACCTTTrUrArArUrUrCrUrArCrUrUrGrUrArGrArUrUrCrUrGrCrArUrGrArUrCrUrUrCrCrCrGrU (SEQ ID NO:26), ATGTGTTTTGTCAAAAGACCTT-TrUrArArUrUrCrUrArCrUrUrGrUrArGrArUrArCrUrGrArCrArGrCrUrGrArArCrArGrGrUrArG (SEQ ID NO: 1164), or ATGTGTTTTGTCAAAAGACCTT-TrUrArArUrUrCrUrArCrUrUrGrUrArGrArUrUrGrArUrUrGrArUrGrUrGrArUrUrUrCrCrArCrCrU (SEQ ID NO: 1166). It will be understood that the exemplary targeting sequences provided herein are not limiting, and additional suitable sequences, e.g., variants of the specific sequences disclosed herein, will be apparent to the skilled artisan based on the present disclosure in view of the general knowledge in the art.

[0131] In some embodiments the gRNA for use in the disclosure is a gRNA targeting TGFbetaR2 (TGF β R2 gRNA). In some embodiments, the gRNA targeting TGF-betaR2 is one or more of the gRNAs described in Table 4.

TABLE 4

TGFbetaR2 gRNAs					
Name	gRNA Targeting Domain Sequence (DNA)	Length	SEQ ID NO:	Enzyme	
TGFBR24326	CAGGACGATGTGCAGCGGCC	20	540	AsCpf1 RR	
TGFBR24327	ACCGCACGTTCAGAAGTCGG	20	541	AsCpf1 RR	
TGFBR24328	ACAAACTGTGTAAATTGTG	20	542	AsCpf1 RR	
TGFBR24329	CAACTGTGTAAATTGTGA	20	543	AsCpf1 RR	
TGFBR24330	ACCTGTGACAACCAGAAATC	20	544	AsCpf1 RR	
TGFBR24331	CCTGTGACAACCAGAAATCC	20	545	AsCpf1 RR	
TGFBR24332	TGTGGCTCTCACAGATGGA	20	546	AsCpf1 RR	
TGFBR24333	TCTGTGAGAACGCCACAGGAA	20	547	AsCpf1 RR	
TGFBR24334	AAGCTCCCTACCATGACTT	20	548	AsCpf1 RR	
TGFBR24335	GAATAAAGTCATGGTAGGG	20	549	AsCpf1 RR	
TGFBR24336	AGAATAAAGTCATGGTAGGG	20	550	AsCpf1 RR	
TGFBR24337	CTACCATGACTTTATTCTGG	20	551	AsCpf1 RR	
TGFBR24338	TACCATGACTTTATTCTGG	20	552	AsCpf1 RR	
TGFBR24339	TAATGCACTTGGAGAAGCA	20	553	AsCpf1 RR	
TGFBR24340	TTCATAATGCACTTGGAGA	20	554	AsCpf1 RR	
TGFBR24341	AAGTGCATTATGAAGGAAAA	20	555	AsCpf1 RR	
TGFBR24342	TGTGTTCTGTAGCTCTGAT	20	556	AsCpf1 RR	
TGFBR24343	TGTAGCTCTGATGAGTGCAA	20	557	AsCpf1 RR	

TABLE4-continued

TGFbetaR2 gRNAs					
Name	gRNA Targeting Domain Sequence (DNA)	Length	SEQ ID NO:	Enzyme	
TGFBR24344	AGTGACAGGCATCAGCCTCC	20	558	AsCpf1 RR	
TGFBR24345	AGTGGTGGCAGGAGCTGAT	20	559	AsCpf1 RR	
TGFBR24346	AGGTTGAACTCAGCTTCTGC	20	560	AsCpf1 RR	
TGFBR24347	CAGGTTGAACTCAGCTTCTG	20	561	AsCpf1 RR	
TGFBR24348	ACCTGGAAACCGGCAAGAC	20	562	AsCpf1 RR	
TGFBR24349	CGTCTTGCCGGTTCCAGG	20	563	AsCpf1 RR	
TGFBR24350	GCGTCTTGCCGGTTCCAG	20	564	AsCpf1 RR	
TGFBR24351	TGAGCTTCCCGTCTTCCCG	20	565	AsCpf1 RR	
TGFBR24352	GCGAGCACTGTGCCATCATC	20	566	AsCpf1 RR	
TGFBR24353	GGATGATGGCACAGTGCTCG	20	567	AsCpf1 RR	
TGFBR24354	AGGATGATGGCACAGTGCTC	20	568	AsCpf1 RR	
TGFBR24355	CGTGTGCCAACACATCAAC	20	569	AsCpf1 RR	
TGFBR24356	GCTCAATGGGCAGCAGCTCT	20	570	AsCpf1 RR	
TGFBR24357	ACCAGGGTGTCCAGCTCAAT	20	571	AsCpf1 RR	
TGFBR24358	CACCAGGGTGTCCAGCTCAA	20	572	AsCpf1 RR	
TGFBR24359	CCACCAGGGTGTCCAGCTCA	20	573	AsCpf1 RR	
TGFBR24360	GCTTGGCATTAGACCTCA	20	574	AsCpf1 RR	
TGFBR24361	GAGCAGTTGAGACAGTGGC	20	575	AsCpf1 RR	
TGFBR24362	AGAGGCATACTCCTCATAGG	20	576	AsCpf1 RR	
TGFBR24363	CTATGAGGAGTATGCCCTTT	20	577	AsCpf1 RR	
TGFBR24364	AAGAGGCATACTCCTCATAG	20	578	AsCpf1 RR	
TGFBR24365	TATGAGGAGTATGCCCTTTG	20	579	AsCpf1 RR	
TGFBR24366	GATTGATGTCTGAGAAGATG	20	580	AsCpf1 RR	
TGFBR24367	CTCCTCAGCCGTAGGAAC	20	581	AsCpf1 RR	
TGFBR24368	GTTCCCTGACGGCTGAGGAGC	20	582	AsCpf1 RR	
TGFBR24369	GCTCCTCAGCCGTAGGAAC	20	583	AsCpf1 RR	
TGFBR24370	TGACGGCTGAGGAGCGGAAG	20	584	AsCpf1 RR	
TGFBR24371	TCTTCCGCTCCTCAGCCGTC	20	585	AsCpf1 RR	
TGFBR24372	AACTCCGTCTTCCGCTCCTC	20	586	AsCpf1 RR	
TGFBR24373	CAACTCCGTCTTCCGCTCCT	20	587	AsCpf1 RR	
TGFBR24374	CCAACTCCGTCTTCCGCTCC	20	588	AsCpf1 RR	
TGFBR24375	ACGCCAAGGGCAACCTACAG	20	589	AsCpf1 RR	
TGFBR24376	CGCCAAGGGCAACCTACAGG	20	590	AsCpf1 RR	
TGFBR24377	AGCTGATGACATGCCGCGTC	20	591	AsCpf1 RR	
TGFBR24378	GGGCGAGGGAGCTGCCAGC	20	592	AsCpf1 RR	
TGFBR24379	CGGGCGAGGGAGCTGCCAG	20	593	AsCpf1 RR	

TABLE4-continued

TGFbetaR2 gRNAs					
Name	gRNA Targeting Domain Sequence (DNA)	Length	SEQ ID NO:	Enzyme	
TGFBR24380	CCGGGCGAGGGAGCTGCCCA	20	594	AsCpf1 RR	
TGFBR24381	TCGCCCCGGGGATTGCTCAC	20	595	AsCpf1 RR	
TGFBR24382	ACATGGAGTGTGATCACTGT	20	596	AsCpf1 RR	
TGFBR24383	CAGTGATCACACTCCATGTG	20	597	AsCpf1 RR	
TGFBR24384	TGTGGGAGGCCAAGATGCC	20	598	AsCpf1 RR	
TGFBR24385	TGTGCACGATGGGCATCTTG	20	599	AsCpf1 RR	
TGFBR24386	CGAGGGATATTGGAGCTTTG	20	600	AsCpf1 RR	
TGFBR24387	ATATCCTCGTGAAGAACGAC	20	601	AsCpf1 RR	
TGFBR24388	GACGCAGGAAAGCCCAAAG	20	602	AsCpf1 RR	
TGFBR24389	CTGCGTCTGGACCCTACTCTG	20	603	AsCpf1 RR	
TGFBR24390	TGCGTCTGGACCCTACTCTG	20	604	AsCpf1 RR	
TGFBR24391	CAGACAGAGTAGGGTCCAGA	20	605	AsCpf1 RR	
TGFBR24392	GCCAGCACGATCCCACCGCA	20	606	AsCpf1 RVR	
TGFBR24393	AAGGAAAAAAAAGCCTGG	20	607	AsCpf1 RVR	
TGFBR24394	ACACCAGCAATCCTGACTTG	20	608	AsCpf1 RVR	
TGFBR24395	ACTAGCAACAAGTCAGGATT	20	609	AsCpf1 RVR	
TGFBR24396	GCAAATCCCAGTGGTGGCAG	20	610	AsCpf1 RVR	
TGFBR24397	TGTCATCATCATCTTCTACT	20	611	AsCpf1 RVR	
TGFBR24398	GACCTCAGCAAAGCGACCTT	20	612	AsCpf1 RVR	
TGFBR24399	AGGCCAAGCTGAAGCAGAAC	20	613	AsCpf1 RVR	
TGFBR24400	AGGAGTATGCCCTCTTGGAAAG	20	614	AsCpf1 RVR	
TGFBR24401	CCTCTTGGAAAGACAGAGAAAG	20	615	AsCpf1 RVR	
TGFBR24402	TTCTCATGCTTCAGATTGAT	20	616	AsCpf1 RVR	
TGFBR24403	CTCGTGAAGAACGACCTAAC	20	617	AsCpf1 RVR	
TGFbR2036	GGCCGCTGCACATCGTCCTG	20	618	SpyCas9	
TGFbR2037	GCGGGGTCTGCCATGGTCG	20	619	SpyCas9	
TGFbR2038	AGTTGCTCATGCAGGATTTC	20	620	SpyCas9	
TGFbR2039	CCAGAATAAAGTCATGGTAG	20	621	SpyCas9	
TGFbR2040	CCCCTACCATGACTTTATTC	20	622	SpyCas9	
TGFbR2041	AAGTCATGGTAGGGGAGCTT	20	623	SpyCas9	
TGFbR2042	AGTCATGGTAGGGGAGCTTG	20	624	SpyCas9	
TGFbR2043	ATTGCACTCATCAGAGCTAC	20	625	SpyCas9	
TGFbR2044	CCTAGAGTGAAGAGATTCAT	20	626	SpyCas9	
TGFbR2045	CCAATGAATCTCTTCACTCT	20	627	SpyCas9	
TGFbR2046	AAAGTCATGGTAGGGGAGCT	20	628	SpyCas9	
TGFbR2047	GTGAGCAATCCCCGGCGA	20	629	SpyCas9	

TABLE4-continued

TGFbetaR2 gRNAs					
Name	gRNA Targeting Domain Sequence (DNA)	Length	SEQ ID NO:	Enzyme	
TGFbR2048	GTCGTTCTTCACGAGGGATAT	20	630	SpyCas9	
TGFbR2049	GCCCGCGTCAGGTACTCCTGT	20	631	SpyCas9	
TGFbR2050	GACGCGGCATGTCATCAGCT	20	632	SpyCas9	
TGFbR2051	GCTTCTGCTGCCGGTTAACG	20	633	SpyCas9	
TGFbR2052	GTGGATGACCTGGCTAACAG	20	634	SpyCas9	
TGFbR2053	GTGATCACACTCCATGTGGG	20	635	SpyCas9	
TGFbR2054	GCCCATTGAGCTGGACACCC	20	636	SpyCas9	
TGFbR2055	GCGGTCATCTTCCAGGATGA	20	637	SpyCas9	
TGFbR2056	GGGAGCTGCCAGCTTGC	20	638	SpyCas9	
TGFbR2057	GTTGATGTTGGCACACG	20	639	SpyCas9	
TGFbR2058	GGCATCTGGGCCTCCCACA	20	640	SpyCas9	
TGFbR2059	GCGGCATGTCATCAGCTGG	20	641	SpyCas9	
TGFbR2060	GCTCCTCAGCCGTAGAAC	20	642	SpyCas9	
TGFbR2061	GCTGGTGTATATTCTGATG	20	643	SpyCas9	
TGFbR2062	CCGACTTCTGAACGTGCGG	20	644	SpyCas9	
TGFbR2063	TGCTGGCGATACTCGTCCAC	20	645	SpyCas9	
TGFbR2064	CCCGACTTCTGAACGTGCGG	20	646	SpyCas9	
TGFbR2065	CCACCGCACGTTCAGAAC	20	647	SpyCas9	
TGFbR2066	TCACCCGACTTCTGAACGTG	20	648	SpyCas9	
TGFbR2067	CCCACCGCACGTTCAGAA	20	649	SpyCas9	
TGFbR2068	CGAGCAGCGGGGCTGCCAT	20	650	SpyCas9	
TGFbR2069	ACGAGCAGCGGGGCTGCCA	20	651	SpyCas9	
TGFbR2070	AGCGGGGCTGCCATGGTC	20	652	SpyCas9	
TGFbR2071	CCTGAGCAGCCCCGACCCA	20	653	SpyCas9	
TGFbR2072	CCATGGGTGGGGCTGCTC	20	654	SpyCas9	
TGFbR2073	AACGTGCGGTGGATCGTGC	20	655	SpyCas9	
TGFbR2074	GGACGATGTGCAGCGGCCAC	20	656	SpyCas9	
TGFbR2075	GTCCACAGGACGATGTGCAG	20	657	SpyCas9	
TGFbR2076	CATGGGTGGGGCTGCTCA	20	658	SpyCas9	
TGFbR2077	CAGCGGGGCTGCCATGGGT	20	659	SpyCas9	
TGFbR2078	ATGGGTGGGGCTGCTCAG	20	660	SpyCas9	
TGFbR2079	CGGGGTCTGCCATGGTCGG	20	661	SpyCas9	
TGFbR2080	AGGAAGTCTGTGGCTGTA	20	662	SpyCas9	
TGFbR2081	CTCCATCTGTGAGAACCCAC	20	663	SpyCas9	
TGFbR2082	ATGATAGTCACTGACAACAA	20	664	SpyCas9	
TGFbR2083	GATGCTGCAGTTGCTCATGC	20	665	SpyCas9	

TABLE4-continued

TGFbetaR2 gRNAs					
Name	gRNA Targeting Domain Sequence (DNA)	Length	SEQ ID NO:	Enzyme	
TGFbR2084	ACAGGCCACACAGACTTCCTG	20	666	SpyCas9	
TGFbR2085	GAAGGCCACAGGAAGTCTGTG	20	667	SpyCas9	
TGFbR2086	TTCCCTGTGGCTTCTCACAGA	20	668	SpyCas9	
TGFbR2087	CTGTGGCTTCTCACAGATGG	20	669	SpyCas9	
TGFbR2088	TCACAAAATTACACAGTTG	20	670	SpyCas9	
TGFbR2089	GACAACATCATCTTCTCAGA	20	671	SpyCas9	
TGFbR2090	TCCAGAATAAAGTCATGGTA	20	672	SpyCas9	
TGFbR2091	GGTAGGGGAGCTTGGGTCA	20	673	SpyCas9	
TGFbR2092	TTCTCCAAAGTGCATTATGA	20	674	SpyCas9	
TGFbR2093	CATCTTCCAGAATAAAAGTCA	20	675	SpyCas9	
TGFbR2094	CACATGAAGAAAAGTCTCAC	20	676	SpyCas9	
TGFbR2095	TTCCAGAATAAAAGTCATGGT	20	677	SpyCas9	
TGFbR2096	TTTTCCCTTCATAATGCACTT	20	678	SpyCas9	
TGFBR24024	CACAGTTGTGAAACTTGAC	20	679	AsCpf1	
TGFBR24039	CCCAACTCCGTCTTCCGCTC	20	680	AsCpf1	
TGFBR24040	GGCTTCCCTCGCGTCTGGAC	20	681	AsCpf1	
TGFBR24036	CTGAGGTCTATAAGGCCAAG	20	682	AsCpf1	
TGFBR24026	TGATGTGAGATTTCCACCT	20	683	AsCpf1	
TGFBR38402	TGATGTGAGATTTCCACCTG	21	1173	AsCpf1	
TGFBR24038	CCTATGAGGAGTATGCCTCT	20	684	AsCpf1	
TGFBR24033	AAGTGACAGGCATCAGCCTC	20	685	AsCpf1	
TGFBR24028	CCATGACCCCCAACGCTCCCCT	20	686	AsCpf1	
TGFBR24031	CTTCATAATGCACTTGGAG	20	687	AsCpf1	
TGFBR24032	TTCATGTGTTCCCTGTAGCTC	20	688	AsCpf1	
TGFBR24029	TTCTGGAAGATGCTGCTTCT	20	689	AsCpf1	
TGFBR24035	CCCACCAGGGTGTCCAGCTC	20	690	AsCpf1	
TGFBR24037	AGACAGTGGCAGTCAAGATC	20	691	AsCpf1	
TGFBR24041	CCTGCGTCTGGACCTACTC	20	692	AsCpf1	
TGFBR24025	CACAACTGTGTAAATTGT	20	693	AsCpf1	
TGFBR24030	GAGAAGCAGCATCTTCCAGA	20	694	AsCpf1	
TGFBR24027	TGGTTGTCACAGGTGGAAAA	20	695	AsCpf1	
TGFBR24034	CCAGGTTGAACTCAGCTTCT	20	696	AsCpf1	
TGFBR24043	ATCACAAAATTACACAGTTG	21	697	SauCas9	
TGFBR24065	GGCATCAGCCTCCTGCCACCA	21	698	SauCas9	
TGFBR24110	GTTAGCCAGGTCACTCACAGA	21	699	SauCas9	
TGFBR24099	GCTGGGCAGCTCCCTCGCCCG	21	700	SauCas9	

TABLE4-continued

TGFbetaR2 gRNAs					
Name	gRNA Targeting Domain Sequence (DNA)	Length	SEQ ID NO:	Enzyme	
TGFBR24064	CAGGAGGCTGATGCCGTGTCAC	21	701	SauCas9	
TGFBR24094	GAGGAGCGGAAGACGGAGTTG	21	702	SauCas9	
TGFBR24108	CGTCTGGACCCTACTCTGTCT	21	703	SauCas9	
TGFBR24058	TTTTTCCTTCATAATGCACCTT	21	704	SauCas9	
TGFBR24075	CCATTGAGCTGGACACCCCTGG	21	705	SauCas9	
TGFBR24057	CTTCTCCAAAGTCATTATGAA	21	706	SauCas9	
TGFBR24103	GCCCAAGATGCCATCGTGCA	21	707	SauCas9	
TGFBR24060	TCATGTGTTCTGTAGCTCTG	21	708	SauCas9	
TGFBR24048	GTGATGCTGCAGTTGCTCATG	21	709	SauCas9	
TGFBR24087	TCTCATGCTTCAGATTGATGT	21	710	SauCas9	
TGFBR24081	TCCCTATGAGGAGTATGCCTC	21	711	SauCas9	
TGFBR24044	CATCACAAAATTACACAGTT	21	712	SauCas9	
TGFBR24077	ATTGAGCTGGACACCCCTGGTG	21	713	SauCas9	
TGFBR24080	CAGTCAGATCTTCCCTATG	21	714	SauCas9	
TGFBR24046	AGGATTCTGGTTGTACAGG	21	715	SauCas9	
TGFBR24101	TCCACAGTGATCACACTCCAT	21	716	SauCas9	
TGFBR24079	AGCAGAACACTTCAGAGCAGT	21	717	SauCas9	
TGFBR24072	CCGGCAAGACGCGGAAGCTCA	21	718	SauCas9	
TGFBR24074	GATGTCAGAGCGGTATCTTC	21	719	SauCas9	
TGFBR24062	TCATTGCACTCATCAGAGCTA	21	720	SauCas9	
TGFBR24054	CTTCCAGAATAAAAGTCATGGT	21	721	SauCas9	
TGFBR24045	AGATTTCCACCTGTGACAAC	21	722	SauCas9	
TGFBR24049	ACTGCAGCATCACCTCCATCT	21	723	SauCas9	
TGFBR24098	AGCTGGGCAGCTCCCTCGCCC	21	724	SauCas9	
TGFBR24090	TGACGGCTGAGGGCGGAAGA	21	725	SauCas9	
TGFBR24076	CATTGAGCTGGACACCCCTGGT	21	726	SauCas9	
TGFBR24078	AGCAAAGCGACCTTCCCCAC	21	727	SauCas9	
TGFBR24067	CGCGTTAACCGGCAGCAGAAG	21	728	SauCas9	
TGFBR24063	GAAATATGACTAGCAACAAGT	21	729	SauCas9	
TGFBR24107	AGACAGAGTAGGGTCCAGACG	21	730	SauCas9	
TGFBR24047	CAGGATTCTGGTTGTACAG	21	731	SauCas9	
TGFBR24096	CTCCTGTAGGGTGCCTTGGC	21	732	SauCas9	
TGFBR24105	ACAGAGTAGGGTCCAGACGCA	21	733	SauCas9	
TGFBR24056	GCTTCTCCAAAGTCATTATG	21	734	SauCas9	
TGFBR24068	GCAGCAGAACGAGTTCAAC	21	735	SauCas9	
TGFBR24093	TGAGGAGCGGAAGACGGAGTT	21	736	SauCas9	

TABLE4-continued

TGFbetaR2 gRNAs					
Name	gRNA Targeting Domain Sequence (DNA)	Length	SEQ ID NO:	Enzyme	
TGFBR24055	CTTTGGAGAAGCAGCATCTTC	21	737	SauCas9	
TGFBR24053	CTCCCCTACCATGACTTTATT	21	738	SauCas9	
TGFBR24106	GACAGAGTAGGGTCCAGACGC	21	739	SauCas9	
TGFBR24092	CTGAGGGAGCGGAAGACGGAGT	21	740	SauCas9	
TGFBR24102	GGGCATCTGGGCCTCCCACA	21	741	SauCas9	
TGFBR24082	CCAAGAGGCATACTCCCTCATA	21	742	SauCas9	
TGFBR24051	AGAATGACGAGAACATAACAC	21	743	SauCas9	
TGFBR24097	CCTGACGCGGCATGTCTCATCG	21	744	SauCas9	
TGFBR24073	AGCGAGCACTGTGCCATCATC	21	745	SauCas9	
TGFBR24104	GCAGGTTAGGTCGTTCTTCAC	21	746	SauCas9	
TGFBR24050	ACCTCCATCTGTGAGAACCCA	21	747	SauCas9	
TGFBR24052	TAAAGTCATGGTAGGGGAGCT	21	748	SauCas9	
TGFBR24061	TCAGAGCTACAGGAACACATG	21	749	SauCas9	
TGFBR24086	TCTCAGACATCAATCTGAAGC	21	750	SauCas9	
TGFBR24066	CATCAGCCTCCTGCCACCAC	21	751	SauCas9	
TGFBR24089	CGCTCCTCAGCCGTAGAAC	21	752	SauCas9	
TGFBR24071	AACCTGGAAACCGGCAAGAC	21	753	SauCas9	
TGFBR24095	TCCACGCCAAGGGCAACCTAC	21	754	SauCas9	
TGFBR24100	GAGGTGAGCAATCCCCGGGC	21	755	SauCas9	
TGFBR24069	CAGCAGAACGCTGAGTTCAACC	21	756	SauCas9	
TGFBR24083	TCCAAGAGGCATACTCCTCAT	21	757	SauCas9	
TGFBR24070	AGCAGAACGCTGAGTTCAACCT	21	758	SauCas9	
TGFBR24088	CCAGTTCTGACGGCTGAGGA	21	759	SauCas9	
TGFBR24085	AGGAGTATGCCCTTGGAAAGA	21	760	SauCas9	
TGFBR24084	TTCAAGAGGCATACTCCTCA	21	761	SauCas9	
TGFBR24042	CAACTGTGTAAATTTGTGAT	21	762	SauCas9	
TGFBR24059	TGAAGGAAAAAAAAAGCCTG	21	763	SauCas9	
TGFBR24091	CGTCTTCCGCTCAGCCGT	21	764	SauCas9	
TGFBR24109	CCAGGTCACTCACAGACAGAG	21	765	SauCas9	
TGFBR2736	GCCTAGAGTGAAGAGATTCA	21	766	SpyCas9	
TGFBR2737	GTTCTCCAAAAGTCATTATGA	21	767	SpyCas9	
TGFBR2738	GCATCTCCAGAATAAGTCA	21	768	SpyCas9	

[0132] In some embodiments the gRNA for use in the disclosure is a gRNA targeting CISH (CISH gRNA). In

some embodiments, the gRNA targeting CISH is one or more of the gRNAs described in Table 5.

TABLE 5

Name	gRNA Targeting Domain Sequence (DNA)	CISH gRNAs			
		Length	SEQ ID NO:		Enzyme
CISH0873	CAACCGTCTGGTGGCCGACG	20	769		SpyCas9
CISH0874	CAGGATCGGGCTGTCGCTT	20	770		SpyCas9
CISH0875	T CGGGCCTCGCTGGCCGTAA	20	771		SpyCas9
CISH0876	GAGGTAGTCGCCATGCGCC	20	772		SpyCas9
CISH0877	CAGGTGTTGTCGGGCCTCGC	20	773		SpyCas9
CISH0878	GGAGGTAGTCGCCATGCGC	20	774		SpyCas9
CISH0879	GGCATACTCAATGCGTACAT	20	775		SpyCas9
CISH0880	CCGCCTTGTCAACCGTC	20	776		SpyCas9
CISH0881	AGGATCGGGCTGTCGCTTC	20	777		SpyCas9
CISH0882	CCTTGTCAACCGTCTGG	20	778		SpyCas9
CISH0883	TACTCAATGCGTACATTGGT	20	779		SpyCas9
CISH0884	GGGTTCCATTACGGCCAGCG	20	780		SpyCas9
CISH0885	GGCACTGCTCTGCGTACAA	20	781		SpyCas9
CISH0886	GGTTGATGACAAGGGGGCAC	20	782		SpyCas9
CISH0887	TGCTGGGGCCTTCCTCGAGG	20	783		SpyCas9
CISH0888	TTGCTGGCTGTGGAGCGGAC	20	784		SpyCas9
CISH0889	TTCTCCTACCTTCGGGAATC	20	785		SpyCas9
CISH0890	GACTGGCTTGGCAGTTCCA	20	786		SpyCas9
CISH0891	CATGCAGCCCTTGCGCTG	20	787		SpyCas9
CISH0892	AGCAAAGGACGAGGTCTAGA	20	788		SpyCas9
CISH0893	GCCTGCTGGGCCTTCCTCG	20	789		SpyCas9
CISH0894	CAGACTCACCAAGATTCCCGA	20	790		SpyCas9
CISH0895	ACCTCGTCCTTGCTGGCTG	20	791		SpyCas9
CISH0896	CTCACCAAGATTCCCGAAGGT	20	792		SpyCas9
CISH7048	TACGCAGAACAGCAGTGGCCGC	20	793		AsCpf1
CISH7049	AGGTGTACAGCAGTGGCTGG	20	794		AsCpf1
CISH7050	GGTGTACAGCAGTGGCTGGT	20	795		AsCpf1
CISH7051	CGGATGTGGTCAGCCTTGT	20	796		AsCpf1
CISH7052	CACTGACAGCGTGAACAGGT	20	797		AsCpf1
CISH7053	ACTGACAGCGTGAACAGGT	20	798		AsCpf1
CISH7054	GCTCACTCTGTCTGGGCT	20	799		AsCpf1
CISH7055	CTGGCTGTGGAGCGGACTGG	20	800		AsCpf1
CISH7056	GCTCTGACTGTACGGGGCAA	20	801	RR	AsCpf1 RR
CISH7057	AGCTCTGACTGTACGGGGCA	20	802	RR	AsCpf1 RR
CISH7058	ACAGTACCCCTTCCAGCTCT	20	803	RR	AsCpf1 RR

TABLE5-continued

CISH gRNAs					
Name	gRNA Targeting Domain Sequence (DNA)	Length	SEQ ID NO:	Enzyme	
CISH7059	CGTCGGCCACCAGACGGTTG	20	804	AsCpf1	RR
CISH7060	CCAGCCACTGCTGTACACCT	20	805	AsCpf1	RR
CISH7061	ACCCCGGCCCTGCCTATGCC	20	806	AsCpf1	RR
CISH7062	GGTATCAGCAGTGCAGGAGG	20	807	AsCpf1	RR
CISH7063	GATGTGGTCAGCCTTGTGCA	20	808	AsCpf1	RR
CISH7064	GGATGTGGTCAGCCTTGTGCA	20	809	AsCpf1	RR
CISH7065	GGCCACGCATCCTGGCCTT	20	810	AsCpf1	RR
CISH7066	GAAAGGCCAGGATGCGTGGC	20	811	AsCpf1	RR
CISH7067	ACTGCTTGTCCAGGCCACGC	20	812	AsCpf1	RR
CISH7068	TCTGGACTCCAAGTGCTTGT	20	813	AsCpf1	RR
CISH7069	GTCTGGACTCCAAGTGCTTGT	20	814	AsCpf1	RR
CISH7070	GCTTCCGTCTGGACTCCAAC	20	815	AsCpf1	RR
CISH7071	GACGGAAGCTGGAGTCGGCA	20	816	AsCpf1	RR
CISH7072	CGCTGTCAGTGAAAACACT	20	817	AsCpf1	RR
CISH7073	CTGACAGCGTGAACAGGTAG	20	818	AsCpf1	RR
CISH38401	ACTGACAGCGTGAACAGGTAG	21	1174	AsCpf1	RR
CISH7074	TTACGGCCAGCGAGGCCGA	20	819	AsCpf1	RR
CISH7075	ATTACGGCCAGCGAGGCCGA	20	820	AsCpf1	RR
CISH7076	GGAATCTGGTGAGTCTGAGG	20	821	AsCpf1	RR
CISH7077	CCCTCAGACTCACCAGATT	20	822	AsCpf1	RR
CISH7078	CGAAGGTAGGAGAACAGGTCTT	20	823	AsCpf1	RR
CISH7079	GAAGGTAGGAGAACAGGTCTG	20	824	AsCpf1	RR
CISH7080	GCACCTTGGCTCACTCTCT	20	825	AsCpf1	RR
CISH7081	TCGAGGAGGTGGCAGAGGGT	20	826	AsCpf1	RR
CISH7082	TGGAACTGCCAAGCCAGTC	20	827	AsCpf1	RR
CISH7083	AGGGACGGGGCCCCACAGGGG	20	828	AsCpf1	RR
CISH7084	GGGACGGGGCCCCACAGGGG	20	829	AsCpf1	RR
CISH7085	CTCCACAGCCAGCAAAGGAC	20	830	AsCpf1	RR
CISH7086	CAGCCAGCAAAGGACGAGGT	20	831	AsCpf1	RR
CISH7087	CTGCCTTCTAGACCTCGTCC	20	832	AsCpf1	RR
CISH7088	CCTAAGGAGGATGCGCCTAG	20	833	AsCpf1	RVR
CISH7089	TGGCCTCCTGCAGTGCCTGAT	20	834	AsCpf1	RVR
CISH7090	AGCAGTGCAGGAGGCCACAT	20	835	AsCpf1	RVR
CISH7091	CCGACTCCAGCTCCGTCTG	20	836	AsCpf1	RVR
CISH7092	GGGGTTCCATTACGGCCAGC	20	837	AsCpf1	RVR
CISH7093	CACAGCAGATCCTCCTCTGG	20	838	AsCpf1	RVR

TABLE5-continued

CISH gRNAs				
Name	gRNA Targeting Domain Sequence (DNA)	Length	SEQ ID NO:	Enzyme
CISH7094	ATTGCCCGTACAGTCAGAG	21	839	SauCas9
CISH7095	CCCGTACAGTCAGAGCTGGA	21	840	SauCas9
CISH7096	TGGTGGAGGAGCAGGCAGTG	21	841	SauCas9
CISH7097	TCCTTAGGCATAGGCAGGGC	21	842	SauCas9
CISH7098	CGGCCCTGCCTATGCCTAAG	21	843	SauCas9
CISH7099	TAGGCATAGGCAGGGCCGGG	21	844	SauCas9
CISH7100	AGGCAGGGCCGGGTGGGAG	21	845	SauCas9
CISH7101	GCAGGATCGGGCTGTCGCT	21	846	SauCas9
CISH7102	CTGCACAAGGCTGACCACAT	21	847	SauCas9
CISH7103	TGCACAAGGCTGACCACATC	21	848	SauCas9
CISH7104	CTGACCACATCCGGAAAGGC	21	849	SauCas9
CISH7105	GGCCACGCATCCTGGCCTTT	21	850	SauCas9
CISH7106	GCGTGGCCTGGACAAGCAGT	21	851	SauCas9
CISH7107	GACAAGCAGTTGGAGTCCAG	21	852	SauCas9
CISH7108	GTTGGAGTCCAGACGGAAAGC	21	853	SauCas9
CISH7109	ATGCGTACATTGGTGGGCC	21	854	SauCas9
CISH7110	TGGCCCCACCAATGTACGCA	21	855	SauCas9
CISH7111	GCTACCTGTTCACGCTGTCA	21	856	SauCas9
CISH7112	TGACAGCGTGACACAGGTAGC	21	857	SauCas9
CISH7113	GTCGGGCCTCGCTGGCCGTA	21	858	SauCas9
CISH7114	GCACTTGCCTAGGCTGGTAT	21	859	SauCas9
CISH7115	GGGAATCTGGTGAGTCTGAG	21	860	SauCas9
CISH7116	CTCACCAAGATTCCCGAAGGT	21	861	SauCas9
CISH7117	CTCCTACCTTCGGAATCTG	21	862	SauCas9
CISH7118	CAAGACCTTCTCCTACCTTC	21	863	SauCas9
CISH7119	CCAAGACCTTCTCCTACCTT	21	864	SauCas9
CISH7120	GCCAAGACCTTCTCCTACCT	21	865	SauCas9
CISH7121	TATGCACAGCAGATCCTCCT	21	866	SauCas9
CISH7122	CAAAGGTGCTGGACCCAGAG	21	867	SauCas9
CISH7123	GGCTCACTCTCTGTCTGGC	21	868	SauCas9
CISH7124	AGGGTACCCAGCCCCAGACA	21	869	SauCas9
CISH7125	AGAGGGTACCCAGCCCCAGA	21	870	SauCas9
CISH7126	GTACCCTCTGCCACCTCCTC	21	871	SauCas9

TABLE5-continued

CISH gRNAs					
Name	gRNA Targeting Domain Sequence (DNA)	Length	SEQ ID NO:	Enzyme	
CISH7127	CCTTCCTCGAGGAGGTGGCA	21	872	SauCas9	
CISH7128	ATGACTGGCTTGGGCAGTTC	21	873	SauCas9	
CISH7129	GCCCCCTGTGGGCCCGTCC	21	874	SauCas9	
CISH7130	AGGACGAGGTCTAGAAGGCA	21	875	SauCas9	

RNA-Guided Nucleases

[0133] RNA-guided nucleases according to the present disclosure include, but are not limited to, naturally-occurring Class 2 CRISPR nucleases such as Cas9, and Cpf1, as well as other nucleases derived or obtained therefrom. In functional terms, RNA-guided nucleases are defined as those nucleases that: (a) interact with (e.g., complex with) a gRNA; and (b) together with the gRNA, associate with, and optionally cleave or modify, a target region of a DNA that includes (i) a sequence complementary to the targeting domain of the gRNA and, optionally, (ii) an additional sequence referred to as a “protospacer adjacent motif,” or “PAM,” which is described in greater detail below. As the following examples will illustrate, RNA-guided nucleases can be defined, in broad terms, by their PAM specificity and cleavage activity, even though variations may exist between individual RNA-guided nucleases that share the same PAM specificity or cleavage activity. Skilled artisans will appreciate that some aspects of the present disclosure relate to systems, methods and compositions that can be implemented using any suitable RNA-guided nuclease having a certain PAM specificity and/or cleavage activity. For this reason, unless otherwise specified, the term RNA-guided nuclease should be understood as a generic term, and not limited to any particular type (e.g. Cas9 vs. Cpf1), species (e.g. *S. pyogenes* vs. *S. aureus*) or variation (e.g., full-length vs. truncated or split; naturally-occurring PAM specificity vs. engineered PAM specificity, etc.) of RNA-guided nuclease.

[0134] The PAM sequence takes its name from its sequential relationship to the “protospacer” sequence that is complementary to gRNA targeting domains (or “spacers”). Together with protospacer sequences, PAM sequences define target regions or sequences for specific RNA-guided nuclease/gRNA combinations.

[0135] Various RNA-guided nucleases may require different sequential relationships between PAMs and protospacers. For example, Cas9 nucleases recognize PAM sequences that are 3' of the protospacer, while

[0136] Cpf1, on the other hand, generally recognizes PAM sequences that are 5' of the protospacer.

[0137] In addition to recognizing specific sequential orientations of PAMs and protospacers, RNA-guided nucleases can also recognize specific PAM sequences. *S. aureus* Cas9, for instance, recognizes a PAM sequence of NNGRRT or NNGRRV, wherein the N residues are immediately 3' of the region recognized by the gRNA targeting domain. *S. pyogenes* Cas9 recognizes NGG PAM sequences. And *F. novicida* Cpf1 recognizes a TTN PAM sequence. PAM

sequences have been identified for a variety of RNA-guided nucleases, and a strategy for identifying novel PAM sequences has been described by Shmakov et al., 2015, Molecular Cell 60, 385-397, Nov. 5, 2015. It should also be noted that engineered RNA-guided nucleases can have PAM specificities that differ from the PAM specificities of reference molecules (for instance, in the case of an engineered RNA-guided nuclease, the reference molecule may be the naturally occurring variant from which the RNA-guided nuclease is derived, or the naturally occurring variant having the greatest amino acid sequence homology to the engineered RNA-guided nuclease).

[0138] In addition to their PAM specificity, RNA-guided nucleases can be characterized by their DNA cleavage activity: naturally-occurring RNA-guided nucleases typically form DSBs in target nucleic acids, but engineered variants have been produced that generate only SSBs (discussed above) Ran & Hsu, et al., Cell 154(6), 1380-1389, Sep. 12, 2013 (Ran), incorporated by reference herein), or that do not cut at all.

Cas9

[0139] Crystal structures have been determined for *S. pyogenes* Cas9 (Jinek 2014), and for *S. aureus* Cas9 in complex with a unimolecular guide RNA and a target DNA (Nishimasu 2014; Anders 2014; and Nishimasu 2015).

[0140] A naturally occurring Cas9 protein comprises two lobes: a recognition (REC) lobe and a nuclease (NUC) lobe; each of which comprise particular structural and/or functional domains. The REC lobe comprises an arginine-rich bridge helix (BH) domain, and at least one REC domain (e.g. a REC1 domain and, optionally, a REC2 domain). The REC lobe does not share structural similarity with other known proteins, indicating that it is a unique functional domain. While not wishing to be bound by any theory, mutational analyses suggest specific functional roles for the BH and REC domains: the BH domain appears to play a role in gRNA:DNA recognition, while the REC domain is thought to interact with the repeat:anti-repeat duplex of the gRNA and to mediate the formation of the Cas9/gRNA complex.

[0141] The NUC lobe comprises a RuvC domain, an HNH domain, and a PAM-interacting (PI) domain. The RuvC domain shares structural similarity to retroviral integrase superfamily members and cleaves the non-complementary (i.e. bottom) strand of the target nucleic acid. It may be formed from two or more split RuvC motifs (such as RuvC I, RuvCII, and RuvCIII in *S. pyogenes* and *S. aureus*). The HNH domain, meanwhile, is structurally similar to HNN

endonuclease motifs, and cleaves the complementary (i.e. top) strand of the target nucleic acid. The PI domain, as its name suggests, contributes to PAM specificity.

[0142] While certain functions of Cas9 are linked to (but not necessarily fully determined by) the specific domains set forth above, these and other functions may be mediated or influenced by other Cas9 domains, or by multiple domains on either lobe. For instance, in *S. pyogenes* Cas9, as described in Nishimasu 2014, the repeat:antirepeat duplex of the gRNA falls into a groove between the REC and NUC lobes, and nucleotides in the duplex interact with amino acids in the BH, PI, and REC domains. Some nucleotides in the first stem loop structure also interact with amino acids in multiple domains (PI, BH and REC1), as do some nucleotides in the second and third stem loops (RuvC and PI domains).

Cpf1

[0143] The crystal structure of *Acidaminococcus* sp. Cpf1 in complex with crRNA and a double-stranded (ds) DNA target including a TTTN PAM sequence has been solved by Yamano et al. (Cell. 2016 May 5; 165(4): 949-962 (Yamano), incorporated by reference herein). Cpf1, like Cas9, has two lobes: a REC (recognition) lobe, and a NUC (nuclease) lobe. The REC lobe includes REC1 and REC2 domains, which lack similarity to any known protein structures. The NUC lobe, meanwhile, includes three RuvC domains (RuvC-I, -II and -III) and a BH domain. However, in contrast to Cas9, the Cpf1 REC lobe lacks an HNH domain, and includes other domains that also lack similarity to known protein structures: a structurally unique PI domain, three Wedge (WED) domains (WED-I, —II and —III), and a nuclease (Nuc) domain.

[0144] While Cas9 and Cpf1 share similarities in structure and function, it should be appreciated that certain Cpf1 activities are mediated by structural domains that are not analogous to any Cas9 domains. For instance, cleavage of the complementary strand of the target DNA appears to be mediated by the Nuc domain, which differs sequentially and spatially from the HNH domain of Cas9. Additionally, the non-targeting portion of Cpf1 gRNA (the handle) adopts a pseudoknot structure, rather than a stem loop structure formed by the repeat:antirepeat duplex in Cas9 gRNAs.

Modifications of RNA-Guided Nucleases

[0145] The RNA-guided nucleases described above have activities and properties that can be useful in a variety of applications, but the skilled artisan will appreciate that RNA-guided nucleases can also be modified in certain instances, to alter cleavage activity, PAM specificity, or other structural or functional features.

[0146] Turning first to modifications that alter cleavage activity, mutations that reduce or eliminate the activity of domains within the NUC lobe have been described above. Exemplary mutations that may be made in the RuvC domains, in the Cas9 HNH domain, or in the Cpf1 Nuc domain are described in Ran and Yamano, as well as in Cotta-Ramusino. In general, mutations that reduce or eliminate activity in one of the two nuclease domains result in

RNA-guided nucleases with nickase activity, but it should be noted that the type of nickase activity varies depending on which domain is inactivated. As one example, inactivation of a RuvC domain or of a Cas9 HNH domain results in a nickase.

[0147] Modifications of PAM specificity relative to naturally occurring Cas9 reference molecules has been described by Kleinstiver et al. for both *S. pyogenes* (Kleinstiver et al., Nature. 2015 Jul. 23; 523(7561):481-5 (Kleinstiver I) and *S. aureus* (Kleinstiver et al., Nat Biotechnol. 2015 December; 33(12): 1293-1298 (Kleinsterver II)). Kleinstiver et al. have also described modifications that improve the targeting fidelity of Cas9 (Nature, 2016 Jan. 28; 529, 490-495 (Kleinsterver III)). Each of these references is incorporated by reference herein.

[0148] RNA-guided nucleases have been split into two or more parts, as described by Zetsche et al. (Nat Biotechnol. 2015 February; 33(2):139-42 (Zetsche II), incorporated by reference), and by Fine et al. (Sci Rep. 2015 Jul. 1; 5:10777 (Fine), incorporated by reference).

[0149] RNA-guided nucleases can be, in certain embodiments, size-optimized or truncated, for instance via one or more deletions that reduce the size of the nuclease while still retaining gRNA association, target and PAM recognition, and cleavage activities. In certain embodiments, RNA guided nucleases are bound, covalently or non-covalently, to another polypeptide, nucleotide, or other structure, optionally by means of a linker. Exemplary bound nucleases and linkers are described by Guilinger et al., Nature Biotechnology 32, 577-582 (2014), which is incorporated by reference for all purposes herein.

[0150] RNA-guided nucleases also optionally include a tag, such as, but not limited to, a nuclear localization signal to facilitate movement of RNA-guided nuclease protein into the nucleus. In certain embodiments, the RNA-guided nuclease can incorporate C- and/or N-terminal nuclear localization signals. Nuclear localization sequences are known in the art and are described in Maeder and elsewhere.

[0151] The foregoing list of modifications is intended to be exemplary in nature, and the skilled artisan will appreciate, in view of the instant disclosure, that other modifications may be possible or desirable in certain applications. For brevity, therefore, exemplary systems, methods and compositions of the present disclosure are presented with reference to particular RNA-guided nucleases, but it should be understood that the RNA-guided nucleases used may be modified in ways that do not alter their operating principles. Such modifications are within the scope of the present disclosure.

[0152] Exemplary suitable nuclease variants include, but are not limited to, AsCpf1 variants comprising an M537R substitution, an H800A substitution, and/or an F870L substitution, or any combination thereof (numbering scheme according to AsCpf1 wild-type sequence). Other suitable modifications of the AsCpf1 amino acid sequence are known to those of ordinary skill in the art. Some exemplary sequences of wild-type AsCpf1 and AsCpf1 variants are provided below.

His-AsCpf1-sNLS-sNLS H800A amino acid sequence (SEQ ID NO: 1142)
MGHHHHHHGSTQFEGFTNLYQVSKTLRFELIPQGTLKHIQEQQFIEEDKARNDHYKELKPIIDRIYK
TYADQCLQLVqLDWENLSAAIDSYRKETEETRNALIEEQATYRNAIHDYFIGRTDNLTDAINKRHAЕ
IYKGLFKAEFLNGKVLKQLGTVTTEHENALLRSFDKFETYFSGFYENRKNVFAEDISTAIPHRIVQ
DNFPKFKENCHIFTRLI TAVPSLREHFENVKAIGIFVSTSIEEVFSFPFYNQLTQTQIDLQNL
GISREAGTEKIKGLNEVLNLAIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFPKSD
SFCKYKTLLRNENVLETAEALFNELNISDLTHIFSHKKLETISSALCDHWDTLRNALYERRISELTG
KITKSAKEKVQRSLKHEDINLQEIISAAGKELSEAFQKQTSEILSHAHAALDQPLPTTLKKQEEKEIL
KSQLDSSLGLYHLLDWFAVDESNEVDPEFSARLTGIKLEMEPSLSFYNKARNYATKKPYSVEKF
QMPTLASGWDVNKEKNNGAILFVKNGLYLGIMPQKGRYKALSPEPTKTESEGFDKMYDYFPDAAK
MIPKCASTQLKAVTAHFQTHTPILLSNNFIEPLEITKEIYDLNNPEKEPKFQTYAKKTGDQKG
YRE ALCKWIDFTRDPLSKYTKTTSIDLSSLRPSSQYKDLGEYYAELNPPLYHISFQRIA
KEIMDAVETGKLYLFQIYNKDFAKGHHGKPNLHTLYWTGLFSPENLAKTSIKLNGQAELFYR
PKSRMKRMAARLGEKML NKKLKDKTPIPDTLYQELYDVNHRLSHDLSDEARALLPN
VITKEVSHEIIKDRRFTSDKFFFHVPI TLNYQAANSPSKFNQRVNAYLKEHP
ETPIIGIDRGERNLIYITVIDSTGKILEQRS LNTIQQFDYQKK LDNREK
VRAARQAWSVVGTI KDLKQGYLSQVIHEIVDLMIH
YQAVVVLENLNFGFKSKRTGIAEKAV YQQFEKMLIDKL
NCLVLKDYP
AEKVGGVLNPYQ
LTDQFTSFAK
MGTOQSGFL
FYVPAPY
TSKIDPLTG
F VDPFWK
T IKNHESR
KHFLEG
FDLHYD
VKTGDF
ILHF
KMNRN
LSFQR
GLPG
FMPA
DIVFE
KNETQF
DAK
GTPPIAG
KRV
IPV
IENHR
FTGRY
RDLY
PANEL
IAL
LEEKG
IVFRD
GSN
ILPKL
LEDD
SHAI
DTM
VALIR
SVLQ
MQR
NSNA
ATGED
YINSP
VRDL
NGCF
DSRF
QNPE
WPMD
DANG
AYHIA
LKQ
GQLL
NLKE
SKDL
KLONG
ISNQ
DWL
AYIQ
ELRN
GSP
KKRK
VGSP
KKRK
V

Cpf1 variant 1 amino acid sequence (SEQ ID NO: 1143)
MTQFEGFTNLYQVSKTLRFELIPQGTLKHIQEQQFIEEDKARNDHYKELKPIIDRIYKTYADQCLQL
VQLDWENLSAAIDSYRKETEETRNALIEEQATYRNAIHDYFIGRTDNLTDAINKRHAЕIYKGLF
KAE LFNGKVLKQLGTVTTEHENALLRSFDKFETYFSGFYENRKNVFAEDISTAIPHRIVQDNFP
PKP
KEN CHIFTRLITAVPSLREHFENVKAIGIFVSTSIEEVFSFPFYNQLTQTQIDLQNL
GGISREAGTE
KIKGLNEVLNLAIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFPKSD
EEVIQSFC
KYKTLL
RNENVLETAEALFNELNISDLTHIFSHKKLETISSALCDHWDTLRNALYERRISELTG
KITKSAKE
K VQRSLKHEDINLQEIISAAGKELSEAFQKQTSEILSHAHAALDQPLPTTLKKQEEKEIL
SQL
DSLL
GLYHLL
DWFAV
DESNEVD
PEFSARLT
GIKLE
MEPSLSF
YNKARNY
ATKKPYS
VEKF
KLN
FQR
PTLASGW
DVN
KEKNNG
AILFVK
NGLYLG
IMPQKGR
YKALS
PEPTK
TESEG
FDKMYDY
FPDAAK
MIPK
CSTQL
KAVTA
HFQTH
TPILLS
NNFIE
PLEIT
KEIYD
LNNPE
KEPK
KFQTYAK
KTGDQKG
YREAL
CKWIDFT
RDPLSK
YTKTTS
IDLSS
LRPSSQ
YKDL
GEYYAEL
NPPLYH
ISFQRIA
KEIMDA
VETGK
LYLFQ
IYNKDF
AKGHHG
KPNLHT
LYWTGL
FSPEN
LAKTSIK
LNGQAEL
FYRPK
SRMKR
MAHRL
GEKML
NKKLK
DQKT
PIPDT
LYQELYD
VNHRL
SHDLSD
EARALL
PNVIT
KEVSHE
IIKDRR
FTSDKFL
PHVP
ITLNYQA
ANS
PSKFN
QRVNAYL
KEHP
ETPIIG
IDRGER
NLIYIT
VIDSTG
KILEQ
RS LNTI
QQFDYQ
KKLDN
REKERV
AARQ
AWSV
VGTTIK
DLKQ
GYLSQ
VIHE
IVDLM
IH
YQAV
VVLEN
LNFG
FKSKRT
GIAEK
AVYQQ
FEKML
D
KLN
CLVL
KDYP
AEKV
GGVL
NPYQ
LTDQ
FTSFA
KMGTO
QSGFL
FYVP
APY
TSKID
PLTG
FVDP
FWK
T
IKN
HESR
KHF
LEG
FDL
HYD
VKT
GDF
ILHF
KMNR
NLS
FQR
GLPG
FMP
A
DIV
FEK
NETQ
FDAK
GTP
FIA
GKRI
VPVI
ENHR
FTGRY
RDLY
PANEL
IAL
LEEKG
IVFR
GSN
ILPKL
LEDD
SHAI
DTM
VALIR
SVLQ

- continued

MRNSNAATGEDYINSPVRDLNGVCFDSRFQNPWPMADANGAYHIALKGQLLNHLKESKDLKLQNG
ISNQDWLAIQELRNGRSSDDEATADSOHAAPPKKRKVGSSGGSGSGSGSGSGSGSLEHHH
HHH

Cpf1 variant 2 amino acid sequence (SEQ ID NO: 1144)
MTQFEGFTNLYQVSCTLRFELIPQGKTLKHIQEQQFIEEDKARNDHYKELKPIIDRIYKTYADQCLQL
VQLDWENLSAAIDSYRKETEETRNALIEEQATYRNAIHDFIGRTDNLTDAINKRHAEIYKGLPKAE
LFNGKVLKQLGTVTTEHENALLRSFDKFETYFSGFYENRKVNFAEDISTAIPHIVQDNFPKPEN
CHIFTRLI TAVPSLREHFENVKAIGIFVSTSIEEVFSFPFYQNQLTQTIDLYNQLGGISREAGTE
KIKGLNEVNLAIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFKSDEEVIQSFCKYKTLL
RNENVLETAEALFNELNDSLTHIFSHKKLETISALCDHWDTLRNALYERRISELTGKITSAEK
VQRSLKHEDINLQEIIASAAGKELSEAFQKTSEILSHAHAALDQPLPTTLKKQEEKEILKSQLDSLLG
LYHLLDWFADVDESNEVDPEFSARLTGIKLEMESPLSFYNKARNYATKKPYSVEKFKLNQFQMPTLASGW
DVNKEKNNGAILFVKNGLYLGIMPQKGRYKALSPEPTEKTSEGFDKMYDYFPDAAKMIPKCSTQL
KAVTAHFQTHTPILLSNNFIEPLEITKEIYDLNNPEKEPKKFQTYAKKTGDQKGYREALCKWIDFT
RDPLSKYTKTTSIDLSSLRPSSQYKDLGEYYAELNPLLYHISFQRIAEEKIMDAVETGKLYLFQIYNK
DFAKGHGKPNLHTLYWTGLFSPENLAKTSIKLNGQAELFYRPKSRMKRMAHRLGEKMLNKKLDQKT
PIPDTLYQELYDYVNHRSLHDLSDEARALLPNVITKEVSHEIICKRRFTSDKFFFHVPITLNYQAANS
PSKFNQRVNAYLKEHPETPIIGIDRGERNLIYITVIDSTGKILEQRSLNNTIQQFDYQKKLDNREKERV
AARQAWSVVGTIKDLQGQYLSQVIHEIVDLMIHQAVVVLENLNGFGFKSKRTGIAEKAVYQQFEKMLI
DKLNCLVLKDYPAAEKVGVLNPYQLTQDFTSFAKMGTOQSGFLFYVPAPYTSKIDPLTGFDVFVWKT
KNHESRKHFLEGFDLHYDVKTGDFILHFKMNRLSFQRLPGFMPAWDIVFEKNETQFDAKGTPFIA
GKRIVPVIEHNRFGRYRDLYPANELIALLEEKGIVFRDGSNLIPKLLENDDASHAIDTMVALIRSVLQ
MRNSNAATGEDYINSPVRDLNGVCFDSRFQNPWPMADANGAYHIALKGQLLNHLKESKDLKLQNG
ISNQDWLAIQELRNGRSSDDEATADSOHAAPPKKRKVGSSGGSGSGSGSGSGSLEHHH
HHH

Cpf1 variant 3 amino acid sequence (SEQ ID NO: 1145)
MTQFEGFTNLYQVSCTLRFELIPQGKTLKHIQEQQFIEEDKARNDHYKELKPIIDRIYKTYADQCLQL
VQLDWENLSAAIDSYRKETEETRNALIEEQATYRNAIHDFIGRTDNLTDAINKRHAEIYKGLPKAE
LFNGKVLKQLGTVTTEHENALLRSFDKFETYFSGFYENRKVNFAEDISTAIPHIVQDNFPKPEN
CHIFTRLI TAVPSLREHFENVKAIGIFVSTSIEEVFSFPFYQNQLTQTIDLYNQLGGISREAGTE
KIKGLNEVNLAIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFKSDEEVIQSFCKYKTLL
RNENVLETAEALFNELNDSLTHIFSHKKLETISALCDHWDTLRNALYERRISELTGKITSAEK
VQRSLKHEDINLQEIIASAAGKELSEAFQKTSEILSHAHAALDQPLPTTLKKQEEKEILKSQLDSLLG
LYHLLDWFADVDESNEVDPEFSARLTGIKLEMESPLSFYNKARNYATKKPYSVEKFKLNQFQMPTLASGW
DVNKEKNNGAILFVKNGLYLGIMPQKGRYKALSPEPTEKTSEGFDKMYDYFPDAAKMIPKCSTQL
KAVTAHFQTHTPILLSNNFIEPLEITKEIYDLNNPEKEPKKFQTYAKKTGDQKGYREALCKWIDFT
RDPLSKYTKTTSIDLSSLRPSSQYKDLGEYYAELNPLLYHISFQRIAEEKIMDAVETGKLYLFQIYNK
DFAKGHGKPNLHTLYWTGLFSPENLAKTSIKLNGQAELFYRPKSRMKRMAHRLGEKMLNKKLDQKT
PIPDTLYQELYDYVNHRSLHDLSDEARALLPNVITKEVSHEIICKRRFTSDKFLFHVPITLNYQAANS
PSKFNQRVNAYLKEHPETPIIGIDRGERNLIYITVIDSTGKILEQRSLNNTIQQFDYQKKLDNREKERV

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AARQAWSVVGTIKDLKQGYLSQVIHEIVDLMIHQAVVLENLNFGFKSKRTGIAEKAVYQQFEKMLI
DKLNCLVLKDYPAAEKVGGVLNPYQLTDQFTSFAKMGTOSGFLFYVPAPYTSKIDPLTGFVDPFWKTI
KNHESRKHFLEGDFLHYDVKTGDFILHFKNMRNLSFQRGLPGFMPAWDIVFEKNETQFDAGTPFIA
GKRVIPVIEHNHRFTGRYRDLYPANELIALLEEKGIVERDGNSNILPKLLENDSSHADTMVALIRSVLQ
MRNSNAATGEDYINSPVRDLNGVCFDSRFQNPWPMADANGAYHIALKGQLLNHLKESKDLKLQNG
ISNQDWLAYIQELRNNGRSSDEATADSOHAAPPKKRKVGGSGGSGSGGGSGSSLEHHH
HHH

Cpf1 variant 4 amino acid sequence (SEQ ID NO: 1146)
MTQFEGFTNLYQVSCTLRFELIPQGKTLKHIQEQQFIEEDKARNDHYKELKPIIDRIYKTYADQCLQL
VQLDWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHDYFIGRTDNLTDAINKRHAEIYKGLPKAE
LFNGKVLKQLGTVTTEHENALLRSFDKFRTYFSGFYENRKNVSAEDISTAIPIHIVQDNFPKPEN
CHIFTRLITAVPSLREHFENVKKAIGIFVSTSIEEVFSFPPYNQLLTQTQIDLYNQLGGISREAGTE
KIKGLNEVNLAIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEKSDEEVIQSFCKYKTL
RNENVLETAEALFNELNISIDLTHIFSHKKLETISALCDHWDTLRNALYERRISELTGKITSAEK
VQRSLKHEDINLQEIIASAAGKELSEAFKQKTSEILSHAHAALDQPLPTTLKKQEEKEILKSQLDSLLG
LYHLLDWFADVDESNEVDPEFSARLTGIKLEMPSLSFYNKARNYATKKPYSVEFKLNFQRPTLASGW
DVNKEKNNGAILFVKNGLYLGIMPQKQGRYKALSFEPEKTSEGFDKMYDYFPDAAKMIPKCSTQL
KAVTAHFQTHHTTPILLSNNFIEPLEITKEIYDNNPEKEPKFQTYAKKTDQKGYREALCKWIDFT
RDPLSKYTKTTSIDLSSLRPSSQYKDLGEYYAELNPLLHISFQRIAEEKIMDAVTGKLYLFQIYNK
DFAKGHHGKPNLHTLYWTGLFSPENLAKTSIKLNGQAEFLYRPKSRMKRMAARLGEKMLNKKLDQKT
PIPDTLYQELYDYVNHRSLHDLSDEARALLPNVITKEVSHEIKDRRFTSDKFLFHVPIILNYQAANS
PSKFNQRVNAYLKEHPETPIIGDIRGERNLITYITVIDSTGKILEQRSNLNTIQQFDYQKQLDNREKERV
AARQAWSVVGTIKDLKQGYLSQVIHEIVDLMIHQAVVLENLNFGFKSKRTGIAEKAVYQQFEKMLI
DKLNCLVLKDYPAAEKVGGVLNPYQLTDQFTSFAKMGTOSGFLFYVPAPYTSKIDPLTGFVDPFWKTI
KNHESRKHFLEGDFLHYDVKTGDFILHFKNMRNLSFQRGLPGFMPAWDIVFEKNETQFDAGTPFIA
GKRVIPVIEHNHRFTGRYRDLYPANELIALLEEKGIVFRDGNSNILPKLLENDSSHADTMVALIRSVLQ
MRNSNAATGEDYINSPVRDLNGVCFDSRFQNPWPMADANGAYHIALKGQLLNHLKESKDLKLQNG
ISNQDWLAYIQELRNNGRSSDEATADSOHAAPPKKRKV

Cpf1 variant 5 amino acid sequence (SEQ ID NO: 1147)
MTQFEGFTNLYQVSCTLRFELIPQGKTLKHIQEQQFIEEDKARNDHYKELKPIIDRIYKTYADQCLQL
VQLDWENLSAAIDSYRKEKTEETRNALIEEQATYRNAIHDYFIGRTDNLTDAINKRHAEIYKGLPKAE
LFNGKVLKQLGTVTTEHENALLRSFDKFRTYFSGFYENRKNVSAEDISTAIPIHIVQDNFPKPEN
CHIFTRLITAVPSLREHFENVKKAIGIFVSTSIEEVFSFPPYNQLLTQTQIDLYNQLGGISREAGTE
KIKGLNEVNLAIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEKSDEEVIQSFCKYKTL
RNENVLETAEALFNELNISIDLTHIFSHKKLETISALCDHWDTLRNALYERRISELTGKITSAEK
VQRSLKHEDINLQEIIASAAGKELSEAFKQKTSEILSHAHAALDQPLPTTLKKQEEKEILKSQLDSLLG
LYHLLDWFADVDESNEVDPEFSARLTGIKLEMPSLSFYNKARNYATKKPYSVEFKLNFQRPTLASGW
DVNKEKNNGAILFVKNGLYLGIMPQKQGRYKALSFEPEKTSEGFDKMYDYFPDAAKMIPKCSTQL
KAVTAHFQTHHTTPILLSNNFIEPLEITKEIYDNNPEKEPKFQTYAKKTDQKGYREALCKWIDFT
RDPLSKYTKTTSIDLSSLRPSSQYKDLGEYYAELNPLLHISFQRIAEEKIMDAVTGKLYLFQIYNK

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DFAKGHHGKPNLHTLYWTGLFSPENLAKTSIKLNGQAELFYRPKSRMCRMARLGEKMLNKKLDQKT
 PIPDTLYQELYDYVNHRSLHDLSDEARALLPNVITKEVSHEIIKDRRTSDKFLFHPITLNQQAANS
 PSKFNQRVNAYLKEHPETPIIGIDRGERNLIYITVIDSTGKILEQRSNLNTIQQFDYQKKLDNREKERV
 AARQAWSVVGTIKDLKQGYLSQVIHEIVDLMIHQAVVVLENLFNGFKSKRTGIAEKAVYQQFEKMLI
 DKLNCVLKDYPAEKVGVLNPYQLTDQFTSFAKMGTOQSGFLFYVPAPYTSKIDPLTGFVDPFWKTI
 KNHESRKHFLEGDFLHYDVKTGDFILHFKNMRNLSFORGLPGFMPAWDIVFEKNETQFDAKGTPFIA
 GKRIVPVIENHRFTGRYRDLYPANELIALLEEKGIVFRDGSNILPKLLEDDSHAIDTMVALIRSVLQ
 MRNSNAATGEDYINSPVRDLNGVCFDSPRFQNPEWPMADANGAYHIALKGQLLNHLKESKDLKLQNG
 ISNQDWLAYIQELRNGRSSDDEATADSOHAAPPKKRKV

Cpf1 variant 6 amino acid sequence (SEQ ID NO: 1148)
 MTQFEGFTNLYQVSCTLRFELIPQGKTLKHIQEQQFIEEDKARNDHYKELKPIIDRIYKTYADQCLQL
 VQLDWENLSAAIDSYRKETEETRNALIEEQATYRNAIHDFIGRTDNLTDAINKRHAEIYKGLPKAE
 LFNGKVLKQLGTVTTEHENALLRSFDKFITYFSGFYENRKNVSAEDISTAIPHRIVQDNFPKPKEN
 CHIFTRLITAVPSLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQTQIDLYNQLLGGISREAGTE
 KIKGLNEVNLAIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFKSDEEVIQSFCKYKTL
 RNNENVLETAEALFNELNISIDLTHIFSHKKLETISALCDHWDTLRNALYERRISELTGKITSAEK
 VQRSLKHEDINLQEIIASAAGKELSEAFKQKTSEILSHAHAALDQPLPTTLKKQEEKEILKSQDSLLG
 LYHLLDWFADVDESNEVDPEFSARLTGKLEMPSLSFYNKARNYATKKPYSVEFKLNFQRPtasGW
 DVNKEKNNGAILFKNGLYLGIMPQKGRYKALSFEPTEKTSEGFDKMYDYFPDAAKMIPKCSTQL
 KAVTAHFQTHHTTPILLSNNFIEPLEITKEIYDLNNPEKEPKKFQTYAKKTGDQKGYREALCKWIDFT
 RDPLSKYTKTTSIDLSSLRPSSQYKDLGEYYAELNPPLYHISFQRIAEEIMDAVETGKLYLFQIYNK
 DFAKGHHGKPNLHTLYWTGLFSPENLAKTSIKLNGQAELFYRPKSRMCRMARLGEKMLNKKLDQKT
 PIPDTLYQELYDYVNHRSLHDLSDEARALLPNVITKEVSHEIIKDRRTSDKFLFHPITLNQQAANS
 PSKFNQRVNAYLKEHPETPIIGIDRGERNLIYITVIDSTGKILEQRSNLNTIQQFDYQKKLDNREKERV
 AARQAWSVVGTIKDLKQGYLSQVIHEIVDLMIHQAVVVLENLFNGFKSKRTGIAEKAVYQQFEKMLI
 DKLNCVLKDYPAEKVGVLNPYQLTDQFTSFAKMGTOQSGFLFYVPAPYTSKIDPLTGFVDPFWKTI
 KNHESRKHFLEGDFLHYDVKTGDFILHFKNMRNLSFORGLPGFMPAWDIVFEKNETQFDAKGTPFIA
 GKRIVPVIENHRFTGRYRDLYPANELIALLEEKGIVFRDGSNILPKLLEDDSHAIDTMVALIRSVLQ
 MRNSNAATGEDYINSPVRDLNGVCFDSPRFQNPEWPMADANGAYHIALKGQLLNHLKESKDLKLQNG
 ISNQDWLAYIQELRNGRSSDDEATADSOHAAPPKKRKVGGSGGGSGGGSGGGSGGSLEHHH
 HHH

Cpf1 variant 7 amino acid sequence (SEQ ID NO: 1149)
 MGRDPGKPIPPLLGLDSTAPKKRKVGIHGVAATQFEGFTNLYQVSCTLRFELIPQGKTLKHIQEQQ
 GFIEEDKARNDHYKELKPIIDRIYKTYADQCLQLVQLDWENLSAAIDSYRKETEETRNALIEEQATY
 RNAIHDFIGRTDNLTDAINKRHAEIYKGLPKAELPNGKVLKQLGTVTTEHENALLRSFDKFITYFS
 GFYENRKNVSAEDISTAIPHRIVQDNFPKPKENCHIFTRLITAVPSLREHFENVKKAIGIFVSTSIE
 EVFSFPFYNQLLTQTQIDLYNQLLGGISREAGTEKIKGLNEVNLAIQKNDETAHIIASLPHRFIPLF
 KQILSDRNTLSFILEEFKSDEEVIQSFCKYKTLRNENVLETAEALFNELNISIDLTHIFSHKKLETI
 SSALCDHWDTLRNALYERRISELTGKITSAEKVQRSLKHEDINLQEIIASAAGKELSEAFKQKTSEI
 LSHAHAAALDQPLPTTLKKQEEKEILKSQDSLLGLYHLLDWFADVDESNEVDPEFSARLTGKLEMPS

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LSFYNKARNYATKKPYSVEFKLNFQMPQLASGWDVNKEKNNGAILFVKNGLYYLGIMPQKGRYKAL
SFEPEKTEKTSEGFDKMYDYFPDAAKMIPKCSTQLKAVTAHFQTHTPILLSNNFIEPLEITKEIYDLN
NPEKEPKKFQTAKKTGDQKGYREALCKWIDFTRDFLSKYTCTTSIDLSSLRPSSQYKDLGEYYAEL
NPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNKDFAKGHGKPNLHTLYWTGLFSPENLAKTSIKLN
GQAELFYRPKSRMKRMAHRLGEKMLNKKLDQKTPIDPTLYQELYDYVNHLSDLSDEARALLPNVI
TKEVSHEIIKDRRTSDKFFFHVPI TLNYQAANS PSKFNQRVNAYLKEHPETPIIGIDRGERNLIYIT
VIDSTGKILEQRSLNTIQQFDYQKKLDNREREKERAARQAWSVVGTIKDLKQGYLSQVIHEIVDLMIH
QAVVYLENLPNGFKSKRTGIAEKAVYQQFEKMLIDKLNCVLKDYPAEKVGGVLNPYQLTDQFTSFAK
MGTQSGFLFYVPAPYTSKIDPLTGFVDPFWKTIKNHESRKHFLEGDFLHYDVKTGDFILHFKMNRN
LSFQRGLPGMPAWDIVFEKNETQFDAKGTPIAGKRIVPVIEHNRFTRGRYRDLYPANELIALEEKG
IVFRDGSNILPKLLENDASHAIDTMVALIRSVLQMRNSNAATGEDYIINSPVRDLNGVCFDSRFQNPEW
PMDADANGAYHIALKGQLLLNLKESKDLKLQNGISNQDWLAYIQELRNPKKKRKVKLAAALEHHHHH
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Exemplary AsCpf1 wild-type amino acid sequence (SEQ ID NO: 1150) :

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MTQFEGFTNLYQVSCTLRFELIPQGKTLKHQEQGPIEEDKARNDHYKELKPIIDRIYKTYADQCLQL
VQLDWENLSAAIDSYRKETKETEETRNALIEEQATYRNAIHDFIGRTDNLTDAINKRHAEIYKGLPKAE
LFNGKVLKQLGTVTTEHENALLRSFDKFETYFSGFYENRKNVFAEDISTAIPIHRIVQDNFPKPKEN
CHIFTRLITAVPSLREHFENVKKAIGIFVSTSIEEVFSFPFYNQLLTQIDLYNQLLGGISREAGTE
KIKGLNEVLNLAIQKNDETAHIIASLPHRFIPLFKQILSDRNTLSFILEEFKSDEEVIQSFCKYKTL
RNENVLETAEALFNELNISIDLTHIFSHKKLETISSALCDHWDTLRNALYERRISELTGKITSAEK
VQRSLKHEDINLQEIIASAAGKELSEAFQKQTSEILSHAHAALDQPLPTTLKKQEEKEILKSQDSLLG
LYHLLLDWFADVDESNEVDPEFSARLTGIKLEMESPLSFYNNKARYATKKPYSVEFKLNFQMPQLASGW
DVNKEKNNGAILFVKNGLYYLGIMPQKGRYKALSFEPEKTETSSEGFDKMYDYFPDAAKMIPKCSTQL
KAVTAHFQTHTPILLSNNFIEPLEITKEIYDLNNPKEPKKFQTAKKTGDQKGYREALCKWIDFT
RDFLSKYTCTTSIDLSSLRPSSQYKDLGEYYAELNPLLYHISFQRIAEKEIMDAVETGKLYLFQIYNK
DFAKGHGKPNLHTLYWTGLFSPENLAKTSIKLNGQAELEYRPKSRMKRMAHRLGEKMLNKKLDQKTP
PIPDLYQELYDYVNHLSDLSDEARALLPNVITKEVSHEIIKDRRTSDKFFFHVPI TLNYQAANS
PSKFNQRVNAYLKEHPETPIIGIDRGERNLIYITVIDSTGKILEQRSLNTIQQFDYQKKLDNREREKERV
AARQAWSVVGTIKDLKQGYLSQVIHEIVDLMIHQAVVYLENLPNGFKSKRTGIAEKAVYQQFEKMLI
DKLNCLVLKDYPAEKVGGVLNPYQLTDQFTSFAKMGTOQSGFLFYVPAPYTSKIDPLTGFVDPFWKTI
KNHESRKHFLEGDFLHYDVKTGDFILHFKMNRNLSFQRGLPGMPAWDIVFEKNETQFDAKGTPIAG
KRIVPVIEHNRFTRGRYRDLYPANELIALEEKGIVFRDGSNILPKLLENDASHAIDTMVALIRSVLQ
MRNSNAATGEDYIINSPVRDLNGVCFDSRFQNPEWPMADANGAYHIALKGQLLLNLKESKDLKLQNG
ISNQDWLAYIQELRN

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Nucleic Acids Encoding RNA-Guided Nucleases

[0153] Nucleic acids encoding RNA-guided nucleases, e.g., Cas9, Cpf1 or functional fragments thereof, are provided herein. Exemplary nucleic acids encoding RNA-guided nucleases have been described previously (see, e.g., Cong 2013; Wang 2013; Mali 2013; Jinek 2012).

[0154] In some cases, a nucleic acid encoding an RNA-guided nuclease can be a synthetic nucleic acid sequence.

For example, the synthetic nucleic acid molecule can be chemically modified. In certain embodiments, an mRNA encoding an RNA-guided nuclease will have one or more (e.g., all) of the following properties: it can be capped; polyadenylated; and substituted with 5-methylcytidine and/or pseudouridine.

[0155] Synthetic nucleic acid sequences can also be codon optimized, e.g., at least one non-common codon or less-common codon has been replaced by a common codon. For

example, the synthetic nucleic acid can direct the synthesis of an optimized messenger mRNA, e.g., optimized for expression in a mammalian expression system, e.g., described herein. Examples of codon optimized Cas9 coding sequences are presented in Cotta-Ramusino.

[0156] In addition, or alternatively, a nucleic acid encoding an RNA-guided nuclease may comprise a nuclear localization sequence (NLS). Nuclear localization sequences are known in the art.

[0157] As an example, the nucleic acid sequence for Cpf1 variant 4 is set forth below as SEQ ID NO:1175:

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ATGACCCAGTTGAAGGTTACCAATCTGTATCAGGTTAGCAAAACCT
GCGTTTGAACTGATTCCGCAGGGTAAACCCCTGAAACATATTCAAGAAC
AGGGCTTCATCGAAGAGGATAAAGCACGTAACGATCACTACAAAAGAAC
AAACCGATTATCGACCGCATCTATAAAACCTATGCAGATCAGTGTCTGC
GCTGGTTCAGCTGGATTGGAAAATCTGAGCGCAGCAATTGATAGTTATC
GCAAAGAAAAACCGAAGAAACCCGTAATGCACTGATTGAAGAACAGGCC
ACCTATCGTAATGCCATCCATGATTATTCATTGGCTGTACCGATAATCT
GACCGATGCAATTAAACACGTACCGCGAACTCTATAAAGGGCTGTTA
AAGCCGAACACTGTTAATGGCAAAGTTCTGAAACAGCTGGCACCGTTACC
ACCAACCGAACATGAAATGCACTGCTGCGTAGCTTGATAAAATTACCCAC
CTATTCAGCGGTTTATGAGAATCGCAAAACGTGTTAGCGCAGAAG
ATATTAGACCGCAATTCCGCATCGATTGTGCAAGGATAATTCCCGAAA
TTCAAAGAGAACGTGCCACATTTCACCGCTGATTACCGCAGTCCGAG
CCTCGTGAACATTGAAAACGTTAAAAAGCCATGGCATTCTTGTAA
GCACCCAGCATTGAAGAACGTTTTAGCTCCGTTTACAATCAGCTGCTG
ACCCAGACCCAGATTGATCTGTATAACCAACTGCTGGGTATTAGCGC
TGAAGCAGGCACCGAAAAATCAAAGGTCTGAATGAAGTGCTGAATCTGG
CCATTCAAGAAAATGATGAAACCGCACATATTATGCAAGCCCTGCCAT
CGTTTATTCCGCTGTTCAAACAAATTCTGAGCGATCGTAATACCGTAG
CTTATTCTGGAAGAACATTCAAACTCGATGAAGAGGTGATTCAAGAGCTT
GCAAATACAAAACGCTGCGCAATGAAAATGTTCTGAAACTGCCGAA
GCACTGTTAACGAACTGAATGCACTGATCTGACCCACATCTTATCAG
CCACAAAAAACTGGAAACCATTCAGCGCAGCTGTGATCATTGGGATA
CCCTCGCTGTAATGCCGCTATGAACGCTGATTAGCGAACTGACCGGTAA
ATTACCAAAAGCGCAGGAAAAGAGTTCAAGCGCAGTCTGAAACATGAGGA
TATTAATCTGCAAGAGATTATTAGCGCAGCGGTTAAAAGAACGTGCAAG
CATTAAACAGAAAACCGCAGGAAATTCTGTCACATGCACATGCGACACTG
GATCAGCCGCTGCCGACCCCTGAAAAACAAAGAACGAAAGAAAATCCT
GAAAAGCCAGCTGGATAGCCTGCTGGGTCTGATCATCTGCTGGACTGGT
TTGCACTGATGAAAGCAATGAAGTTGATCCGAAATTAGCGCACGCTG
ACCGGCATTAAACTGGAAACTGGGATTTAGCTGCTGGTATTGAAACATG
CCGTAATTATGCCACCAAAACCGTATAGCGTCGAAAATTCAAACCTGA

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ACTTTCAAGCGTCCGACCCCTGGCAAGCGGTTGGATGTTAATAAGAAAAA
AACAAACGGTGCATCCTGTCGTGAAAATGGCCTGTATTATCTGGTAT
TATGCCGAAACAGAAAAGGTGTTGATAAAATGACTACGACTATTTCCGGAT
GCAGCCAAAATGATTCCGAAATGAGCACCCAGCTGAAAGCAGTTACCGC
ACATTTTCAGACCCATACCACCCGATTCTGCTGAGCAATAACTTTATTG
AACCGCTGAAATCACCAAAGAGATCTACGATCTGAATAACCCGAAAAA
GAGCCGAAAAAATTCCAGACCGCATATGCAAAAAACCGGTGATCAGAA
AGGTTATCGTGAAGCGCTGTGTAATGGATTGATTTCACCGTGATTTTC
TGAGCAAATACACCAAACCCAGTATCGATCTGAGCAGCTGCGTCCG
AGCAGCCAGTATAAAGATCTGGCGAATATTATGCAAGAACTGAATCCGCT
GCTGTATCATATTAGCTTCAGCGTATTGCGAGAAAATCATGGACG
CAGTTGAAACCGTAAACTGTACCTGTTCCAGATCTACAATAAAGATTT
GCCAAAGGCCATCATGGCAAACCGAATCTGCATACCTGTATTGGACCGG
TCTGTTAGCCCTGAAAATCTGCCAAAACCTCGATTAAACTGAATGGTC
AGGCGGAACGTGTTTATCGTCCGAAAGCCGTATGAAACGTATGGCAGCT
CGTCTGGTGAACAAATGCTGAACAAAAACTGAAAGACCGAGAAAACCC
GATCCGGATAACTGTATCAAGAACTGTATGATTGTAACCATCGTC
TGAGCCATGATCTGAGTGTGAAGCACGTGCCCCGCTGCGGAATGTTATT
ACCAAAGAACGTTAGCCACGAGATCATTAAAGATCGTCGTTTACCGCGA
CAAATTCCTGTTCATGCGCATTACCGTGAATTATCAGGAGCAAATA
GCCCGAGCAAATTAAACCCAGCTGTTATGCAATCTGAAAGAACATCCA
GAAACCCGATTATTGGTATTGATCGTGGTAACGTAACCTGATTATAT
CACCGTTATTGATAGCACCGGAAACCTGGAACACCGTAGCCTGAATA
CCATTCAAGCTGTTGATTACCGAAAAACTGGATAATCGCAGAAAGAA
CGTGTGCACTGAGCGATGGCAGTTGTTGGTACAATTAAAGACCT
GAAACAGGGTTATCTGAGCCAGGTTATTGATGAAATTGTTGATCTGATGA
TTCACTATCAGGCCGTTGTTGCTGGAAAACCTGAATTGGCTTAAA
AGCAAAACGTACCGGCATTGCAAGGAAACGAGTTTATCAGCAGTCGAGAA
AATGCTGATTGACAAACTGAATTGCGCTGCTGAAAGATTATCCGGCTG
AAAAAGGGTTATCTGAGCCAGGTTATTGATGAAATTGTTGATCTGATGA
AGCTTGCAGGAAATGGCAGGTTCTGAGGTTATTGTTATGTTCCGGC
ACCGTATACGAGCAAATTGATCCGCTGACCGGTTTGTGATCCGTTG
TTGGAAAACCATCAAAACCATGAAAGCCGAAACATTCTGGAAGGT
TTGCACTTCTGCACTGAGCTTAAACGGGTGATTCTACCTGCACCT
TAAATGAATCGCAATCTGAGTTTCAAGCGTGGCTGCTGGTTTATGC
CTGCACTGAGCTTAAACGGGTGATTCTACCTGCACCT
GGCACCCGTTATTGAGCGTAAACGTTATTGTTCCGGTATTGAAACATCA
TCGTTCACCGGCTGTTATCGCAGTCTGATCTGCACTGAGCTG

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CACTGCTGGAAGAGAAAGGTATTGTTTCTGATGGCTCAAACATTCTG
CCGAAACTGCTGGAAAATGATGATAGCCATGCAATTGATACCATGGTGC
ACTGATTCTGTAAGCGTTCTGCAGATGCGTAATAGCAATGCAGCAACCGGTG
AAGATTACATTAATAGTCGGTCTGATCTGAATGGTGTGTTGAT
AGCCGTTTCAGAATCCGAATGGCGATGGATGCAGATGCAAATGGTGC
ATATCATATTGCACTGAAAGGACAGCAGCTGCTGCTGAACCACCTGAAAGAAA
GCAAAGATCTGAAACTGCAAAACGGCATTAGCAATCAGGATTGGCTGGCA
TATATCCAAGAACTGCGTAACGGTCTGAGCAGTGATGATGAGCAACCGC
AGATAGCCAGCATGCAAGCACCCCTAAAAAGAACGTAAGATT

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Functional Analysis of Candidate Molecules

[0158] Candidate RNA-guided nucleases, gRNAs, and complexes thereof, can be evaluated by standard methods known in the art. See, e.g. Cotta-Ramusino. The stability of RNP complexes may be evaluated by differential scanning fluorimetry, as described below.

Differential Scanning Fluorimetry (DSF)

[0159] The thermostability of ribonucleoprotein (RNP) complexes comprising gRNAs and RNA-guided nucleases can be measured via DSF. The DSF technique measures the thermostability of a protein, which can increase under favorable conditions such as the addition of a binding RNA molecule, e.g., a gRNA.

[0160] A DSF assay can be performed according to any suitable protocol, and can be employed in any suitable setting, including without limitation (a) testing different conditions (e.g. different stoichiometric ratios of gRNA: RNA-guided nuclease protein, different buffer solutions, etc.) to identify optimal conditions for RNP formation; and (b) testing modifications (e.g. chemical modifications, alterations of sequence, etc.) of an RNA-guided nuclease and/or a gRNA to identify those modifications that improve RNP formation or stability. One readout of a DSF assay is a shift in melting temperature of the RNP complex; a relatively high shift suggests that the RNP complex is more stable (and may thus have greater activity or more favorable kinetics of formation, kinetics of degradation, or another functional characteristic) relative to a reference RNP complex characterized by a lower shift. When the DSF assay is deployed as a screening tool, a threshold melting temperature shift may be specified, so that the output is one or more RNPs having a melting temperature shift at or above the threshold. For instance, the threshold can be 5-10° C. (e.g. 5°, 6°, 7°, 8°, 9°, 10°) or more, and the output may be one or more RNPs characterized by a melting temperature shift greater than or equal to the threshold.

[0161] Two non-limiting examples of DSF assay conditions are set forth below:

[0162] To determine the best solution to form RNP complexes, a fixed concentration (e.g. 2 μM) of Cas9 in water+10×SYPRO Orange® (Life Technologies cat #S-6650) is dispensed into a 384 well plate. An equimolar amount of gRNA diluted in solutions with varied pH and salt is then added. After incubating at room temperature for 10' and brief centrifugation to remove any bubbles, a Bio-Rad CFX384™

Real-Time System C1000 Touch™ Thermal Cycler with the Bio-Rad CFX Manager software is used to run a gradient from 20° C. to 90° C. with a 1° C. increase in temperature every 10 seconds.

[0163] The second assay consists of mixing various concentrations of gRNA with fixed concentration (e.g. 2 μM) Cas9 in optimal buffer from assay 1 above and incubating (e.g. at RT for 10') in a 384 well plate. An equal volume of optimal buffer+10×SYPRO Orange® (Life Technologies cat #S-6650) is added and the plate sealed with Microseal® B adhesive (MSB-1001). Following brief centrifugation to remove any bubbles, a Bio-Rad CFX384™ Real-Time System C1000 Touch™ Thermal Cycler with the Bio-Rad CFX Manager software is used to run a gradient from 20° C. to 90° C. with a 1° C. increase in temperature every 10 seconds.

Genome Editing Strategies

[0164] The genome editing systems described above are used, in various embodiments of the present disclosure, to generate edits in (i.e. to alter) targeted regions of DNA within or obtained from a cell. Various strategies are described herein to generate particular edits, and these strategies are generally described in terms of the desired repair outcome, the number and positioning of individual edits (e.g. SSBs or DSBs), and the target sites of such edits.

[0165] Genome editing strategies that involve the formation of SSBs or DSBs are characterized by repair outcomes including: (a) deletion of all or part of a targeted region; (b) insertion into or replacement of all or part of a targeted region; or (c) interruption of all or part of a targeted region. This grouping is not intended to be limiting, or to be binding to any particular theory or model, and is offered solely for economy of presentation. Skilled artisans will appreciate that the listed outcomes are not mutually exclusive and that some repairs may result in other outcomes. The description of a particular editing strategy or method should not be understood to require a particular repair outcome unless otherwise specified.

[0166] Replacement of a targeted region generally involves the replacement of all or part of the existing sequence within the targeted region with a homologous sequence, for instance through gene correction or gene conversion, two repair outcomes that are mediated by HDR pathways. HDR is promoted by the use of a donor template, which can be single-stranded or double stranded, as described in greater detail below. Single or double stranded templates can be exogenous, in which case they will promote gene correction, or they can be endogenous (e.g. a homologous sequence within the cellular genome), to promote gene conversion. Exogenous templates can have asymmetric overhangs (i.e. the portion of the template that is complementary to the site of the DSB may be offset in a 3' or 5' direction, rather than being centered within the donor template), for instance as described by Richardson et al. (Nature Biotechnology 34, 339-344 (2016), (Richardson), incorporated by reference). In instances where the template is single stranded, it can correspond to either the complementary (top) or non-complementary (bottom) strand of the targeted region.

Gene Constructs

[0167] In some aspects, the present disclosure provides complex editing strategies, and resulting modified cells

having complex genomic alterations, that allow for the generation of advanced NK cell products for clinical applications, e.g., for immunooncology therapeutic approaches.

[0168] In some embodiments, the genomic alterations are introduced by use of one or more HDR expression constructs. In some embodiments, the genomic alterations are introduced by use of one or more HDR expression constructs. In some embodiments, the one or more HDR expression constructs comprise one or more donor HDR templates. In some embodiments, the one or more donor HDR templates comprise one or more expression cassettes encoding one or more cDNAs. In some embodiments, the donor HDR template comprises one expression cassette. In some embodiments, the donor HDR template comprises two expression cassettes. In some embodiments, the donor HDR template comprises three expression cassettes. In some embodiments, the donor HDR template comprises four expression cassettes. In some embodiments, the donor HDR template comprises five expression cassettes. In some embodiments, the donor HDR template comprises six expression cassettes. In some embodiments, the donor HDR template comprises seven expression cassettes. In some embodiments, the donor HDR template comprises eight expression cassettes. In some embodiments, the donor HDR template comprises nine expression cassettes. In some embodiments, the donor HDR template comprises ten expression cassettes. In some embodiments, the one or more expression cassette is monocistronic. In some embodiments, the one or more expression cassette is bicistronic.

[0169] In some embodiments, the one or more expression cassettes comprise one cDNA. In some embodiments, the one or more expression cassettes comprise two cDNAs. In some embodiments, the one or more expression cassettes comprise three cDNAs. In some embodiments, the one or more expression cassettes comprise four cDNAs. In some embodiments, the one or more expression cassettes comprise five cDNAs. In some embodiments, the one or more expression cassettes comprise six cDNAs. In some embodiments, the one or more expression cassettes comprise seven cDNAs. In some embodiments, the one or more expression cassettes comprise eight cDNAs. In some embodiments, the one or more expression cassettes comprise nine cDNAs. In some embodiments, the one or more expression cassettes comprise ten cDNAs. In some embodiments, the one or more expression cassettes comprise one or more cDNAs separated by a 2A sequence. In some embodiments, the one or more expression cassettes comprise two cDNAs separated by a 2A sequence. In some embodiments, the one or more expression cassettes comprise three cDNAs separated by a 2A sequence.

[0170] In some embodiments, the HDR expression construct comprises one or more cDNAs driven by a heterologous promoter.

[0171] In some embodiments, the HDR expression construct comprises one or more donor templates for inserting an inactivating mutation in a target gene, wherein the gene product has less, or no, function (being partially or wholly inactivated). In some embodiments, the HDR expression construct comprises one or more donor templates for inserting an inactivating mutation in a target gene, wherein the gene product has no function (wholly inactivated).

[0172] Gene conversion and gene correction are facilitated, in some cases, by the formation of one or more nicks in or around the targeted region, as described in Ran and

Cotta-Ramusino. In some cases, a dual-nickase strategy is used to form two offset SSBs that, in turn, form a single DSB having an overhang (e.g. a 5' overhang).

[0173] Interruption and/or deletion of all or part of a targeted sequence can be achieved by a variety of repair outcomes. As one example, a sequence can be deleted by simultaneously generating two or more DSBs that flank a targeted region, which is then excised when the DSBs are repaired, as is described in Maeder for the LCA10 mutation. As another example, a sequence can be interrupted by a deletion generated by formation of a double strand break with single-stranded overhangs, followed by exonucleolytic processing of the overhangs prior to repair.

[0174] One specific subset of target sequence interruptions is mediated by the formation of an indel within the targeted sequence, where the repair outcome is typically mediated by NHEJ pathways (including Alt-NHEJ). NHEJ is referred to as an “error prone” repair pathway because of its association with indel mutations. In some cases, however, a DSB is repaired by NHEJ without alteration of the sequence around it (a so-called “perfect” or “scarless” repair); this generally requires the two ends of the DSB to be perfectly ligated. Indels, meanwhile, are thought to arise from enzymatic processing of free DNA ends before they are ligated that adds and/or removes nucleotides from either or both strands of either or both free ends.

[0175] Because the enzymatic processing of free DSB ends may be stochastic in nature, indel mutations tend to be variable, occurring along a distribution, and can be influenced by a variety of factors, including the specific target site, the cell type used, the genome editing strategy used, etc. Even so, it is possible to draw limited generalizations about indel formation: deletions formed by repair of a single DSB are most commonly in the 1-50 bp range, but can reach greater than 100-200 bp. Insertions formed by repair of a single DSB tend to be shorter and often include short duplications of the sequence immediately surrounding the break site. However, it is possible to obtain large insertions, and in these cases, the inserted sequence has often been traced to other regions of the genome or to plasmid DNA present in the cells.

[0176] Indel mutations—and genome editing systems configured to produce indels—are useful for interrupting target sequences, for example, when the generation of a specific final sequence is not required and/or where a frameshift mutation would be tolerated. They can also be useful in settings where particular sequences are preferred, insofar as the certain sequences desired tend to occur preferentially from the repair of an SSB or DSB at a given site. Indel mutations are also a useful tool for evaluating or screening the activity of particular genome editing systems and their components. In these and other settings, indels can be characterized by (a) their relative and absolute frequencies in the genomes of cells contacted with genome editing systems and (b) the distribution of numerical differences relative to the unedited sequence, e.g. +1, +2, +3, etc. As one example, in a lead-finding setting, multiple gRNAs can be screened to identify those gRNAs that most efficiently drive cutting at a target site based on an indel readout under controlled conditions. Guides that produce indels at or above a threshold frequency, or that produce a particular distribution of indels, can be selected for further study and development. Indel frequency and distribution can also be useful as a readout for evaluating different genome editing system

implementations or formulations and delivery methods, for instance by keeping the gRNA constant and varying certain other reaction conditions or delivery methods.

Multiplex Strategies

[0177] While exemplary strategies discussed above have focused on repair outcomes mediated by single DSBs, genome editing systems according to this disclosure may also be employed to generate two or more DSBs, either in the same locus or in different loci. Strategies for editing that involve the formation of multiple DSBs, or SSBs, are described in, for instance, Cotta-Ramusino. In some embodiments, where multiple edits are made in the genome of an NK cell, or a cell that an NK cell is derived from, the edits are made at the same time or in close temporal proximity. In some such embodiments, two or more genomic edits are effected by two or more different RNA-guided nucleases. For example, one of the genomic edits may be effected by saCas9 (in connection with the respective saCas9 guide RNA), and a different genomic edit may be effected by Cpf1 (in connection with the respective Cpf1 guide RNA). In some embodiments, using different RNA-guided nucleases in the context of multiplex genomic editing approaches is advantageous as compared to using the same RNA-guided nuclease for two or more edits, e.g., in that it allows to decrease the likelihood or frequency of undesirable effects, such as, for example, off-target cutting, and the occurrence of genomic translocations.

Donor Template Design

[0178] Donor template design is described in detail in the literature, for instance in Cotta-Ramusino. DNA oligomer donor templates (oligodeoxynucleotides or ODNs), which can be single stranded (ssODNs) or double-stranded (dsODNs), can be used to facilitate HDR-based repair of DSBs, and are particularly useful for introducing alterations into a target DNA sequence, inserting a new sequence into the target sequence, or replacing the target sequence altogether.

[0179] Whether single-stranded or double stranded, donor templates generally include regions that are homologous to regions of DNA within or near (e.g. flanking or adjoining) a target sequence to be cleaved. These homologous regions are referred to here as “homology arms,” and are illustrated schematically below:

[5' homology arm]-[replacement sequence]--[3'
homology arm].

[0180] The homology arms can have any suitable length (including 0 nucleotides if only one homology arm is used), and 3' and 5' homology arms can have the same length, or can differ in length. The selection of appropriate homology arm lengths can be influenced by a variety of factors, such as the desire to avoid homologies or microhomologies with certain sequences such as Alu repeats or other very common elements. For example, a 5' homology arm can be shortened to avoid a sequence repeat element. In other embodiments, a 3' homology arm can be shortened to avoid a sequence repeat element. In some embodiments, both the 5' and the 3' homology arms can be shortened to avoid including certain sequence repeat elements. In addition, some homology arm designs can improve the efficiency of editing or increase the frequency of a desired repair outcome. For example, Richardson et al. *Nature Biotechnology* 34, 339-344 (2016)

(Richardson), which is incorporated by reference, found that the relative asymmetry of 3' and 5' homology arms of single stranded donor templates influenced repair rates and/or outcomes.

[0181] Replacement sequences in donor templates have been described elsewhere, including in Cotta-Ramusino et al. A replacement sequence can be any suitable length (including zero nucleotides, where the desired repair outcome is a deletion), and typically includes one, two, three or more sequence modifications relative to the naturally-occurring sequence within a cell in which editing is desired. One common sequence modification involves the alteration of the naturally-occurring sequence to repair a mutation that is related to a disease or condition of which treatment is desired. Another common sequence modification involves the alteration of one or more sequences that are complementary to, or code for, the PAM sequence of the RNA-guided nuclease or the targeting domain of the gRNA(s) being used to generate an SSB or DSB, to reduce or eliminate repeated cleavage of the target site after the replacement sequence has been incorporated into the target site.

[0182] Where a linear ssODN is used, it can be configured to (i) anneal to the nicked strand of the target nucleic acid, (ii) anneal to the intact strand of the target nucleic acid, (iii) anneal to the plus strand of the target nucleic acid, and/or (iv) anneal to the minus strand of the target nucleic acid. An ssODN may have any suitable length, e.g., about, at least, or no more than 150-200 nucleotides (e.g., 150, 160, 170, 180, 190, or 200 nucleotides).

[0183] It should be noted that a template nucleic acid can also be a nucleic acid vector, such as a viral genome or circular double stranded DNA, e.g., a plasmid. Nucleic acid vectors comprising donor templates can include other coding or non-coding elements. For example, a template nucleic acid can be delivered as part of a viral genome (e.g. in an AAV or lentiviral genome) that includes certain genomic backbone elements (e.g. inverted terminal repeats, in the case of an AAV genome) and optionally includes additional sequences coding for a gRNA and/or an RNA-guided nuclease. In certain embodiments, the donor template can be adjacent to, or flanked by, target sites recognized by one or more gRNAs, to facilitate the formation of free DSBs on one or both ends of the donor template that can participate in repair of corresponding SSBs or DSBs formed in cellular DNA using the same gRNAs. Exemplary nucleic acid vectors suitable for use as donor templates are described in Cotta-Ramusino.

[0184] Whatever format is used, a template nucleic acid can be designed to avoid undesirable sequences. In certain embodiments, one or both homology arms can be shortened to avoid overlap with certain sequence repeat elements, e.g., Alu repeats, LINE elements, etc.

Quantitative Measurement of On-Target Gene Editing

[0185] It should be noted that the genome editing systems of the present disclosure allow for the detection and quantitative measurement of on-target gene editing outcomes, including targeted integration. The compositions and methods described herein can rely on the use of donor templates comprising a 5' homology arm, a cargo, a one or more priming sites, a 3' homology arm, and optionally stuffer sequence. For example, International Patent Publication No. WO2019/014564 by Ramusino et al. (Ramusino), which is

incorporated by reference herein in its entirety, describes compositions and methods which allow for the quantitative analysis of on-target gene editing outcomes, including targeted integration events, by embedding one or more primer binding sites (i.e., priming sites) into a donor template that are substantially identical to a priming site present at the targeted genomic DNA locus (i.e., the target nucleic acid). The priming sites are embedded into the donor template such that, when homologous recombination of the donor template with a target nucleic acid occurs, successful targeted integration of the donor template integrates the priming sites from the donor template into the target nucleic acid such that at least one amplicon can be generated in order to quantitatively determine the on-target editing outcomes.

[0186] In some embodiments, the target nucleic acid comprises a first priming site (P1) and a second priming site (P2), and the donor template comprises a cargo sequence, a first priming site (P1'), and a second priming site (P2'), wherein P2' is located 5' from the cargo sequence, wherein P1' is located 3' from the cargo sequence (i.e., A1--P2'--N--P1'--A2), wherein P1' is substantially identical to P1, and wherein P2' is substantially identical to P2. After accurate homology-driven targeted integration, three amplicons are produced using a single PCR reaction with two oligonucleotide primers. The first amplicon, Amplicon X, is generated from the primer binding sites originally present in the genomic DNA (P1 and P2), and may be sequenced to analyze on-target editing events that do not result in targeted integration (e.g., insertions, deletions, gene conversion). The remaining two amplicons are mapped to the 5' and 3' junctions after homology-driven targeted integration. The second amplicon, Amplicon Y, results from the amplification of the nucleic acid sequence between P1 and P2' following a targeted integration event at the target nucleic acid, thereby amplifying the 5' junction. The third amplicon, Amplicon Z, results from the amplification of the nucleic acid sequence between P1' and P2 following a targeted integration event at the target nucleic acid, thereby amplifying the 3' junction. Sequencing of these amplicons provides a quantitative assessment of targeted integration at the target nucleic acid, in addition to information about the fidelity of the targeted integration. To avoid any biases inherent to amplicon size, stuffer sequence may optionally be included in the donor template to keep all three expected amplicons the same length.

Implementation of Genome Editing Systems: Delivery, Formulations, and Routes of Administration

[0187] As discussed above, the genome editing systems of this disclosure can be implemented in any suitable manner, meaning that the components of such systems, including without limitation the RNA-guided nuclease, gRNA, and optional donor template nucleic acid, can be delivered, formulated, or administered in any suitable form or combination of forms that results in the transduction, expression or introduction of a genome editing system and/or causes a desired repair outcome in a cell, tissue or subject. The genome editing systems according to this disclosure can incorporate multiple gRNAs, multiple RNA-guided nucleases, and other components such as proteins, and a variety of implementations will be evident to the skilled artisan based on the principles illustrated in systems of the disclosure. In some embodiments the genome editing system of the disclosure are delivered into cells as an ribonucleoprotein (RNP) complex. In some embodiments, one or more RNP complexes are delivered to the cell sequentially in any order, or simultaneously.

[0188] Nucleic acids encoding the various elements of a genome editing system according to the present disclosure can be administered to subjects or delivered into cells by art-known methods or as described herein. For example, RNA-guided nuclease-encoding and/or gRNA-encoding DNA, as well as donor template nucleic acids can be delivered by, e.g., vectors (e.g., viral or non-viral vectors), non-vector based methods (e.g., using naked DNA or DNA complexes), or a combination thereof. In some embodiments the genome editing system of the disclosure are delivered by AAV.

[0189] Nucleic acids encoding genome editing systems or components thereof can be delivered directly to cells as naked DNA or RNA, for instance by means of transfection or electroporation, or can be conjugated to molecules (e.g., N-acetylgalactosamine) promoting uptake by the target cells (e.g., erythrocytes, HSCs). In some embodiments the genome editing system of the disclosure are delivered into cells by electroporation.

[0190] One promising solution to improve cell therapy processes consists on the direct delivery of active proteins into human cells. A protein delivery agent, the Feldan Shuttle, is a protein-based delivery agent, which is designed for cell therapy (Del'Guidice et al., PLoS One. 2018 Apr. 4; 13(4):e0195558; incorporated in its entirety herein by reference). In some embodiments the genome editing system of the disclosure are delivered into cells by the Feldan Shuttle.

[0191] The modified cells of the disclosure can be administered by any known routes of administration known to a person of skill in the art, at the time of filing this application. In some embodiments the modified cells of the disclosure are administered intravenously (IV). In some embodiments the modified NK cells of the disclosure are administered intravenously (IV).

[0192] As used herein, "dose" refers to a specific quantity of a pharmacologically active material for administration to a subject for a given time. Unless otherwise specified, the doses recited refer to NK cells having complex genomic alterations, that allow for the generation of advanced NK cell products for clinical applications. In some embodiments, a dose of modified NK cells refers to an effective amount of modified NK cells. For example, in some embodiments a dose or effective amount of modified NK cells refers to about 1×10^9 - 5×10^9 modified NK cells, or about 2×10^9 - 5×10^9 modified NK cells per dose. In some embodiments a dose or effective amount of modified NK cells refers to about 3×10^9 - 5×10^9 modified NK cells, or about 4×10^9 - 10^9 modified NK cells per dose.

Generation of Modified iNK Cells

[0193] Some aspects of this disclosure relate to the generation of genetically modified NK cells that are derived from stem cells, e.g., from multipotent cells, such as, e.g., HSCs, or from pluripotent stem cells, such as, e.g., ES cells or iPS cells. In some embodiments, where genetically modified iNK cells are derived from iPS cells, the iPS cells are derived from a somatic donor cell. In some embodiments, where genetically modified iNK cells are derived from iPS cells, the iPS cells are derived from a multipotent donor cell, e.g., from an HSC.

[0194] The genomic edits present in the final iNK cell can be made at any stage of the process of reprogramming the donor cell to the iPS cell state, during the iPS cell state, and/or at any stage of the process of differentiating the iPS cell to an iNK state, e.g., at an intermediary state, such as, for example, an iPS cell-derived HSC state, or even up to or at the final iNK cell state. In some embodiments, one or more genomic edits present in a modified iNK cell provided herein is made before reprogramming the donor cell to the iPS cell state. In some embodiments, all edits present in a modified iNK cell provided herein are made at the same time, in close temporal proximity, and/or at the same cell stage of the reprogramming/differentiation process, e.g., at the donor cell stage, during the reprogramming process, at the iPS cell stage, or during the differentiation process. In some embodiments, two or more edits present in a modified iNK cell provided herein are made at different times and/or at different cell stages of the reprogramming/differentiation process. For example, in some embodiments, an edit is made at the donor cell stage and a different edit is made at the iPS cell stage; in some embodiments, an edit is made at the reprogramming stage and a different edit is made at the iPS cell stage. These examples are provided to illustrate some of the strategies provided herein, and are not meant to be limiting.

[0195] A variety of cell types can be used as a donor cell that can be subjected to the reprogramming, differentiation, and genomic editing strategies provided herein for the derivation of modified iNK cells. The donor cell to be subjected to the reprogramming, differentiation, and genomic editing strategies provided herein can be any suitable cell type. For example, the donor cell can be a pluripotent stem cell or a differentiated cell, e.g., a somatic cell, such as, for example, a fibroblast or a T lymphocyte.

[0196] In some embodiments, the donor cell is a human cell. In some embodiments, the donor cell is a non-human primate cell. In some embodiments, the donor cell is a mammalian cell. In some embodiments, the donor cell is a somatic cell. In some embodiments, the donor cell is a stem or progenitor cell. In certain embodiments, the donor cell is not part of a human embryo and its derivation does not involve the destruction of a human embryo.

[0197] In some embodiments, iNK cells, and methods of deriving such iNK cells, having one or more genomic alterations (e.g., a knock-out of a gene undesirable for immunooncology therapeutic approaches, and/or a knock-in of an exogenous nucleic acid, e.g. an expression construct encoding a gene product desirable for immunooncology therapeutic approaches) are provided herein. In some embodiments, the iNK cells are derived from an iPS cell, which in turn is derived from a somatic donor cell. Any suitable somatic cell can be used in the generation of iPS cells, and in turn, the generation of iNK cells. Suitable strategies for deriving iPS cells from various somatic donor cell types have been described and are known in the art. In some embodiments, the somatic donor cell is a fibroblast cell. In some embodiments, the somatic donor cell is a mature T cell.

[0198] For example, in some embodiments, the somatic donor cell, from which an iPS cell, and subsequently an iNK cell is derived, is a developmentally mature T cell (a T cell that has undergone thymic selection). One hallmark of developmentally mature T cells is a rearranged T cell receptor locus. During T cell maturation, the TCR locus

undergoes V(D)J rearrangements to generate complete V-domain exons. These rearrangements are retained throughout reprogramming of a T cells to an induced pluripotent stem (iPS) cell, and throughout differentiation of the resulting iPS cell to a somatic cell.

[0199] In certain embodiments, the somatic donor cell is a CD8⁺ T cell, a CD8⁺ naïve T cell, a CD4⁺ central memory T cell, a CD8⁺ central memory T cell, a CD4⁺ effector memory T cell, a CD4⁺ effector memory T cell, a CD4⁺ T cell, a CD4⁺ stem cell memory T cell, a CD8⁺ stem cell memory T cell, a CD4⁺ helper T cell, a regulatory T cell, a cytotoxic T cell, a natural killer T cell, a CD4⁺ naïve T cell, a TH17 CD4⁺ T cell, a TH1 CD4⁺ T cell, a TH2 CD4⁺ T cell, a TH9 CD4⁺ T cell, a CD4⁺ Foxp3⁺ T cell, a CD4⁺ CD25⁺ CD127⁻ T cell, or a CD4⁺ CD25⁺ CD127⁻ Foxp3⁺ T cell.

[0200] One advantage of using T cells for the generation of iPS cells is that T cells can be edited with relative ease, e.g., by CRISPR-based methods or other gene-editing methods. Another advantage of using T cells for the generation of iPS cells is that the rearranged TCR locus allows for genetic tracking of individual cells and their daughter cells. If the reprogramming, expansion, culture, and/or differentiation strategies involved in the generation of NK cells a clonal expansion of a single cell, the rearranged TCR locus can be used as a genetic marker unambiguously identifying a cell and its daughter cells. This, in turn, allows for the characterization of a cell population as truly clonal, or for the identification of mixed populations, or contaminating cells in a clonal population.

[0201] A third advantage of using T cells in generating iNK cells carrying multiple edits is that certain karyotypic aberrations associated with chromosomal translocations are selected against in T cell culture. Such aberrations pose a concern when editing cells by CRISPR technology, and in particular when generating cells carrying multiple edits.

[0202] A fourth advantage of using T cell derived iPS cells as a starting point for the derivation of therapeutic lymphocytes is that it allows for the expression of a pre-screened TCR in the lymphocytes, e.g., via selecting the T cells for binding activity against a specific antigen, e.g., a tumor antigen, reprogramming the selected T cells to iPS cells, and then deriving lymphocytes from these iPS cells that express the TCR (e.g., T cells). This strategy would also allow for activating the TCR in other cell types, e.g., by genetic or epigenetic strategies.

[0203] A fifth advantage of using T cell derived iPS cells as a starting point for iNK differentiation is that the T cells retain at least part of their “epigenetic memory” throughout the reprogramming process, and thus subsequent differentiation of the same or a closely related cell type, such as iNK cells will be more efficient and/or result in higher quality cell populations as compared to approaches using non-related cells, such as fibroblasts, as a starting point for iNK derivation.

[0204] In certain embodiments, the donor cell being manipulated, e.g., the cell being reprogrammed and/or the cell, the genome of which is being edited, is a long term hematopoietic stem cell, a short term hematopoietic stem cell, a multipotent progenitor cell, a lineage restricted progenitor cell, a lymphoid progenitor cell, a myeloid progenitor cell, a common myeloid progenitor cell, an erythroid progenitor cell, a megakaryocyte erythroid progenitor cell, a retinal cell, a photoreceptor cell, a rod cell, a cone cell, a retinal pigmented epithelium cell, a trabecular meshwork

cell, a cochlear hair cell, an outer hair cell, an inner hair cell, a pulmonary epithelial cell, a bronchial epithelial cell, an alveolar epithelial cell, a pulmonary epithelial progenitor cell, a striated muscle cell, a cardiac muscle cell, a muscle satellite cell, a neuron, a neuronal stem cell, a mesenchymal stem cell, an induced pluripotent stem (iPS) cell, an embryonic stem cell, a fibroblast, a monocyte-derived macrophage or dendritic cell, a megakaryocyte, a neutrophil, an eosinophil, a basophil, a mast cell, a reticulocyte, a B cell, e.g., a progenitor B cell, a Pre B cell, a Pro B cell, a memory B cell, a plasma B cell, a gastrointestinal epithelial cell, a biliary epithelial cell, a pancreatic ductal epithelial cell, an intestinal stem cell, a hepatocyte, a liver stellate cell, a Kupffer cell, an osteoblast, an osteoclast, an adipocyte, a preadipocyte, a pancreatic islet cell (e.g., a beta cell, an alpha cell, a delta cell), a pancreatic exocrine cell, a Schwann cell, or an oligodendrocyte.

[0205] In certain embodiments, the donor cell is a circulating blood cell, e.g., a reticulocyte, megakaryocyte erythroid progenitor (MEP) cell, myeloid progenitor cell (CMP/GMP), lymphoid progenitor (LP) cell, hematopoietic stem/progenitor cell (HSC), or endothelial cell (EC). In certain embodiments, the donor cell is a bone marrow cell (e.g., a reticulocyte, an erythroid cell (e.g., erythroblast), an MEP cell, myeloid progenitor cell (CMP/GMP), LP cell, erythroid progenitor (EP) cell, HSC, multipotent progenitor (MPP) cell, endothelial cell (EC), hemogenic endothelial (HE) cell, or mesenchymal stem cell). In certain embodiments, the donor cell is a myeloid progenitor cell (e.g., a common myeloid progenitor (CMP) cell or granulocyte macrophage progenitor (GMP) cell). In certain embodiments, the donor cell is a lymphoid progenitor cell, e.g., a common lymphoid progenitor (CLP) cell. In certain embodiments, the donor cell is an erythroid progenitor cell (e.g., an MEP cell). In certain embodiments, the donor cell is a hematopoietic stem/progenitor cell (e.g., a long term HSC (LT-HSC), short term HSC (ST-HSC), MPP cell, or lineage restricted progenitor (LRP) cell). In certain embodiments, the donor cell is a CD34⁺ cell, CD34⁺ CD90 cell, CD34⁺ CD38⁻ cell, CD34⁺ CD90⁺ CD49f⁺CD38⁻CD45RA⁻ cell, CD105⁺ cell, CD31⁺, or CD133⁺ cell, or a CD34⁺ CD90⁺ CD133⁺ cell. In certain embodiments, the donor cell is an umbilical cord blood CD34+ HSPC, umbilical cord venous endothelial cell, umbilical cord arterial endothelial cell, amniotic fluid CD34⁺ cell, amniotic fluid endothelial cell, placental endothelial cell, or placental hematopoietic CD34⁺ cell. In certain embodiments, the donor cell is a mobilized peripheral blood hematopoietic CD34⁺ cell (after the patient is treated with a mobilization agent, e.g., G-CSF or Plerixafor). In certain embodiments, the donor cell is a peripheral blood endothelial cell.

[0206] In some embodiments, the donor cell is a dividing cell. In other embodiments, the donor cell is a non-dividing cell.

[0207] In some embodiments, the modified iNK cells resulting from the methods and strategies of reprogramming, differentiating, and editing provided herein, are administered to a subject in need thereof, e.g., in the context of an immunooncology therapeutic approach. In some embodiments, donor cells, or any cells of any stage of the reprogramming, differentiating, and editing strategies provided herein can be maintained in culture or stored (e.g., frozen in

liquid nitrogen) using any suitable method known in the art, e.g., for subsequent characterization or administration to a subject in need thereof.

Cell Reprogramming

[0208] A cell that has an increased cell potency has more developmental plasticity (i.e., can differentiate into more cell types) compared to the same cell in the non-reprogrammed state. In other words, a reprogrammed cell is one that is in a less differentiated state than the same cell in a non-reprogrammed state.

[0209] The reprogramming of the cells of the disclosure can be performed by utilizing several methods. Examples of some methods for reprogramming somatic cells of the disclosure are described in, but are not limited to, Valamehr et al. WO2017/078807 ("Valamehr") and Mendlein et al. WO2010/108126 ("Mendlein"), which are hereby incorporated by reference in their entireties.

[0210] Briefly, a method for directing differentiation of pluripotent stem cells into cells of a definitive hematopoietic lineage, may comprise: (i) contacting pluripotent stem cells with a composition comprising a BMP activator, and optionally bFGF, to initiate differentiation and expansion of mesodermal cells from the pluripotent stem cells; (ii) contacting the mesodermal cells with a composition comprising a BMP activator, bFGF, and a GSK3 inhibitor, wherein the composition is optionally free of TGF β receptor/ALK inhibitor, to initiate differentiation and expansion of mesodermal cells having definitive HE potential from the mesodermal cells; (iii) contacting the mesodermal cells having definitive HE potential with a composition comprising a ROCK inhibitor; one or more growth factors and cytokines selected from the group consisting of bFGF, VEGF, SCF, IGF, EPO, IL6, and IL11; and optionally, a Wnt pathway activator, wherein the composition is optionally free of TGF β receptor/ALK inhibitor, to initiate differentiation and expansion of definitive hemogenic endothelium from pluripotent stem cell-derived mesodermal cells having definitive hemogenic endothelium potential; and optionally, subjecting pluripotent stem cells, pluripotent stem cell-derived mesodermal cells, mesodermal cells having hemogenic endothelium, and/or definitive hemogenic endothelium under low oxygen tension between about 2% to about 10%.

[0211] In some embodiments of the method for directing differentiation of pluripotent stem cells into cells of a hematopoietic lineage, the method further comprises contacting pluripotent stem cells with a composition comprising a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor, wherein the composition is free of TGF β receptor/ALK inhibitors, to seed and expand the pluripotent stem cells. In some embodiments, the pluripotent stem cells are iPSCs. In some embodiments, the iPSCs are naïve iPSCs. In some embodiments, the iPSC comprises one or more genetic imprints, and wherein the one or more genetic imprints comprised in the iPSC are retained in the pluripotent stem cell derived hematopoietic cells differentiated therefrom.

[0212] In some embodiments of the method for directing differentiation of pluripotent stem cells into cells of a hematopoietic lineage, the differentiation of the pluripotent stem cells into cells of hematopoietic lineage is void of generation of embryoid bodies, and is in a monolayer culturing form.

[0213] In some embodiments of the above method, the obtained pluripotent stem cell-derived definitive hemogenic

endothelium cells are CD34+. In some embodiments, the obtained definitive hemogenic endothelium cells are CD34+ CD43-. In some embodiments, the definitive hemogenic endothelium cells are CD34+CD43-CXCR4-CD73-. In some embodiments, the definitive hemogenic endothelium cells are CD34+CXCR4-CD73-. In some embodiments, the definitive hemogenic endothelium cells are CD34+CD43-CD93-. In some embodiments, the definitive hemogenic endothelium cells are CD34+CD93-.

[0214] In some embodiments of the above method, the method further comprises (i) contacting pluripotent stem cell-derived definitive hemogenic endothelium with a composition comprising a ROCK inhibitor; one or more growth factors and cytokines selected from the group consisting of VEGF, bFGF, SCF, Flt3L, TPO, and IL7; and optionally a BMP activator; to initiate the differentiation of the definitive hemogenic endothelium to pre-T cell progenitors; and optionally, (ii) contacting the pre-T cell progenitors with a composition comprising one or more growth factors and cytokines selected from the group consisting of SCF, Flt3L, and IL7, but free of one or more of VEGF, bFGF, TPO, BMP activators and ROCK inhibitors, to initiate the differentiation of the pre-T cell progenitors to T cell progenitors or T cells. In some embodiments of the method, the pluripotent stem cell-derived T cell progenitors are CD34+CD45+ CD7+. In some embodiments of the method, the pluripotent stem cell-derived T cell progenitors are CD45+CD7+.

[0215] In yet some embodiments of the above method for directing differentiation of pluripotent stem cells into cells of a hematopoietic lineage, the method further comprises: (i) contacting pluripotent stem cell-derived definitive hemogenic endothelium with a composition comprising a ROCK inhibitor; one or more growth factors and cytokines selected from the group consisting of VEGF, bFGF, SCF, Flt3L, TPO, IL3, IL7, and IL15; and optionally, a BMP activator, to initiate differentiation of the definitive hemogenic endothelium to pre-NK cell progenitor; and optionally, (ii) contacting pluripotent stem cells-derived pre-NK cell progenitors with a composition comprising one or more growth factors and cytokines selected from the group consisting of SCF, Flt3L, IL3, IL7, and IL15, wherein the medium is free of one or more of VEGF, bFGF, TPO, BMP activators and ROCK inhibitors, to initiate differentiation of the pre-NK cell progenitors to NK cell progenitors or NK cells. In some embodiments, the pluripotent stem cell-derived NK progenitors are CD3-CD45+CD56+CD7+. In some embodiments, the pluripotent stem cell-derived NK cells are CD3-CD45+ CD56+, and optionally further defined by NKp46+, CD57+ and CD16+.

[0216] In yet some embodiments of the above method for directing differentiation of pluripotent stem cells into NK cells, the method further comprises knocking out the gene Nrg1 in the pluripotent stem cells.

[0217] In some embodiments, the disclosure provides a method for generating pluripotent stem cell-derived T lineage cells, which comprises: (i) contacting pluripotent stem cells with a composition comprising a BMP activator, and optionally bFGF, to initiate differentiation and expansion of mesodermal cells from pluripotent stem cells; (ii) contacting the mesodermal cells with a composition comprising a BMP activator, bFGF, and a GSK3 inhibitor, but free of TGF β receptor/ALK inhibitor, to initiate differentiation and expansion of the mesodermal cells having definitive HE potential from the mesodermal cells; (iii) contacting mesodermal cells

having definitive HE potential with a composition comprising a ROCK inhibitor; one or more growth factors and cytokines selected from the group consisting of bFGF, VEGF, SCF, IGF, EPO, IL6, and IL11; and optionally, a Wnt pathway activator; wherein the composition is free of TGF β receptor/ALK inhibitor, to initiate differentiation and expansion of definitive hemogenic endothelium from mesodermal cells having definitive HE potential; (iv) contacting definitive hemogenic endothelium with a composition comprising a ROCK inhibitor; one or more growth factors and cytokines selected from the group consisting of VEGF, bFGF, SCF, Flt3L, TPO, and IL7; and optionally a BMP activator; to initiate differentiation of the definitive hemogenic endothelium to pre-T cell progenitors; and (v) contacting the pre-T cell progenitors with a composition comprising one or more growth factors and cytokines selected from the group consisting of SCF, Flt3L, and IL7, wherein the composition is free of one or more of VEGF, bFGF, TPO, BMP activators and ROCK inhibitors; to initiate differentiation of the pre-T cell progenitors to T cell progenitors or T cells; and optionally, the seeded pluripotent stem cells, mesodermal cells, mesodermal cells having definitive HE potential, and/or definitive hemogenic endothelium may be subject to low oxygen tension between about 2% to about 10%. In some embodiments, group II of the above method further comprises: contacting iPSCs with a composition comprising a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor, but free of TGF β receptor/ALK inhibitors, to seed and expand pluripotent stem cells; and/or wherein the pluripotent stem cells. In some embodiments, the pluripotent stem cells are iPSCs. In some embodiments, the iPSCs are naïve iPSC. In some embodiments of the method, the differentiation of the pluripotent stem cells into T cell lineages is void of generation of embryoid bodies, and is in a monolayer culturing format.

[0218] In some embodiments, the disclosure provides a method for generating pluripotent stem cell-derived NK lineage cells, which comprises: (i) contacting pluripotent stem cells with a composition comprising a BMP activator, and optionally bFGF, to initiate differentiation and expansion of mesodermal cells from the pluripotent stem cells; (ii) contacting mesodermal cells with a composition comprising a BMP activator, bFGF, and a GSK3 inhibitor, and optionally free of TGF β receptor/ALK inhibitor, to initiate differentiation and expansion of mesodermal cells having definitive HE potential from mesodermal cells; (iii) contacting mesodermal cells having definitive HE potential with a composition comprising one or more growth factors and cytokines selected from the group consisting of bFGF, VEGF, SCF, IGF, EPO, IL6, and IL11; a ROCK inhibitor; optionally a Wnt pathway activator; and optionally free of TGF β receptor/ALK inhibitor, to initiate differentiation and expansion of pluripotent stem cell-derived definitive hemogenic endothelium from the pluripotent stem cell-derived mesodermal cells having definitive HE potential; (iv) contacting pluripotent stem cell-derived definitive hemogenic endothelium with a composition comprising a ROCK inhibitor; one or more growth factors and cytokines selected from the group consisting of VEGF, bFGF, SCF, Flt3L, TPO, IL3, IL7, and IL15, and optionally, a BMP activator, to initiate differentiation of the pluripotent stem cell-derived definitive hemogenic endothelium to pre-NK cell progenitors; and (v) contacting pluripotent stem cell-derived pre-NK cell progenitors with a composition comprising one or more growth

factors and cytokines selected from the group consisting of SCF, Flt3L, IL3, IL7, and IL15, but free of one or more of VEGF, bFGF, TPO, BMP activators and ROCK inhibitors, to initiate differentiation of the pluripotent stem cell-derived pre-NK cell progenitors to pluripotent stem cell-derived NK cell progenitors or NK cells; and optionally, subjecting seeded pluripotent stem cells, pluripotent stem cell-derived-mesodermal cells, and/or definitive hemogenic endothelium under low oxygen tension between about 2% to about 10%. In some embodiments, the method for generating pluripotent stem cell-derived NK lineage cells of group II further comprises contacting iPSCs with a composition comprising a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor, but free of TGF β receptor/ALK inhibitors, to seed and expand the iPSCs. In some embodiments, the iPSCs are naïve iPSCs. In some embodiments, the method for generating pluripotent stem cell-derived NK lineage cells is void of generation of embryoid bodies, and is in a monolayer culturing format.

[0219] In some embodiments, the disclosure provides a method for generating pluripotent stem cell-derived definitive hemogenic endothelium, the method comprises: (i) contacting iPSCs with a composition comprising a BMP activator, and optionally bFGF, to initiate differentiation and expansion of pluripotent stem cell-derived mesodermal cells from pluripotent stem cells; (ii) contacting pluripotent stem cell-derived mesodermal cells with a composition comprising a BMP activator, bFGF, and a GSK3 inhibitor, and optionally free of TGF β receptor/ALK inhibitor, to initiate differentiation and expansion of pluripotent stem cell-derived mesodermal cells having definitive HE potential from pluripotent stem cell-derived mesodermal cells; (iii) contacting pluripotent stem cell-derived mesodermal cells having definitive HE potential with a composition comprising one or more growth factors and cytokines selected from the group consisting of bFGF, VEGF, SCF, IGF, EPO, IL6, and IL11; a ROCK inhibitor; and optionally a Wnt pathway activator, and optionally free of TGF β receptor/ALK inhibitor, to initiate differentiation and expansion of pluripotent stem cell-derived definitive hemogenic endothelium from the pluripotent stem cell-derived mesodermal cells having definitive HE potential; and optionally, subjecting seeded pluripotent stem cells, pluripotent stem cell-derived mesodermal cells, and/or definitive hemogenic endothelium under low oxygen tension between about 2% to about 10%. In some embodiments, the above method for generating pluripotent stem cell-derived definitive hemogenic endothelium, further comprises: contacting iPSCs with a composition comprising a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor, but free of TGF β receptor/ALK inhibitors, to seed and expand the iPSCs; and/or wherein the iPSCs are naïve iPSCs. In some embodiments, the iPSC comprises one or more genetic imprints, and wherein the one or more genetic imprints comprised in the iPSC are retained in the pluripotent stem cell derived definitive hemogenic endothelium cells differentiated therefrom. In some embodiments, the above method of differentiating iPSCs into cells of a definitive hemogenic endothelium is void of generation of embryoid bodies, and is in monolayer culturing format.

[0220] In some embodiments, the disclosure provides a method for generating pluripotent stem cell-derived multipotent progenitors of hematopoietic lineage, comprising: (i) contacting iPSCs with a composition comprising a BMP activator, and optionally bFGF, to initiate differentiation and

expansion of pluripotent stem cell-derived mesodermal cells from iPSCs; (ii) contacting pluripotent stem cell-derived mesodermal cells with a composition comprising a BMP activator, bFGF, and a GSK3 inhibitor, but free of TGF β receptor/ALK inhibitor, to initiate differentiation and expansion of the mesodermal cells having definitive HE potential from the mesodermal cells; (iii) contacting mesodermal cells having definitive HE potential with a composition comprising a ROCK inhibitor; one or more growth factors and cytokines selected from the group consisting of bFGF, VEGF, SCF, IGF, EPO, IL6, and IL11; and optionally, a Wnt pathway activator, wherein the composition is free of TGF β receptor/ALK inhibitor, to initiate differentiation and expansion of definitive hemogenic endothelium from mesodermal cells having definitive HE potential; (iv) contacting definitive hemogenic endothelium with a composition comprising a BMP activator, a ROCK inhibitor, one or more growth factors and cytokines selected from the group consisting of TPO, IL3, GMCSF, EPO, bFGF, VEGF, SCF, IL6, Flt3L and IL11, to initiate differentiation of definitive hemogenic endothelium to pre-HSC; and (v) contacting pre-HSC with a composition comprising a BMP activator, one or more growth factors and cytokines selected from the group consisting of TPO, IL3, GMCSF, EPO, bFGF, VEGF, SCF, IL6, and IL11, but free of ROCK inhibitor, to initiate differentiation of the pre-HSC to hematopoietic multipotent progenitors; and optionally, subjecting seeded pluripotent stem cells, mesodermal cells, and/or definitive hemogenic endothelium under low oxygen tension between about 2% to about 10%. In some embodiments, the above method for generating pluripotent stem cell-derived hematopoiesis multipotent progenitors further comprises contacting pluripotent stem cells with a composition comprising a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor, but free of TGF β receptor/ALK inhibitors, to seed and expand the pluripotent stem cells. In some embodiments, the pluripotent stem cells are iPSCs. In some embodiments, the iPSCs are naïve iPSCs. In some embodiments, the iPSC comprises one or more genetic imprints, and wherein the one or more genetic imprints comprised in the iPSC are retained in the pluripotent stem cell derived hematopoietic multipotent progenitor cells differentiated therefrom. In some embodiments, the differentiation of the pluripotent stem cells into hematopoiesis multipotent progenitors using the above method is void of generation of embryoid bodies, and is in monolayer culturing format.

[0221] In some embodiments, the disclosure provides a composition comprising: one or more cell populations generated from the culture platform disclosed herein: pluripotent stem cells-derived (i) CD34+ definitive hemogenic endothelium (iCD34), wherein the iCD34 cells have capacity to differentiate into multipotent progenitor cells, T cell progenitors, NK cell progenitors, T cells, NK cells, NKT cells and B cells, and wherein the iCD34 cells are CD34+ CD43-; (ii) definitive hemogenic endothelium (iHE), wherein the iHE cells are CD34+, and at least one of CD43-, CD93-, CXCR4-, CD73-, and CXCR4-CD73-; (iii) pluripotent stem cell-derived definitive HSCs, wherein the iHSC is CD34+CD45+; (iv) hematopoietic multipotent progenitor cells, wherein the iMPP cells are CD34+CD45+; (v) T cell progenitors, wherein the T cell progenitors are CD34+ CD45+CD7+ or CD34-CD45+CD7+; (vi) T cells, wherein the T cells are CD45+CD3+CD4+ or CD45+CD3+CD8+; (vii) NK cell progenitors, wherein the NK cell progenitors

are CD45+CD56+CD7+; (viii) NK cells, wherein the NK cells are CD3-CD45+CD56+, and optionally further defined by NKp46+, CD57+, and CD16+; (ix) NKT cells, wherein the NKT cells are CD45+V α 24J α 18+CD3+; and (x) B cells, wherein the B cells are CD45+CD19+.

[0222] In some embodiments, the disclosure provides one or more cell lines, or clonal cells generated using the methods disclosed herein: pluripotent stem cell-derived (i) CD34+ definitive hemogenic endothelium (iCD34), wherein the iCD34 cells have capacity to differentiate into multipotent progenitor cells, T cell progenitors, NK cell progenitors, T cells, NK cells, and NKT cells, and wherein the iCD34 cells are CD34+CD43-; (ii) definitive hemogenic endothelium (iHE), wherein the iHE cell line or clonal cells are CD34+, and at least one of CD43-, CD93-, CXCR4-, CD73-, and CXCR4-CD73-; (iii) definitive HSCs, wherein the iHSCs is CD34+CD45+; (iv) hematopoietic multipotent progenitor cells (iMPP), wherein the iMPP cells are CD34+CD45+; (v) T cell progenitors, wherein the T cell progenitors are CD34+CD45+CD7+ or CD34-CD45+CD7+; (vi) T cells, wherein the T cells are CD45+CD3+CD4+ or CD45+CD3+CD8+; (vii) NK cell progenitors, wherein the NK cell progenitors are CD45+CD56+CD7+; (viii) NK cells, wherein the NK cells are CD3-CD45+CD56+, and optionally further defined by NKp46+, CD57+, and CD16+; (ix) NKT cells, wherein the NKT cells are CD45+V α 24J α 18+CD3+; and (x) B cells, wherein the B cells are CD45+CD19+.

[0223] In some embodiments, the present disclosure provides a method of promoting hematopoietic self-renewal, reconstitution or engraftment using one or more of cell populations, cell lines or clonal cells generated using methods as disclosed: pluripotent stem cell-derived (i) CD34+ definitive hemogenic endothelium (iCD34), wherein the iCD34 cells have capacity to differentiate into multipotent progenitor cells, T cell progenitors, NK cell progenitors, T cells NK cells and NKT cells, and wherein the iCD34 cells are CD34+CD43-; (ii) definitive hemogenic endothelium (iHE), wherein the iHE cell line or clonal cells are CD34+, and at least one of CD43-, CD93-, CXCR4-, CD73-, and CXCR4-CD73-; (iii) definitive HSCs, wherein the iHSCs are CD34+CD45+; (iv) hematopoietic multipotent progenitor cells, wherein the iMPP cells are CD34+CD45+; (v) T cell progenitors, wherein the T cell progenitors are CD34+CD45+CD7+ or CD34-CD45+CD7+; (vi) T cells, wherein the T cells are CD45+CD3+CD4+ or CD45+CD3+CD8+; (vii) NK cell progenitors, wherein the NK cell progenitors are CD45+CD56+CD7+; (viii) NK cells, wherein the NK cells are CD3-CD45+CD56+, and optionally further defined by NKp46+, CD57+, and CD16+; (ix) NKT cells, wherein the NKT cells are CD45+V α 24J α 18+CD3+; and (x) B cells, wherein the B cells are CD45+CD19+.

[0224] In some embodiments, the present disclosure provides a method of generating hematopoietic lineage cells with enhanced therapeutic properties, and the method comprises: obtaining iPSCs comprising one or more genetic imprints; and directing differentiation of iPSCs to hematopoietic lineage cells. The step of directed differentiation further comprises: (i) contacting the pluripotent stem cells with a composition comprising a BMP pathway activator, and optionally bFGF, to obtain mesodermal cells; and (ii) contacting the mesodermal cells with a composition comprising a BMP pathway activator, bFGF, and a WNT pathway activator, to obtain mesodermal cells having definitive

hemogenic endothelium (HE) potential, wherein the mesodermal cells having definitive hemogenic endothelium (HE) potential are capable of providing hematopoietic lineage cells. Preferably, the mesodermal cells and mesodermal cells having definitive HE potential are obtained in steps (i) and (ii) without the step of forming embryoid bodies, and the obtained hematopoietic lineage cells comprise definitive hemogenic endothelium cells, hematopoietic stem and progenitor cells (HSC), hematopoietic multipotent progenitor cell (MPP), pre-T cell progenitor cells, pre-NK cell progenitor cells, T cell progenitor cells, NK cell progenitor cells, T cells, NK cells, NKT cells, or B cells. Moreover, the hematopoietic lineage cells retain the genetic imprints comprised in the iPSCs for directed differentiation.

[0225] In some embodiments, the step of directed differentiation of the above method further comprises: (i) contacting the mesodermal cells having definitive HE potential with a composition comprising bFGF and a ROCK inhibitor to obtain definitive HE cells; (ii) contacting the definitive HE cells with a composition comprising a BMP activator, and optionally a ROCK inhibitor, and one or more growth factors and cytokines selected from the group consisting of TPO, IL3, GMCSF, EPO, bFGF, VEGF, SCF, IL6, Flt3L and IL11 to obtain hematopoietic multipotent progenitor cells (MPP); (iii) contacting the definitive HE cells with a composition comprising one or more growth factors and cytokines selected from the group consisting of SCF, Flt3L, and IL7; and optionally one or more of a BMP activator, a ROCK inhibitor, TPO, VEGF and bFGF to obtain pre-T cell progenitors, T cell progenitors, and/or T cells; or (iv) contacting the definitive HE cells with a composition comprising one or more growth factors and cytokines selected from the group consisting of SCF, Flt3L, TPO, IL7 and IL15, and optionally one or more of a BMP activator, a ROCK inhibitor, VEGF and bFGF to obtain pre-NK cell progenitors, NK cell progenitors, and/or NK cells.

[0226] Briefly, the method may comprise reprogramming a mature source T or B cell to obtain induced pluripotent stem cells (iPSCs); and detecting the presence, in the iPSCs or the hematopoietic lineage cells derived therefrom, of a specific V(D)J recombination that is same as the one comprised in the mature T or B cell for generating the iPSC. In some embodiments, the above method further comprises isolating iPSCs or hematopoietic lineage cells comprising the same V(D)J recombination as that of the mature source T or B cell. In some embodiments, the above method comprises, prior to reprogramming the source cells, obtaining a mature source T or B cell for reprogramming; and determining V(D)J recombination comprised in immunoglobulins (Ig) or T cell receptors (TCR) that is specific to the mature source T or B cell.

[0227] A “pluripotency factor,” or “reprogramming factor,” refers to an agent capable of increasing the developmental potency of a cell, either alone or in combination with other agents. Pluripotency factors include, without limitation, polynucleotides, polypeptides, and small molecules capable of increasing the developmental potency of a cell. Exemplary pluripotency factors include, for example, transcription factors and small molecule reprogramming agents.

[0228] A number of various cell types from all three germ layers have been shown to be suitable for somatic cell reprogramming, including, but not limited to liver and stomach (Aoi et al., 2008); pancreatic f cells (Stadtfeld et al., 2008); mature B lymphocytes (Hanna et al., 2008); human

dermal fibroblasts (Takahashi et al., 2007; Yu et al., 2007; Lowry et al., 2008; Aasen et al., 2008); meningoicytes (Qin et al., 2008); neural stem cells (DiStefano et al., 2008); and neural progenitor cells (Eminli et al., 2008). Thus, the present disclosure contemplates, in part, methods to reprogram and/or program cells from any cell lineage.

[0229] The present disclosure contemplates, in part, to alter the potency of a cell by contacting the cell with one or more repressors and/or activators to modulate the epigenetic state, chromatin structure, transcription, mRNA splicing, post-transcriptional modification, mRNA stability and/or half-life, translation, post-translational modification, protein stability and/or half-life and/or protein activity of a component of a cellular pathway associated with determining or influencing cell potency.

[0230] Thus, in various embodiments, the present disclosure uses predictable and highly controlled methods for gene expression, as discussed elsewhere herein, that enable the reprogramming or de-differentiation and programming or differentiation of somatic cells ex vivo or in vivo. As, noted above, the intentional genetic engineering of cells, however, is not preferred, since it alters the cellular genome and would likely result in genetic or epigenetic abnormalities. In contrast, the compositions and methods of the present disclosure provide repressors and/or activators that non-genetically alter the potency of a cell by mimicking the cell's endogenous developmental potency pathways to achieve reprogramming and/or programming of the cell.

Small Molecules in Reprogramming

[0231] Reprogramming of somatic cells into induced pluripotent stem cells has also been achieved by retroviral infection of defined genes (e.g., Oct-3/4, Sox-2, Klf-4, c-Myc, and Lin28, and the like) in combination with small molecules.

[0232] In some embodiments, the present disclosure provides a method of altering the potency of a cell that comprises contacting the cell with one or more repressors and/or activators or a composition comprising the same, wherein said one or more repressors and/or activators modulates at least one component of a cellular pathway associated with the potency of the cell, thereby altering the potency of the cell. In particular embodiments, the one or more repressors and/or activators modulate one or more components of a cellular pathway associated with the potency of the cell and thereby alter the potency of the cell. In certain embodiments, the one or more repressors and/or activators modulate one or more components of one or more cellular pathways associated with the potency of the cell and thereby alter the potency of the cell. In certain related embodiments, the modulation of the component(s) is synergistic and increases the overall efficacy of altering the potency of a cell. The potency of the cell can be altered, compared to the ground potency state, to a more potent state (e.g., from a differentiated cell to a multipotent, pluripotent, or totipotent cell) or a less potent state (e.g., from a totipotent, pluripotent, or multipotent cell to a differentiated somatic cell). In still yet other embodiments, the potency of a cell may be altered more than once. For example, a cell may first be reprogrammed to a more potent state, then programmed to a particular somatic cell.

[0233] In another embodiment, the methods of the present disclosure provide for increasing the potency a cell, wherein the cell is reprogrammed or dedifferentiated to a totipotent

state, comprising contacting the cell with a composition comprising one or more repressors and/or activators, wherein the one or more repressors and/or activators modulates at least one component of a cellular pathway associated with the totipotency of the cell, thereby increasing the potency of the cell to a totipotent state.

[0234] In a particular embodiment, a method of increasing the potency a cell to a pluripotent state comprises contacting the cell with one or more repressors and/or activators, wherein the one or more repressors and/or activators modulates at least one component of a cellular pathway associated with the potency of the cell, thereby increasing the potency of the cell to a pluripotent state.

[0235] In another particular embodiment, a method of increasing the potency a cell to a multipotent state comprises contacting the cell with one or more repressors and/or activators, wherein the one or more repressors and/or activators modulates at least one component of a cellular pathway associated with the potency of the cell, thereby increasing the potency of the cell to a multipotent state.

[0236] In certain embodiments, a method of increasing the potency of a cell further comprises a step of contacting the totipotent cell, the pluripotent cell or the multipotent cell with a second composition, wherein the second composition modulates the at least one component of a cellular potency pathway to decrease the totipotency, pluripotency or multipotency of the cell and differentiate the cell to a mature somatic cell.

[0237] In another related embodiment, the present disclosure provides a method of reprogramming a cell that comprises contacting the cell with a composition comprising one or more repressors and/or activators, wherein the one or more repressors and/or activators modulates at least one component of a cellular pathway or pathways associated with the reprogramming of a cell, thereby reprogramming the cell.

[0238] In other embodiments, the present disclosure provides a method of dedifferentiating a cell to a more potent state, comprising contacting the cell with the composition comprising one/or more activators, wherein the one or more repressors and/or activators modulates at least one component of a cellular pathway or pathways associated with the dedifferentiation of the cell to the more potent state, thereby dedifferentiating the cell to an impotent state.

[0239] According to various embodiments of the present disclosure a repressor can be an antibody or an antibody fragment, an intrabody, a transbody, a DNAzyme, an ssRNA, a dsRNA, an mRNA, an antisense RNA, a ribozyme, an antisense oligonucleotide, a pri-miRNA, an shRNA, an antagomir, an aptamer, an siRNA, a dsDNA, a ssDNA; a polypeptide or an active fragment thereof, a peptidomimetic, a peptoid, or a small organic molecule. Polypeptide-based repressors include, but are not limited to fusion polypeptides. Polypeptide-based repressors also include transcriptional repressors, which can further be fusion polypeptides and/or artificially designed transcriptional repressors as described elsewhere herein.

[0240] According to other various embodiments, an activator can be an antibody or an antibody fragment, an mRNA, a bifunctional antisense oligonucleotide, a dsDNA, a polypeptide or an active fragment thereof, a peptidomimetic, a peptoid, or a small organic molecule.

[0241] In some embodiments, repressors modulate at least one component of a cellular potency pathway by a) repress-

ing the at least one component; b) de-repressing a repressor of the at least one component; or c) repressing an activator of the at least one component. In related embodiments, one or more repressors can modulate at least one component of a pathway associated with the potency of a cell by a) de-repressing the at least one component; b) repressing a repressor of the at least one component; or c) de-repressing an activator of the at least one component.

[0242] In certain embodiments, one or more repressors modulates at least one component of a cellular pathway associated with the potency of a cell by a) repressing a histone methyltransferase or repressing the at least one component's epigenetic state, chromatin structure, transcription, mRNA splicing, post-transcriptional modification, mRNA stability and/or half-life, translation, post-translational modification, protein stability and/or half-life and/or protein activity; or b) de-repressing a demethylase or activating the at least one component's epigenetic state, chromatin structure, transcription, mRNA splicing, post-transcriptional modification, mRNA stability and/or half-life, translation, post-translational modification, protein stability and/or half-life and/or protein activity.

[0243] In related embodiments, activators modulate at least one component of a cellular pathway associated with the potency of a cell by a) activating the at least one component; b) activating a repressor of a repressor of the at least one component; or c) activating an activator of the at least one component.

[0244] In certain embodiments, one or more activators modulates at least one component by a) activating a histone demethylase or activating the at least one component's epigenetic state, chromatin structure, transcription, mRNA splicing, post-transcriptional modification, mRNA stability and/or half-life, translation, post-translational modification, protein stability and/or half-life and/or protein activity; or b) activating a repressor of a histone methyltransferase or activating a repressor of the at least one component's epigenetic state, chromatin structure, transcription, mRNA splicing, post-transcriptional modification, mRNA stability and/or half-life, translation, post-translational modification, protein stability and/or half-life and/or protein activity.

[0245] In various other embodiments, the present disclosure contemplates, in part, a method of reprogramming a cell, comprising contacting the cell with one or more repressors, wherein the one or more repressors modulates at least one component of a cellular pathway associated with the reprogramming of a cell, thereby reprogramming the cell.

[0246] In various other embodiments, the present disclosure contemplates, in part, a method of reprogramming a cell, comprising contacting the cell with a composition comprising one or more activators, wherein the one or more activators modulates at least one component of a cellular pathway associated with the reprogramming of a cell, thereby re-programming the cell.

[0247] While some exemplary methods for reprogramming/NK cell differentiation are provided herein, these are exemplary and not meant to limit the scope of the present disclosure. Additional suitable methods for reprogramming/NK cell differentiation will be apparent to those of skill in the art based on the present disclosure in view of the knowledge in the art.

[0248] Methods for culturing NK cells on feeder layers or with feeder cells are described in detail in, for e.g.,

EP3184109 by Valamehr et al. ("Valamehr") incorporated in its entirety herein by reference.

[0249] In general, any type of NK cell population can be cultured using a variety of methods and devices. Selection of culture apparatus is usually based on the scale and purpose of the culture. Scaling up of cell culture preferably involves the use of dedicated devices. Apparatus for large scale, clinical grade NK cell production is detailed, for example, in Spanholz et al. (PLoS ONE 2010; 5:e9221) and Sutlu et al. (Cytotherapy 2010, Early Online 1-12).

[0250] The methods described hereinabove for ex vivo culturing NK cells populations can result, inter alia, in a cultured population of NK cells.

Types of Edits

[0251] Some aspects of the present disclosure provide complex editing strategies, and resulting NK cells having complex genomic alterations, that allow for the generation of advanced NK cell products for clinical applications, e.g., for immunooncology therapeutic approaches. In some embodiments, the modified NK cells provided herein can serve as an off-the-shelf clinical solution for patients having, or having been diagnosed with, a hyperproliferative disease, such as, for example, a cancer. In some embodiments, the modified NK cells exhibit an enhanced survival, proliferation, NK cell response level, NK cell response duration, resistance against NK cell exhaustion, and/or target recognition as compared to non-modified NK cells. For example, the modified NK cells provided herein may comprise genomic edits that result in: a loss-of-function in TGF beta receptor 2 (TGFbetaR2) and/or a loss-of-function of CISH in the modified NK cell.

[0252] The modified NK cells may exhibit one or more edits in their genome that results in a loss-of-function in a target gene, and/or one or more modifications that results in a gain-of-function, or an overexpression, of a gene product, e.g., of a protein, from an exogenous nucleic acid construct, e.g., from an expression construct comprising a cDNA encoding for the gene product that is integrated into the genome of the modified NK cell or provided in an extrachromosomal manner, e.g., in the form of an episomal expression construct.

[0253] A loss-of-function of a target gene is characterized by a decrease in the expression of a target gene based on a genomic modification, e.g., an RNA-guided nuclease-mediated cut in the target gene that results in an inactivation, or in diminished expression or function, of the encoded gene product.

[0254] A gain-of-function of a gene product is characterized by an increased expression (also referred to herein as overexpression) of a gene product, e.g., of a protein, in a cell, which can include, for example, an increased expression level of the gene product, or expression of the gene product in a cell that does not express the gene product endogenously, e.g., from an endogenous gene.

[0255] In some embodiments, increased expression of a gene product is effected by introducing an exogenous nucleic acid construct that encodes the gene product into a cell, e.g., an exogenous nucleic acid construct that comprises a cDNA encoding the gene product under the control of a heterologous promoter. In some embodiments, the exogenous nucleic acid construct is integrated into a specific locus, e.g., via HDR-mediated gene editing, as described in more detail elsewhere herein. Methods for effecting loss-of-

function edits as well as methods for effecting increased expression of gene products, e.g., via RNA-guided nuclease technology are well known to one of ordinary skill in the art. [0256] The present disclosure embraces modified NK cells exhibiting any of the edits and/or increased expression of gene products listed in TABLE 4 and TABLE 5 combined, as well as any combination of such edits and/or increased expression of gene products listed in these tables.

[0257] It is to be understood that the exemplary embodiments provided herein are meant to illustrate some examples of NK cells embraced by the present disclosure. Additional configurations are embraced that are not described here in detail for the sake of brevity, but such embodiments will be immediately apparent to those of skill in the art based on the present disclosure.

Knock-Ins and Knock-Outs

[0258] In some embodiments, a modified cell may express one or more of a loss of function in TGFbetaR2 and/or a loss of function in CISH.

[0259] As used herein, the term “express” or “expression” refers to the process to produce a polypeptide, including transcription and translation. Expression may be, e.g., increased by a number of approaches, including: increasing the number of genes encoding the polypeptide, increasing the transcription of the gene (such as by placing the gene under the control of a constitutive promoter), increasing the translation of the gene, knocking out of a competitive gene, or a combination of these and/or other approaches.

[0260] As used herein, “knock-in” refers to the addition of a target gene into a genetic locus of a cell.

[0261] As used herein, the term “knock-out” refers to an inactivating mutation in a target gene, wherein the product of the target gene comprises a loss of function.

[0262] As used herein, the term “loss of function” refers to an inactivating mutation in a target gene, wherein the gene product has less, or no, function (being partially or wholly inactivated). As used herein the term “complete loss of function” refers to an inactivating mutation in a target gene, wherein the gene product has no function (wholly inactivated).

[0263] As used herein, the term “TGF β RII” or “TGF-betaR2” refers to a transmembrane protein that has a protein kinase domain, forms a heterodimeric complex with TGF-beta receptor type-1, and binds TGF-beta. This receptor/ligand complex phosphorylates proteins, which then enter the nucleus and regulate the transcription of genes related to cell proliferation, cell cycle arrest, wound healing, immunosuppression, and tumorigenesis. Exemplary sequences of TGF β RII are set forth in KR710923.1, NM_001024847.2, and NM_003242.5.

[0264] As used herein, the term “CISH” refers to the Cytokine Inducible SH2 Containing Protein, for e.g., see Delconte et al., Nat Immunol. 2016 July; 17(7):816-24; incorporated in its entirety herein by reference. Exemplary sequences for CISH are set forth as NG_023194.1.

[0265] As used herein, the term “IL-15/IL15RA” or “Interleukin-15” (IL-15) refers to a cytokine with structural similarity to Interleukin-2 (IL-2). Like IL-2, IL-15 binds to and signals through a complex composed of IL-2/IL-15 receptor beta chain (CD122) and the common gamma chain (gamma-C, CD132). IL-15 is secreted by mononuclear phagocytes (and some other cells) following infection by virus(es). This cytokine induces cell proliferation of natural

killer cells; cells of the innate immune system whose principal role is to kill virally infected cells. IL-15 Receptor alpha (IL15RA) specifically binds IL15 with very high affinity, and is capable of binding IL-15 independently of other subunits. It is suggested that this property allows IL-15 to be produced by one cell, endocytosed by another cell, and then presented to a third party cell. IL15RA is reported to enhance cell proliferation and expression of apoptosis inhibitor BCL2L1/BCL2-XL and BCL2. Exemplary sequences of IL-15 are provided in NG_029605.2, and exemplary sequences of IL-15RA are provided in NM_002189.4.

[0266] IL-15 is a key cytokine in promoting NK cell growth and homeostatic maintenance of memory T cells. IL-15 and its receptor chain, IL-15Ra, are essential for NK survival and do not stimulate regulatory T cells. IL-15/IL-15Ra binds to the beta and gamma subunits of IL-2 receptor and thereby activates JAK1/3 and STAT5. In some embodiments, the modified cell of the disclosure (for e.g., an NK cell) expresses an exogenous IL-15/IL-15Ra. In some embodiments, the exogenous IL-15/IL-15Ra is expressed as a membrane-bound IL15.IL15Ra complex, as described in Imamura et al., Blood. 2014 Aug. 14; 124(7):1081-8 and Hurton L V et al., PNAS, 2016; incorporated in their entirety herein by reference. In some embodiments, the exogenous IL-15/IL-15Ra is expressed as a soluble IL15Ra.IL15 complex, as described in Mortier E et al, JBC 2006; Bessard A, Mol Cancer Ther 2009; and Desbois M, JI 2016; incorporated in their entirety herein by reference. In some embodiments, the modified cell of the disclosure (for e.g., an NK cell) expresses a membrane-bound IL15.IL15Ra complex and a soluble IL15Ra.IL15 complex. In some embodiments, the modified cell of the disclosure (for e.g., an NK cell) express a membrane-bound form of IL15.IL15Ra complex with a cleavable linker. A knockout of CISH is associated with further promoting the IL-15 signaling, as described in Delconte P, Nat Immunol 2016; incorporated in its entirety herein by reference. In some embodiments, the modified cell of the disclosure (for e.g., an NK cell) expresses a loss of function in CISH. In some embodiments, the modified cell of the disclosure (for e.g., an NK cell) express exogenous IL-15/IL-15Ra and a loss of function in CISH.

[0267] The disclosure specifically encompasses variants of the above genes, including variants having at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% percent identity to the above-identified gene sequences. As used herein, the term “percent (%) sequence identity” or “percent (%) identity,” also including “homology,” is defined as the percentage of amino acid residues or nucleotides in a candidate sequence that are identical with the amino acid residues or nucleotides in the reference sequences after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Optimal alignment of the sequences for comparison may be produced, besides manually, by means of the local homology algorithm of Smith and Waterman, 1981, Ads App. Math. 2, 482, by means of the local homology algorithm of Neddleman and Wunsch, 1970, J. Mol. Biol. 48, 443, by means of the similarity search method of Pearson and Lipman, 1988, Proc. Natl. Acad. Sci. USA 85, 2444, or by means of computer programs which use these algorithms (GAP, BESTFIT, FASTA, BLAST P,

BLAST N and TFASTA in Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.).

[0268] Knock-ins and knock-outs can be effected by genome editing technologies known to those of skill in the art and include CRISPR/Cas technologies. Single-cut as well as multiplex editing strategies are suitable to achieve the desired product configurations provided herein, and such strategies are described herein or otherwise known to those of ordinary skill in the art.

[0269] In some embodiments, exemplary modified cells, e.g., modified pluripotent cells or differentiated progeny thereof, e.g., iNK cells or other modified lymphocyte types, are evaluated for their ability to escape the immune system of a non-autologous host, e.g., a patient in need of immunotherapy. In some embodiments, such an evaluation includes an in vitro assay. Suitable in vitro assays for such evaluations are known to those of ordinary skill in the relevant art, and include, without limitation, mixed lymphocyte reactivity (MLR) assays. This assay and other suitable assays are described, e.g., in Abbas et al., *Cellular and Molecular Immunology*, 7th edition, ISBN 9781437735734, the entire contents of which are incorporated herein by reference. Other suitable assays will be apparent to the skilled artisan in view of the present disclosure.

Methods of Use

[0270] A variety of diseases may be ameliorated by introducing the modified cells of the invention to a subject. Examples of diseases are, including but not limited to, cancer, including but not limited to solid tumors, including but not limited to, tumor of the brain, prostate, breast, lung, colon, uterus, skin, liver, bone, pancreas, ovary, testes, bladder, kidney, head, neck, stomach, cervix, rectum, larynx, or esophagus; and hematological malignancies, including but not limited to, acute and chronic leukemias, lymphomas, multiple myeloma and myelodysplastic syndromes.

[0271] Particular embodiments of the present invention are directed to methods of treating a subject in need thereof by administering to the subject a composition comprising any of the cells described herein. In particular embodiments, the terms “treating,” “treatment,” and the like are used herein to generally mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. “Treatment” as used herein covers any treatment of a disease in a mammal, and includes: preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; inhibiting the disease, i.e., arresting its development; or relieving the disease, i.e., causing regression of the disease. The therapeutic agent or composition may be administered before, during or after the onset of disease or injury. The treatment of ongoing disease, where the treatment stabilizes or reduces the undesirable clinical symptoms of the patient, is of particular interest.

[0272] In particular embodiments, the subject has a disease, condition, and/or an injury that can be treated, ameliorated, and/or improved by a cell therapy. Some embodiments contemplate that a subject in need of cell therapy is a subject with an injury, disease, or condition, whereby a cell therapy, e.g., a therapy in which a cellular material is

administered to the subject, can treat, ameliorate, improve, and/or reduce the severity of at least one symptom associated with the injury, disease, or condition. Certain embodiments contemplate that a subject in need of cell therapy, includes, but is not limited to, a candidate for bone marrow or stem cell transplantation, a subject who has received chemotherapy or irradiation therapy, a subject who has or is at risk of having a hyperproliferative disorder or a cancer, e.g. a hyperproliferative disorder or a cancer of hematopoietic system, a subject having or at risk of developing a tumor, e.g., a solid tumor, a subject who has or is at risk of having a viral infection or a disease associated with a viral infection.

[0273] According, the embodiments described herein further provide pharmaceutical compositions comprising the cells made by the methods and composition disclosed herein, wherein the pharmaceutical compositions further comprise a pharmaceutically acceptable medium. In some embodiments, the pharmaceutical composition comprises the NK cells made by the methods and composition disclosed herein.

[0274] Additionally, the embodiments described herein provide therapeutic use of the above pharmaceutical compositions by introducing the composition to a subject suitable for adoptive cell therapy, wherein the subject has a solid tumor; a hematological malignancy; an autoimmune disorder; or an infection associated with viral, bacterial, fungal and/or helminth infections, including but not limited to, HIV, RSV, EBV, CMV, adenovirus, or BK polyomavirus infections.

[0275] Particular embodiments described herein are also directed to methods of treating a subject in need thereof by administering to the subject a composition comprising any of the cells described herein with one or more antibodies, or fragments thereof, to induce and/or increase an antibody-dependent cellular cytotoxicity (ADCC) effect in the subject. In some embodiments, the modified NK cells described herein exhibit greater ADCC activity when administered with one or more antibodies, or fragments thereof, to a subject in need thereof, e.g., a subject with a cancer, relative to unmodified NK cells that are administered with the same one or more antibodies, or fragments thereof, to a subject in need thereof. In some embodiments, the modified NK cells described herein kill a greater number of cancer cells when administered with one or more antibodies, or fragments thereof, to a subject in need thereof, e.g., a subject with cancer, relative to unmodified NK cells that are administered with the same one or more antibodies, or fragments thereof, to a subject.

Cancers

[0276] Cancers that are suitable therapeutic targets of the present disclosure include cancer cells from the bladder, blood, bone, bone marrow, brain, breast, colon, esophagus, eye, gastrointestinal, gum, head, kidney, liver, lung, nasopharynx, neck, ovary, prostate, skin, stomach, testis, tongue, or uterus. In addition, the cancer may specifically be of the following histological type, though it is not limited to these: neoplasm, malignant; carcinoma; carcinoma, undifferentiated; giant and spindle cell carcinoma; small cell carcinoma; papillary carcinoma; squamous cell carcinoma; lymphoepithelial carcinoma; basal cell carcinoma; pilomatrix carcinoma; transitional cell carcinoma; papillary transitional cell carcinoma; adenocarcinoma; gastrinoma, malignant; cho-

langiocarcinoma; hepatocellular carcinoma; combined hepatocellular carcinoma and cholangiocarcinoma; trabecular adenocarcinoma; adenoid cystic carcinoma; adenocarcinoma in adenomatous polyp; adenocarcinoma, familial polyposis coli; solid carcinoma; carcinoid tumor, malignant; bronchiolo-alveolar adenocarcinoma; papillary adenocarcinoma; chromophobe carcinoma; acidophil carcinoma; oxyphilic adenocarcinoma; basophil carcinoma; clear cell adenocarcinoma; granular cell carcinoma; follicular adenocarcinoma; papillary and follicular adenocarcinoma; nonencapsulating sclerosing carcinoma; adrenal cortical carcinoma; endometroid carcinoma; skin appendage carcinoma; apocrine adenocarcinoma; sebaceous adenocarcinoma; ceruminous adenocarcinoma; mucoepidermoid carcinoma; cystadenocarcinoma; papillary cystadenocarcinoma; papillary serous cystadenocarcinoma; mucinous cystadenocarcinoma; mucinous adenocarcinoma; signet ring cell carcinoma; infiltrating duct carcinoma; medullary carcinoma; lobular carcinoma; inflammatory carcinoma; paget's disease, mammary; acinar cell carcinoma; adenosquamous carcinoma; adenocarcinoma w/squamous metaplasia; thymoma, malignant; ovarian stromal tumor, malignant; the coma, malignant; granulosa cell tumor, malignant; androblastoma, malignant; sertoli cell carcinoma; leydig cell tumor, malignant; lipid cell tumor, malignant; paraganglioma, malignant; extra-mammary paraganglioma, malignant; pheochromocytoma; glomangiiosarcoma; malignant melanoma; amelanotic melanoma; superficial spreading melanoma; malig melanoma in giant pigmented nevus; epithelioid cell melanoma; blue nevus, malignant; sarcoma; fibrosarcoma; fibrous histiocytoma, malignant; myxosarcoma; liposarcoma; leiomyosarcoma; rhabdomyosarcoma; embryonal rhabdomyosarcoma; alveolar rhabdomyosarcoma; stromal sarcoma; mixed tumor, malignant; mullerian mixed tumor; nephroblastoma; hepatoblastoma; carcinosarcoma; mesenchymoma, malignant; brenner tumor, malignant; phyllodes tumor, malignant; synovial sarcoma; mesothelioma, malignant; dysgerminoma; embryonal carcinoma; teratoma, malignant; struma ovarii, malignant; choriocarcinoma; mesonephroma, malignant; hemangiosarcoma; hemangioendothelioma, malignant; kaposi's sarcoma; hemangiopericytoma, malignant; lymphangiosarcoma; osteosarcoma; juxtacortical osteosarcoma; chondrosarcoma; chondroblastoma, malignant; mesenchymal chondrosarcoma; giant cell tumor of bone; ewing's sarcoma; odontogenic tumor, malignant; ameloblastic odontosarcoma; ameloblastoma, malignant; ameloblastic fibrosarcoma; pinealoma, malignant; chordoma; glioma, malignant; ependymoma; astrocytoma; protoplasmic astrocytoma; fibrillary astrocytoma; astroblastoma; glioblastoma; oligodendrogloma; oligodendroblastoma; primitive neuroectodermal; cerebellar sarcoma; ganglioneuroblastoma; neuroblastoma; retinoblastoma; olfactory neurogenic tumor; meningioma, malignant; neurofibrosarcoma; neurilemmoma, malignant; granular cell tumor, malignant; malignant lymphoma; Hodgkin's disease; Hodgkin's lymphoma; paragranuloma; malignant lymphoma, small lymphocytic; malignant lymphoma, large cell, diffuse; malignant lymphoma, follicular; mycosis fungoides; other specified non-Hodgkin's lymphomas; malignant histiocytosis; multiple myeloma; mast cell sarcoma; immunoproliferative small intestinal disease; leukemia; lymphoid leukemia; plasma cell leukemia; erythroleukemia; lymphosarcoma cell leukemia; myeloid leukemia; basophilic leukemia; eosinophilic

leukemia; monocytic leukemia; mast cell leukemia; megakaryoblastic leukemia; myeloid sarcoma; and hairy cell leukemia.

[0277] In some embodiments, the cancer is head and neck cancer.

[0278] In some embodiments, the cancer is a breast cancer. In another embodiment, the cancer is colon cancer. In another embodiment, the cancer is gastric cancer. In another embodiment, the cancer is RCC. In another embodiment, the cancer is non-small cell lung cancer (NSCLC).

[0279] In some embodiments, solid cancer indications that can be treated with the modified NK cells provided herein, either alone or in combination with one or more additional cancer treatment modality, include: bladder cancer, hepatocellular carcinoma, prostate cancer, ovarian/uterine cancer, pancreatic cancer, mesothelioma, melanoma, glioblastoma, HPV-associated and/or HPV-positive cancers such as cervical and HPV+ head and neck cancer, oral cavity cancer, cancer of the pharynx, thyroid cancer, gallbladder cancer, and soft tissue sarcomas.

[0280] In some embodiments, hematological cancer indications that can be treated with the modified NK cells provided herein, either alone or in combination with one or more additional cancer treatment modality, include: ALL, CLL, NHL, DLBCL, AML, CML, multiple myeloma (MM).

[0281] As used herein, the term "cancer" (also used interchangeably with the terms, "hyperproliferative" and "neoplastic") refers to cells having the capacity for autonomous growth, i.e., an abnormal state or condition characterized by rapidly proliferating cell growth. Cancerous disease states may be categorized as pathologic, i.e., characterizing or constituting a disease state, e.g., malignant tumor growth, or may be categorized as non-pathologic, i.e., a deviation from normal but not associated with a disease state, e.g., cell proliferation associated with wound repair. The term is meant to include all types of cancerous growths or oncogenic processes, metastatic tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathologic type or stage of invasiveness. The term "cancer" includes malignancies of the various organ systems, such as those affecting lung, breast, thyroid, lymphoid, gastrointestinal, and genito-urinary tract, as well as adenocarcinomas which include malignancies such as most colon cancers, renal-cell carcinoma, prostate cancer and/or testicular tumors, non-small cell carcinoma of the lung, cancer of the small intestine and cancer of the esophagus. The term "carcinoma" is art recognized and refers to malignancies of epithelial or endocrine tissues including respiratory system carcinomas, gastrointestinal system carcinomas, genitourinary system carcinomas, testicular carcinomas, breast carcinomas, prostatic carcinomas, endocrine system carcinomas, and melanomas. Exemplary carcinomas include those forming from tissue of the cervix, lung, prostate, breast, head and neck, colon and ovary. The term "carcinoma" also includes carcinosarcomas, e.g., which include malignant tumors composed of carcinomatous and sarcomatous tissues. An "adenocarcinoma" refers to a carcinoma derived from glandular tissue or in which the tumor cells form recognizable glandular structures. The term "sarcoma" is art recognized and refers to malignant tumors of mesenchymal derivation.

[0282] Examples of cellular proliferative and/or differentiative disorders of the lung include, but are not limited to, tumors such as bronchogenic carcinoma, including paraneo-

plastic syndromes, bronchioloalveolar carcinoma, neuroendocrine tumors, such as bronchial carcinoid, miscellaneous tumors, metastatic tumors, and pleural tumors, including solitary fibrous tumors (pleural fibroma) and malignant mesothelioma.

[0283] Examples of cellular proliferative and/or differentiative disorders of the breast include, but are not limited to, proliferative breast disease including, e.g., epithelial hyperplasia, sclerosing adenosis, and small duct papillomas; tumors, e.g., stromal tumors such as fibroadenoma, phyllodes tumor, and sarcomas, and epithelial tumors such as large duct papilloma; carcinoma of the breast including *in situ* (noninvasive) carcinoma that includes ductal carcinoma *in situ* (including Paget's disease) and lobular carcinoma *in situ*, and invasive (infiltrating) carcinoma including, but not limited to, invasive ductal carcinoma, invasive lobular carcinoma, medullary carcinoma, colloid (mucinous) carcinoma, tubular carcinoma, and invasive papillary carcinoma, and miscellaneous malignant neoplasms. Disorders in the male breast include, but are not limited to, gynecomastia and carcinoma.

[0284] Examples of cellular proliferative and/or differentiative disorders involving the colon include, but are not limited to, tumors of the colon, such as non-neoplastic polyps, adenomas, familial syndromes, colorectal carcinogenesis, colorectal carcinoma, and carcinoid tumors.

[0285] Examples of cancers or neoplastic conditions, in addition to the ones described above, include, but are not limited to, a fibrosarcoma, myosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, gastric cancer, esophageal cancer, rectal cancer, pancreatic cancer, ovarian cancer, prostate cancer, uterine cancer, cancer of the head and neck, skin cancer, brain cancer, squamous cell carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular cancer, small cell lung carcinoma, non-small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendrogloma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, lymphoma, or Kaposi's sarcoma.

[0286] Contemplated useful secondary or adjunctive therapeutic agents in this context include, but are not limited to: chemotherapeutic agents include alkylating agents such as thiotepa and CYTOXAN® cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelinamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); betalaphrone; lapachol; colchicines; betulinic acid; a camptothecin (including the synthetic analogue topotecan (HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scopolectin, and 9-aminocamptothecin); bryostatin; callystatin; CC-1065 (including its adoz-

elesin, carzelesin and bizelesin synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide; cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chloramphazine, chlophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammall and calicheamicin omegall (see, e.g., Agnew, Chem. Int. Ed. Engl., 33: 183-186 (1994)); dynemicin, including dynemicin A; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycin, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including ADRIAMYCIN®, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, doxorubicin HCl liposome injection (DOXIL®) and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, que-lamycin, rodarubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate, gemcitabine (GEMZAR®), tegafur (UFTORAL®), capecitabine (XELODA®), an epothilone, and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, flouxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminelevulinic acid; emuracil; amsacrine; bestabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; etogracid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; moperanmol; niraerine; pentostatin; phenacet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine (ELDISINE®, FILDESIN®); dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); thiotepa; taxoids, e.g., paclitaxel (TAXOL®), albumin-engineered nanoparticle formulation of paclitaxel (ABRAXANET™) and doxetaxel (TAXOTERE®); chlorambucil; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine (VELBAN®); platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine (ONCOVIN®); oxaliplatin; leucovorin; vinorelbine (NAVELBINE®); novantrone; edatrexate; daunomycin; aminopterin; cyclosporine, sirolimus, rapamy-

cin, rapalogs, ibandronate; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone, and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATIN™) combined with 5-FU, leucovorin; anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX® tamoxifen), raloxifene (EVISTA®), droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (FARESTON®); anti-progesterones; estrogen receptor down-regulators (ERDs); estrogen receptor antagonists such as fulvestrant (FASLODEX®); agents that function to suppress or shut down the ovaries, for example, leutinizing hormone-releasing hormone (LHRH) agonists such as leuprolide acetate (LUPRON® and ELIGARD®), goserelin acetate, buserelin acetate and triptorelin; other anti-androgens such as flutamide, nilutamide and bicalutamide; and aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, megestrol acetate (MEGASE®), exemestane (AROMASIN®), formestan, fadrozole, vorozole (RIVISOR®), letrozole (FEMARA®), and anastrozole (ARIMIDEX®); bisphosphonates such as clodronate (for example, BONE-FOS® or OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); aptamers, described for example in U.S. Pat. No. 6,344,321, which is herein incorporated by reference in its entirety; anti HGF monoclonal antibodies (e.g., AV299 from Aveo, AMG102, from Amgen); truncated mTOR variants (e.g., CGEN241 from Compugen); protein kinase inhibitors that block mTOR induced pathways (e.g., ARQ197 from Arqule, XL880 from Exelixis, SGX523 from SGX Pharmaceuticals, MP470 from Supergen, PF2341066 from Pfizer); vaccines such as THERATOPE® vaccine and gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; topoisomerase 1 inhibitor (e.g., LURTOTECAN®); rmRH (e.g., ABARELIX®); lapatinib ditosylate (an ErbB-2 and EGFR dual tyrosine kinase small-molecule inhibitor also known as GW572016); COX-2 inhibitors such as celecoxib (CELEBREX®; 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0287] Other compounds that are effective in treating cancer are known in the art and described herein that are suitable for use with the compositions and methods of the present disclosure are described, for example, in the "Physicians Desk Reference, 62nd edition. Oradell, N.J.: Medical Economics Co., 2008"; Goodman & Gilman's "The Pharmacological Basis of Therapeutics, Eleventh Edition. McGraw-Hill, 2005"; "Remington: The Science and Practice of Pharmacy, 20th Edition. Baltimore, Md.: Lippincott Williams & Wilkins, 2000.", and "The Merck Index, Fourteenth Edition. Whitehouse Station, N.J.: Merck Research Laboratories, 2006", incorporated herein by reference in relevant parts.

Antibody-Dependent Cellular Cytotoxicity (ADCC)

[0288] The present disclosure provides modified NK cells (or other lymphocytes) that are useful in NK cell therapy, e.g., in the context of immunotherapeutic approaches, particularly in combination with an antibody, or antigen-binding portion thereof, to generate striking antibody-dependent cellular cytotoxicity (ADCC) effects, thereby surprisingly increasing the effectiveness of the modified NK cells in killing target cells, e.g. cancer cells. ADCC is a mechanism of cell-mediated immune defense, where an immune effector cell actively lyses a target cell after its membrane-surface antigens have been bound by specific antibodies. To participate in ADCC, the immune effector cells must express Fc-gamma receptors (FcγR) to be able to recognize the Fc region of the antibodies that bind to the target cells. Most immune effector cells have both activating and inhibitory FcγR. An advantage of using NK cells to target cancer cells via ADCC is that, unlike other effector cells, NK cells only have activating FcγRs (e.g., FcγR IIIa, also known as CD16a, and FcγR IIc, also known as CD32c) and are believed to be the most important effectors of ADCC in humans. Thus, the use of the modified NK cells disclosed herein and antibodies targeting cancer cell-specific antigens to elicit ADCC provides novel and surprisingly effective immunotherapies.

[0289] In one embodiment, the molecule comprising an Fc domain that binds cancer cells, e.g., antibody, or antigen-binding portion thereof, binds an antigen on a cancer cell, or a "cancer antigen." In one embodiment, the antigen on the cancer cell is epidermal growth factor receptor (EGFR), HER2, CD20, PD-L1, PD-1 (PEMBRO and NIVO), CTLA-4 (IPI), CD73, TIGIT, GD2, VEGF-A, VEGFR-2, PDGFR-2, PDGFRA, RANKL, CD19, CD3. In one embodiment, the antibody is cetuximab, trastuzumab, rituximab, pertuzumab, panitumumab, necitumumab, dinutuximab, bevacizumab, ramucirumab, olaratumab, ipilimumab, nivolumab, blinatumomab, alemtuzumab, bevacizumab, brentuximab, cetuximab, gemtuzumab, ipilimumab, ofatumumab, panitumumab, rituximab, tositumomab, inotuzumab, glembatumumab, lofortuzumab or trastuzumab, or an antigen-binding portion thereof. Additional antibodies include adecatumumab, afutuzumab, bavituximab, belimumab, bivatuzumab, cantuzumab, citatumumab, cixutumumab, conatumumab, dacetuzumab, elotuzumab, etaracizumab, farletuzumab, fitigatumab, iratumumab, labetuzumab, lexatumumab, lintuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, necitumumab, nimotuzumab, olaratumab, oportuzumab, pertuzumab, pritumumab, ranibizumab, robatumumab, sibrotuzumab, siltuximab, tacatumab, tigatuzumab, tucotuzumab, veltuzumab votumumab, and zalutumumab, or an antigen-binding portion thereof.

[0290] In one embodiment, the antibody is cetuximab, or an antigen-binding portion thereof. In one embodiment, the antibody is trastuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is rituximab, or an antigen-binding portion thereof. In one embodiment, the antibody is pertuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is panitumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is necitumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is dinutuximab, or an antigen-binding portion thereof. In one embodiment, the antibody is bevacizumab, or an antigen-binding portion

thereof. In one embodiment, the antibody is ramucirumab, or an antigen-binding portion thereof. In one embodiment, the antibody is olaratumab, or an antigen-binding portion thereof. In one embodiment, the antibody is ipilimumab, or an antigen-binding portion thereof. In one embodiment, the antibody is nivolumab, or an antigen-binding portion thereof. In one embodiment, the antibody is blinatumomab, or an antigen-binding portion thereof. In one embodiment, the antibody is alemtuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is bevacizumab, or an antigen-binding portion thereof. In one embodiment, the antibody is brentuximab, or an antigen-binding portion thereof. In one embodiment, the antibody is gemtuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is ipilimumab, or an antigen-binding portion thereof. In one embodiment, the antibody is ofatumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is panitumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is tositumomab, or an antigen-binding portion thereof. In one embodiment, the antibody is inotuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is glembatumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is lovortuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is adecatumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is afutuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is bavituximab, or an antigen-binding portion thereof. In one embodiment, the antibody is belimumab, or an antigen-binding portion thereof. In one embodiment, the antibody is bivatuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is cantuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is citatuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is cixutumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is conatumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is dacetuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is elotuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is etaracizumab, or an antigen-binding portion thereof. In one embodiment, the antibody is farletuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is figitumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is iratumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is labetuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is lexatumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is lintuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is lucatumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is mapatumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is matuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is milatuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is necitumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is nimotuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is olaratumab, or an antigen-binding portion thereof. In one embodiment, the antibody is oportuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is

pertuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is pritumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is ranibizumab, or an antigen-binding portion thereof. In one embodiment, the antibody is robatumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is sibrotuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is siltuximab, or an antigen-binding portion thereof. In one embodiment, the antibody is tacatuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is tigatuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is tucotuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is veltuzumab, or an antigen-binding portion thereof. In one embodiment, the antibody is votumumab, or an antigen-binding portion thereof. In one embodiment, the antibody is zalutumumab, or an antigen-binding portion thereof.

[0291] All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

[0292] Throughout this specification, unless the context requires otherwise, the words "comprise", "comprises" and "comprising" will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements. By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of." Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory, and that no other elements may be present. By "consisting essentially of" is meant including any elements listed after the phrase, and limited to other elements that do not interfere with or contribute to the activity or action specified in the disclosure for the listed elements. Thus, the phrase "consisting essentially of" indicates that the listed elements are required or mandatory, but that no other elements are optional and may or may not be present depending upon whether or not they affect the activity or action of the listed elements.

[0293] The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety. The contents of database entries, e.g., NCBI nucleotide or protein database entries provided herein, are incorporated herein in their entirety. Where database entries are subject to change over time, the contents as of the filing date of the present application are incorporated herein by reference. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and publications to provide yet further embodiments.

[0294] These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

EXAMPLES

[0295] The following Examples are merely illustrative and are not intended to limit the scope or content of the disclosure in any way.

Example 1: CRISPR-EngCas12a Demonstrated Efficient Editing of CISH and TGFBR2 in NK Cells, and Edited NK Cells Exhibited Improved Effector Functions

[0296] Natural killer (NK) cells distinguish tumor from healthy tissue via multiple mechanisms, including recognition of stress ligands and loss of MHC class I expression. However, effector function of allogeneic NK cells can be diminished by the lack of functional persistence, as well as tumor-intrinsic immunosuppressive mechanisms, such as production of TGF- β . Described herein is a next-generation allogeneic NK cell therapy using CRISPR-Cas12a gene editing to enhance NK cell function through knockout of the CISH and TGFBR2 genes. Knockout of CISH, a negative regulator of IL-2/IL-15 signaling, improves NK cell effector function, while knockout of the TGF- β receptor gene, TGFBR2, renders NK cells resistant to TGF- β mediated suppression.

[0297] Specifically, NK cells derived from healthy human donor NK cells were edited using engineered Cas12a ("EngCas12a"; Cpf1 variant 4 amino acid sequence (SEQ ID NO: 1146)). CD3-depleted peripheral blood mononuclear cells were thawed into IL-15-containing NK MACS media and cultured for 14 days in GREX plates. CRISPR-EngCas12a gene editing was performed by ribonucleoprotein electroporation and cells were cultured for an additional 72 hours prior to analysis or functional assays.

[0298] The following guide RNA sequences were used for editing of CISH and TGFBR2.

TABLE 6

gRNA sequences			
gRNA (Target) Sequence	5' DNA Extension (Target) Sequence	Cas12A-binding Sequence (RNA)	Targeting Domain Sequence (RNA)
CISH8401 ATGTGTTTGTCAAAA GACCTTT (SEQ ID NO: 5) Full Length gRNA Sequence 5' ATGTGTTTGTCAAAAGACCTTTUAAUUUCACUCUUGUAGAUACUGACAGCGUGAACAGGUAG 3' (SEQ ID NO: 1170)	UAAAAUUCACUCUUGUAGAU (SEQ ID NO: 24)	ACUGACAGCGUGAACAGGUAG (SEQ ID NO: 1169)	
TGFBR238 ATGTGTTTGTCAAAA 402 GACCTTT (SEQ ID NO: 5) Full Length gRNA Sequence 5' ATGTGTTTGTCAAAAGACCTTTUAAUUUCACUCUUGUAGAUUGAUGUGAGAUUUUCCACCUG-3' (SEQ ID NO: 1172)	UAAAAUUCACUCUUGUAGAU (SEQ ID NO: 24)	UGAUGUGAGAUUUUCCACCUG (SEQ ID NO: 1171)	

[0299] Indel analysis was performed by polymerase chain reaction amplification of the genomic region surrounding the CRISPR-EngCas12a cut site for each target followed by next-generation sequencing (NGS) and comparison to a reference genome to obtain percentage editing (indels).

[0300] As demonstrated in FIGS. 1A and 1B, robust single and double-gene editing of TGFBR2 and CISH was achieved in NK cells. Greater than 80% indels at both targets

in NK cells in both single and double gene knockout (KO, DKO) contexts were achieved.

[0301] Phosphoflow cytometry assay was performed to determine the phosphorylated state of STAT5 (pSTAT5) and SMAD2/3 (pSMAD2/3) in NK cells. Knockout (KO) of CISH increased pSTAT5 (FIG. 2A) and pSTAT3 levels (data not shown) upon IL-15 stimulation, and KO of TGFBR2 decreased pSMAD2/3 levels upon TGF- β stimulation (FIG. 2B) in both single and double KO NK cells, as compared to unedited NK cells. These data suggest that double KO of CISH and TGFBR2 by CRISPR-EngCas12a increased NK cells' sensitivity to IL-15 and resistance to TGF- β mediated immunosuppression.

[0302] Spheroids were formed by seeding 5,000 SK-OV-3 or PC-3 cells in 96 well ultra low attachment plates. Spheroids were incubated at 37° C. before addition of effector cells and 10 ng/mL TGF- β . AlphaLISA was performed to analyze for TNF- α and IFN- γ secretion after co-culturing of effector cells with tumor spheroids and TGF- β for 120 hrs.

[0303] As shown in FIGS. 3A-3D, double KO (DKO) of CISH and TGFBR2 by CRISPR-EngCas12a increased the secretion of inflammatory cytokines TNF- α and IFN- γ at each of the E:T ratios tested in both SK-OV-3 and PC-3 cells as compared to unedited NK cells.

[0304] These results demonstrate efficient editing of healthy NK cells by CRISPR-EngCas12a, and editing at CISH and TGFBR2 enhanced effector functions of NK cells.

Example 2: CISH/TGFBR2 DKO NK Cells Exhibit Enhanced Anti-Tumor Activity and Antibody-Dependent Cellular Cytotoxicity (ADCC) In Vitro

[0305] Spheroids were formed by seeding 5,000 NucLight Red labeled SK-OV-3 cells in 96 well ultra low attachment

plates. Spheroids were incubated at 37° C. before addition of effector cells and 10 ng/mL TGF- β , followed by imaging of every 2 hours on the Incucyte S3 system for up to 120 hours. Data shown are normalized to the red object intensity at time of effector addition. Normalization of spheroid curves maintains the same efficacy patterns observed in non-normalized data.

[0306] As depicted in FIGS. 4A-4D, both single knockouts (TGFBR2 KO and CISH NK) demonstrated improved

cytotoxicity against tumor targets in the presence of exogenous TGF- β relative to unedited control NK cells ($p<0.0001$ for both single KOs). Furthermore, CISH KO NK cells unexpectedly perform killing at similar level to TGFBR2 KO NK cells, suggesting that knocking out CISH also helped NK cells overcome TGF- β immunosuppression. CISH/TGFBR2 DKO NK cells demonstrated superior rapid and sustained killing of ovarian tumor spheroids SK-OV-3 compared to either single knockouts or unedited control NK cells at the range of tested E:T ratios ($n=7$ independent experiments, 4 unique NK cell donors, $p<0.0001$), demonstrating additive effects of simultaneously targeting both pathways. The unedited, single KO and double KO NK cells also killed PC-3 prostate tumor spheroids in a similar trend (data not shown).

[0307] These data suggest that CISH/TGFBR2 DKO NK cells are very effective at targeting multiple types of tumors.

[0308] Additionally, killing of SK-OV-3 tumor spheroids by the NK cells were examined in the presence of trastuzumab, a monoclonal antibody targeting HER2. The addition of trastuzumab (10 μ g/ml) surprisingly increased killing by the unedited NK cells at a low E:T ratio of 1.25:1 to a great extent, and trastuzumab also significantly enhanced killing by the already effective DKO NK cells (see FIG. 5), which resulted in the greatest amount of tumor spheroid killing. This data shows that trastuzumab and NK cells have a strong antibody-dependent cellular toxicity (ADCC), and the combination of trastuzumab and NK cells, particularly the CISH/TGFBR2 DKO NK cells, has the potential to be an effective oncotherapy. The CISH/TGFBR2 DKO cells also killed the greatest amount of PC-3 prostate tumor spheroids in the presence of certuximab in a similar trend (i.e., more than unedited NK cells or single CISH KO or TGFBR2 KO cells in the presence of certuximab; data not shown).

Example 3: CISH/TGFBR2 DKO NK Cells Exhibit Enhanced Anti-Tumor Activity In Vivo

[0309] In an in vivo NSG mouse xenograft model, 0.5 or 1 million fLuc-SK-OV-3 cells (expressing luciferase) were injected intraperitoneally (i.p.). At 7 days post tumor cell injection, 10 million cells of either unedited control NK cells or DKO NK cells were injected via i.p. Bioluminescence imaging using the IVIS system was performed weekly to monitor tumor burden.

[0310] A single dose of DKO NK cells reduced tumor burden more effectively than unedited control NK cells (FIGS. 6A and 6B), leading to a statistically significant increase in median survival time and lower tumor burden (FIGS. 6C-6D)

[0311] This result suggests that the CISH/TGFBR2 DKO NK cells are promising as cell-based medicine for cancer.

Example 4: Antibody-Dependent-Cellular Cytotoxicity (ADCC) Further Enhanced Anti-Tumor Activity by CISH/TGFBR2 DKO NK In Vivo

[0312] NSG mice ($n=8$ per group) were inoculated via i.p. with 0.5 million luciferase-expressing SK-OV-3 cells. On day 6 post-tumor inoculation, tumor bearing mice were randomized into groups with comparable tumor burden. A day later, mice were injected via i.p. with 2.5 mpk isotype, 2.5 mpk trastuzumab, 10 million unedited CD56+NK cells,

10 million DKO CD56+NK cells or the combination of DKO CD56+NK cells with trastuzumab.

[0313] FIGS. 7A and 7C again show that DKO NK cells were significantly more effective at controlling tumor growth and increased lifespan of mice. Trastuzumab significantly increased these effects of DKO NK treatments, as shown in FIGS. 7B and 7D.

[0314] This data show that trastuzumab can mediate ADCC and promote tumor killing by the DKO NK cells in vivo, and strongly suggest that combination therapy of trastuzumab and the DKO NK cells can be very effective treatment for cancers, such as ovarian cancer.

Example 5: ADCC Effect was Also Observed in Combination Treatment of Rituximab and NK Cells in a Serial Killing Assay

[0315] A 2D Heme Restimulation/Serial Killing Assay was used to determine the endurance of NK cells in serial tumor killing. Specifically, 200 thousand unedited control NK cells or CISH/TGFBR2 DKO NK cells were seeded in each well. 10 thousand Raji tumor cells (a hematological malignant cell line) were added to the NK cells at the beginning of the assay, and subsequently 5 thousand tumor cells and IL-15 were spiked into each well every 48 hours. Surviving tumor cells were quantified by normalized total red object area (see FIG. 8A).

[0316] Rituximab alone did not kill tumor cells without the presence of NK cells (data not shown). For unedited NK cells, the addition of rituximab improved tumor cell killing in both the absence and presence of TGF- β (FIG. 8B, left 2 panels). DKO NK cells were already much more effective than unedited NK cells in killing tumor cells (FIG. 8B, comparing top 2 panels), and the addition of rituximab further enhanced tumor cell killing by DKO NK cells (FIG. 8B, right 2 panels). NK cells were still effective at killing the tumor cells after 7 days in this serial killing assay.

[0317] This experiment shows that rituximab mediates ADCC in the Raji cell killing by NK cells. The combination of rituximab and CISH/TGFBR2 DKO NK cells were most effective at serially killing tumor cells in the presence or absence of TGF- β for at least 7 days in this assay, suggesting that this is an effective combination therapy for cancers, such as hematologic cancer.

[0318] Overall, the experimental results showing that CISH/TGFBR2 DKO NK cells exhibit improved ADCC and effector function in the presence of different therapeutic antibodies for cancer, including trastuzumab and certuximab (Examples 2 and 4) and rituximab (Example 5), show that the CISH/TGFBR2 DKO cells could be combined with a variety of cancer treating antibodies to improve treatment outcomes for a variety of cancers.

Example 6: Functional Characterization of CISH/TGFBR2 DKO NK Cells Reveals Increased Granzyme B and Degranulation Supporting Improved Serial Killing Capacity

[0319] As described above, CISH/TGFBR2 DKO NK cells have increased effector function and are resistant to TGF- β inhibition. These combined activities enable this healthy donor derived NK cell therapy to kill tumor cells more efficiently and for a longer duration than control NK cells in the presence of TGF- β .

[0320] To further investigate the mechanism by which CISH/TGFBR2 double knockout (DKO) NK cells (produced as described in Example 1) have increased serial killing capacity, the transcriptional changes contributed by each gene edit was first explored with a focus on transcripts critical for NK cell effector function and metabolism using Nanostring analysis. Unedited, mock electroporated, and control edited (targeting a biologically irrelevant site) NK cells were included as controls in addition to CISH and TGFBR2 single and double gene knockout (KO) NK cells to interrogate the potential impact of electroporation and double-stranded DNA breaks on NK cell function. All samples included in the analysis were cultured for 3 days in IL-15 (10 ng/mL) post-electroporation. Interestingly, no significant transcriptional changes were detected in all control conditions, while samples that contained CISH editing clearly upregulated transcripts relevant for NK cell effector function, including contents of cytolytic granules (GZMB, GZMA, and GZMH) (FIG. 9A). Furthermore, an average of 22 fold more GZMB transcript was expressed in CISH/TGFBR2 DKO NK cells than control NK cells as measured by RT-qPCR in four unique NK cell donors (FIG. 9B).

[0321] Next, whether the increase in cytolytic signature could be one potential mechanism whereby CISH/TGFBR2 DKO NK cells were functionally superior relative to control NK cells was tested. Consistent with this hypothesis, CISH/TGFBR2 DKO NK cells showed significantly higher levels of CD107a, a marker of degranulation, after 14 hrs of co-culture with SKOV-3 tumor cells, suggesting that CISH/TGFBR2 DKO NK cells had an increased capacity to degranulate relative to control NK cells. To determine the presence of granzyme proteins within tumor cells post engagement with NK cells, a novel GzmB reporter gene was developed and lentiviral vectors were used to introduce this reporter into tumor cell lines (SK-OV-3::GzmB). SK-OV-3 tumor cells were transduced with the reporter, and then co-cultured with CISH/TGFBR2 DKO NK cells or control NK cells. 10^6 NK cells were co-cultured with 5000 SK-OV-3::GzmB cells labelled with NucLight Red; and imaged every 2 hours on the Incucyte S3 system for up to 36 hours (FIG. 9D). GzmB activity was identified 4 hours sooner in the SK-OV-3 tumor cells transduced with the GzmB reporter that were co-cultured with the CISH/TGFBR2 DKO NK cells relative to transduced tumor cells co-cultured with control NK cells. In addition, CISH/TGFBR2 DKO NK cells affected 80% more SK-OV-3 tumor cells with granzyme B compared to control NK cells over a 36-hour period (FIGS. 9C and 9E). Significantly, these data demonstrated that CISH/TGFBR2 DKO NK cells not only released GzmB more rapidly than control NK cells, but also the amount of GzmB degranulated was greater as well (relative to control NK cells), confirming that enhanced degranulation is a key mechanism by which CISH/TGFBR2 DKO NK cells have superior functional capacity relative to control NK cells.

[0322] Together, these data demonstrate that CISH/TGFBR2 DKO NK cells expressed high levels of GzmB and had more rapid and enhanced degranulation activity than unedited NK cells, suggesting this as a potential mechanism by which CISH/TGFBR2 DKO NK cells demonstrate superior cytotoxicity during in vitro killing of SK-OV-3 tumor targets.

Example 7: CISH/TGFBR2 DKO NK Cells Demonstrate Superior Function During Tumor Target Killing in Nutrient Deprived Conditions Through Increased Spare Respiratory Capacity

[0323] Natural killer (NK) cells distinguish tumor from healthy tissue via multiple mechanisms, including recognition of stress ligands and loss of MHC class I expression. As described above, CISH/TGFBR2 DKO NK cells were produced via CRISPR-Cas12a mediated CISH and TGFBR2 double gene knockout in NK cells derived from healthy donors (see Example 1). These cells demonstrated resistance to TGF- β inhibition and increased tumor control both in vitro and in vivo.

[0324] Anti-tumor activity by effector cells requires significant energy expenditure and is constrained by nutrients available in the tumor microenvironment (TME). The TME is known to be nutrient-deprived due to active tumor cell metabolism leading to competition for essential nutrients with infiltrating effector cells, while at the same time being enriched in immunosuppressive metabolites such as lactic acid due to Warburg Metabolism. To explore whether CISH/TGFBR2 DKO NK cells are functional in such hostile metabolic conditions, the metabolic microenvironment was modelled in the established SK-OV-3 ovarian tumor spheroid model.

[0325] To model this hostile microenvironment in vitro, SK-OV-3 ovarian tumor spheroids were generated in decreasing concentrations of glucose (10-0.5 mM, e.g., 10 mM (control), 5 mM, 2.5 mM, 1.0 mM or 0.5 mM) or glutamine (2-0.1 mM, e.g., 2 mM (control), 1 mM, 0.5 mM or 0.1 mM), two important fuels for NK cell metabolism, as well as increasing concentrations of inhibitory metabolite lactate (0-50 mM, e.g., 0.0 mM (control), 25 mM or 50 mM), or decreasing pH (7.2-6.5, e.g., 7.2 (control), 6.9, 6.7, or 6.5). Each of these metabolic conditions are known to suppress effector cell function, and the system was further stressed by performing spheroid cells co-cultures in the absence of TGF- β at a 10:1 effector:target ratio (FIG. 10A). In all of the above conditions, SK-OV-3 tumor spheroids formed at similar rates relative to spheroids formed in standard culture media. Significantly, it was found that in each of these conditions, CISH/TGFBR2 DKO NK cells demonstrated rapid and sustained tumor killing in the absence of critical nutrients or in unfavorable growth conditions relative to control unedited NK cells.

[0326] To further model the complexity of the metabolic conditions in the TME, a multifactorial matrix of metabolic conditions was created where deprivation of multiple nutrients was combined in the presence of lactate and/or acidic cell culture media. Specifically, the cytotoxicity of NK cells was assayed with SK-OV3-tumor spheroid in the presence of 10 ng/mL TGF- β at a 5:1 effector:target ratio (FIG. 10B). The cytotoxicity of NK cells was also assayed with SK-OV3-tumor spheroid that were selectively evolved to grow in nutrient-deprived and/or high lactate media in the presence of 10 ng/mL TGF- β at a 10:1 effector:target ratio at 100 hours (FIG. 10C) or at varying effector:target ratios (FIG. 10D) at 100 hours. Remarkably, in all the matrixed conditions tested, it was surprisingly found that CISH/TGFBR2 DKO NK cells demonstrated increased cytotoxicity against SK-OV-3 spheroids relative to control NK cells, suggesting a clear and robust metabolic advantage of CISH/TGFBR2 DKO NK cells over control NK cells. A corresponding increase in the concentrations of IFN- γ and TNF- α

was further observed by CISH/TGFBR2 DKO NK cells in all of these conditions relative to control NK cells.

[0327] Given that mitochondrial respiration is key to NK cell persistence and function, the mitochondrial function of CISH/TGFBR2 DKO NK cells was next interrogated. CISH/TGFBR2 DKO NK cells consistently demonstrated greater spare respiratory capacity (SRC) relative to control NK cells after overnight IL-15 starvation, suggesting enhanced mitochondrial reserve as a result of CISH and TGFBR2 knockout (FIG. 10E). SRC is a function of mitochondrial mass and fitness. A cell with a larger SRC can produce more ATP and overcome more stress, including oxidative stress. Similar results were observed in NK cells cultured with IL-15 overnight. The increase in SRC likely enables CISH/TGFBR2 DKO NK cells to meet enhanced energy demands necessary to mediate effector function in metabolically challenging conditions, thus sustaining superior cytotoxic capacity and cytokine production.

[0328] In summary, a complex multifactorial in vitro tumor spheroid model was developed to more realistically probe the TME likely to be encountered in vivo. These data demonstrate that enhanced metabolic function of CRISPR-Cas12a CISH and TGFBR2 gene edited NK cells results in superior cytotoxicity during in vitro killing of SK-OV-3 spheroids in metabolically unfavorable conditions that are similar to those experienced by effector cells in tumors. These data further demonstrate the potential of CISH/TGFBR2 DKO NK cells as a novel cell therapy for cancer.

**Example 8. CISH/TGFBR2 DKO NK Cells
Demonstrated Enhanced Anti-Tumor Activity and
Sustained Serial Killing Against Other Tumor Cell
Lines**

[0329] The anti-tumor activity of CISH/TGFBR2 double knockout NK cells (produced as described in Example 1)

was further tested against numerous other tumor cell lines, such as Nalm6 tumor cells and other hematologic tumor cell lines.

[0330] FIGS. 11A and 11B depict that CISH/TGFBR2 double knockout NK cells exhibited enhanced anti-tumor activity against Nalm6 tumor cells in the presence of TGF- β compared to control unedited NK cells. CISH/TGFBR2 DKO NK cells, or unedited control NK cells, were co-cultured with Nalm6 tumor cells at a 20:1 effector tumor ratio in the presence of 5 ng/mL IL-15, without and with the addition of 10 ng/mL TGF- β . Increased cytotoxicity was observed in all conditions while a greater increase was observed when TGF- β was added in the cell culture.

[0331] In addition, as shown in FIG. 12 and FIG. 13, CISH/TGFBR2 DKO NK cells continually killed Nalm6 tumor cells for more than 8 days in an in vitro serial killing assay, whereas the unedited NK cells had limited serial killing effect. Nalm6 tumor cells (5×10^3 cells) were added to the NK cells every 48 hours in the presence of 5 ng/mL IL-15 and 10 ng/mL TGF- β in this assay. Supernatant from this assay were harvested every 48 hours, and CISH/TGFBR2 DKO NK cells were shown to produce higher levels of IFN- γ and TNF- α versus unedited NK cells over the duration of the assay (FIG. 14), suggesting that CISH/TGFBR2 DKO NK cells can continue to produce these inflammatory cytokines even after serial killing.

[0332] Other hematologic tumor cell lines, such as Raji (Burkitt's lymphoma), RPMI8226 (multiple myeloma) and THP-1 (acute monocytic leukemia) cells, were also tested in the serial killing assay. As shown in FIGS. 15A-15C, CISH/TGFBR2 DKO NK cells demonstrated sustained serial killing activity against each of these tumor cell lines in the presence of TGF- β , and the CISH/TGFBR2 DKO NK cells continually killed the cells of each of these tumor cell lines for more than 8 days.

[0333] These data suggest that CISH/TGFBR2 DKO NK cells are very effective at targeting multiple types of tumors.

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<210> SEQ ID NO 6
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 6
aggccagctt gccggtttt tagtcgtgtc gtttgcgtcaa aagacctttt      60

<210> SEQ ID NO 7
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 7
ttttgtcaa aagacctttt                                         20

<210> SEQ ID NO 8
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 8

gcttcatgtg ttttgtcaa aagaccttt

30

<210> SEQ ID NO 9
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 9

gccgggtttt tagtcgtgct gcttcatgtg ttttgtcaa aagaccttt

50

<210> SEQ ID NO 10
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 10

tagtcgtgct gcttcatgtg ttttgtcaa aagaccttt

40

<210> SEQ ID NO 11
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 11

ccgaagttt cttcggttt

20

<210> SEQ ID NO 12
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 12

tttttccgaa gttttcttcg gtttt

25

<210> SEQ ID NO 13
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 13

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aacgctttt ccgaagttt cttcggttt	30
<210> SEQ ID NO 14	
<211> LENGTH: 41	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<221> NAME/KEY: source	
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> SEQUENCE: 14	
gcgttgtttt caacgcttt tccgaagttt tcttcggtt t	41
<210> SEQ ID NO 15	
<211> LENGTH: 62	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<221> NAME/KEY: source	
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> SEQUENCE: 15	
ggttttttt gaaggctttt tggttgttt tcaacgcttt ttccgaagtt ttcttcggtt	60
tt	62
<210> SEQ ID NO 16	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<221> NAME/KEY: source	
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> SEQUENCE: 16	
atgtgtttt gtcaaaagac ctttt	25
<210> SEQ ID NO 17	
<211> LENGTH: 25	
<212> TYPE: RNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<221> NAME/KEY: source	
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> SEQUENCE: 17	
aaaaaaaaaaa aaaaaaaaaa aaaaaa	25
<210> SEQ ID NO 18	
<211> LENGTH: 25	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<221> NAME/KEY: source	
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> SEQUENCE: 18	
ttttttttt tttttttttt tttttt	25
<210> SEQ ID NO 19	

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<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 19

auguguuuuu gucaaaagac cuuuu

25

<210> SEQ ID NO 20
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 20

aaaaaaaaaaa aaaaaaaaaaa aaaaaa

25

<210> SEQ ID NO 21
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 21

uuuuuuuuuuu uuuuuuuuuuu uuuuuu

25

<210> SEQ ID NO 22
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 22

tctgcagaaa tgccccgt

20

<210> SEQ ID NO 23
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 23

ucugcagaaa ugucccccgu

20

<210> SEQ ID NO 24
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 24

uaauuuucuac ucuuguagau

20

<210> SEQ ID NO 25

<211> LENGTH: 40

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 25

uaauuuucuac ucuuguagau ucugcagaaa uguuccccgu

40

<210> SEQ ID NO 26

<211> LENGTH: 65

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Combined DNA/RNA
Molecule: Synthetic oligonucleotide"

<400> SEQUENCE: 26

atgtgtttt gtcaaaagac ctttuauuu ucuacucuuu uagauucugc agaaauguuc

60

cccggu

65

<210> SEQ ID NO 27

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 27

tctgcagaaa tgcccccggt

20

<210> SEQ ID NO 28

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 28

tgcagagaaa ggtgggtcta

20

<210> SEQ ID NO 29

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 29

taatgctgac ttggggtggc

20

<210> SEQ ID NO 30

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 30

taggacacctc aggaagattc

20

<210> SEQ ID NO 31

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 31

tagtcaacgc gaccaccacg

20

<210> SEQ ID NO 32

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 32

tcctgaggtc accttccaca

20

<210> SEQ ID NO 33

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 33

tattgtgcct gtcatcatc

20

<210> SEQ ID NO 34

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 34

tgcacaggcac aatagaaaca a

21

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<210> SEQ ID NO 35
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 35
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gacaggcaca atagaaaacaa c 21

```
<210> SEQ ID NO 36
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 36
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aaacaacggg gAACATTCTC T 21

```
<210> SEQ ID NO 37
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 37
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acaacgggg aCATTTCTGC A 21

```
<210> SEQ ID NO 38
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 38
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tGATAGAGCC ACCTTCTCT G 21

```
<210> SEQ ID NO 39
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 39
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gggtcaacttg tgccgtggtg G 21

```
<210> SEQ ID NO 40
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 40

ggcacacaaggta acccaggtca a

21

<210> SEQ ID NO 41
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 41

gtccctgctgc tcccagttga c

21

<210> SEQ ID NO 42
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 42

tggccatttg taatgttgac t

21

<210> SEQ ID NO 43
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 43

tggcacatct ccccatcctt c

21

<210> SEQ ID NO 44
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 44

catctcccca tccttcaagg a

21

<210> SEQ ID NO 45
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 45

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ccactcgatc cttgaaggat g 21

<210> SEQ ID NO 46
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 46
ggccactcga tccttgaagg a 21

<210> SEQ ID NO 47
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 47
cctggggcca ctcgatcctt g 21

<210> SEQ ID NO 48
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 48
gactggaggg tgaggcccag g 21

<210> SEQ ID NO 49
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 49
atcggtcacg gtcagcgact g 21

<210> SEQ ID NO 50
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 50
gtcgctgacc gtgaacgata c 21

<210> SEQ ID NO 51
<211> LENGTH: 21
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 51

cgctgaccgt gaacgataca g

21

<210> SEQ ID NO 52
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 52

gcatctatca cacctaccct g

21

<210> SEQ ID NO 53
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 53

cctaccctga tgggacgtac a

21

<210> SEQ ID NO 54
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 54

taccctgatg ggacgtacac t

21

<210> SEQ ID NO 55
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 55

ccctgatggg acgtacactg g

21

<210> SEQ ID NO 56
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 56
ttctcccaagt gtacgtccca t

<210> SEQ ID NO 57
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 57
ggagaatctt cctggaggtc c

<210> SEQ ID NO 58
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 58

catggctcca agcaatggaa t

<210> SEQ ID NO 59
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 59
cgcgccatg gctccaagca a

<210> SEQ ID NO 60
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 60
tcgcggccat ggctccaagc a

<210> SEQ ID NO 61
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 61
catcgtggtg gtcgcgttga c

<210> SEQ ID NO 62

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 62
```

```
aaagccctca gaatccattc t
```

21

```
<210> SEQ ID NO 63
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 63
```

```
cattctgtgg aaggtgacct c
```

21

```
<210> SEQ ID NO 64
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 64
```

```
ttctgtggaa ggtgacctca g
```

21

```
<210> SEQ ID NO 65
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 65
```

```
cctgagggtca ctttccacag a
```

21

```
<210> SEQ ID NO 66
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 66
```

```
tttcctgttag gtcacattcc a
```

21

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<210> SEQ ID NO 67
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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"Synthetic oligonucleotide"

<400> SEQUENCE: 67

aggagaaaaat cagctggaca g

21

<210> SEQ ID NO 68

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 68

ggagaaaaatc agctggacag g

21

<210> SEQ ID NO 69

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 69

gccccagtgc tccctcaccc c

21

<210> SEQ ID NO 70

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 70

tggacacagc ttccctggggg t

21

<210> SEQ ID NO 71

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 71

tctgcctgga cacagttcc t

21

<210> SEQ ID NO 72

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 72

agctgcacct gctgggctct g

21

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<210> SEQ ID NO 73
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 73
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```
gctgggctct gtggagagca g 21
```

```
<210> SEQ ID NO 74
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 74
```

```
tgggctctgt ggagagcagc g 21
```

```
<210> SEQ ID NO 75
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 75
```

```
ctgcatgact acttcaatgt c 21
```

```
<210> SEQ ID NO 76
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 76
```

```
aatgtcctga gttacagaag c 21
```

```
<210> SEQ ID NO 77
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 77
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tgggtaactg cagttcttc a 21
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<210> SEQ ID NO 78
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 78

gacaggcaca atagaaaacaa

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<210> SEQ ID NO 79
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 79

acaggcacaat tagaaaacaac

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<210> SEQ ID NO 80
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 80

caggcacaat agaaaacaacg

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<210> SEQ ID NO 81
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 81

gggaacattt ctgcagagaa

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<210> SEQ ID NO 82
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 82

aacatttctg cagagaaagg

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<210> SEQ ID NO 83
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 83

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atgtcaccc tcctccacca 20

<210> SEQ ID NO 84
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 84

cttgcgcgt ggtggaggag 20

<210> SEQ ID NO 85
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 85

ggtcacttgt gccgtggtag 20

<210> SEQ ID NO 86
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 86

caccacggca caagtgaccc 20

<210> SEQ ID NO 87
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 87

ctgggtcact tgtgccgtgg 20

<210> SEQ ID NO 88
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 88

gacctgggtc acttgtgccc 20

<210> SEQ ID NO 89
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 89

cacaagtgac ccaggtcaac

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<210> SEQ ID NO 90
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 90

acaagtgacc caggtcaact

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<210> SEQ ID NO 91
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 91

ccaggtcaac tgggagcagg

20

<210> SEQ ID NO 92
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 92

ctgctgtcc cagttgacct

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<210> SEQ ID NO 93
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 93

cctgctgtcc ccagttgacc

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<210> SEQ ID NO 94
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 94
ggagcagcag gaccagcttc 20

<210> SEQ ID NO 95
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 95
cattacaaat ggccagaagg 20

<210> SEQ ID NO 96
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 96
ggccatttgt aatgctgact 20

<210> SEQ ID NO 97
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 97
gccatttgta atgctgactt 20

<210> SEQ ID NO 98
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 98
ccatttgtaa tgctgacttg 20

<210> SEQ ID NO 99
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 99
tttgtaatgc tgacttgggg 20

<210> SEQ ID NO 100

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 100

ccccaaagtca gcattacaaa

20

<210> SEQ ID NO 101
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 101

gcacatctcc ccatccttca

20

<210> SEQ ID NO 102
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 102

cccatccttc aaggatcgag

20

<210> SEQ ID NO 103
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 103

cactcgatcc ttgaaggatg

20

<210> SEQ ID NO 104
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 104

ccactcgatc cttgaaggat

20

<210> SEQ ID NO 105
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 105

gccactcgat ccttgaagga

20

<210> SEQ ID NO 106

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 106

ttcaaggatc gagtgccccc

20

<210> SEQ ID NO 107

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 107

tggggccact cgatccttga

20

<210> SEQ ID NO 108

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 108

gatcgagtgg ccccagggtcc

20

<210> SEQ ID NO 109

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 109

agtggcccca ggtccggcc

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<210> SEQ ID NO 110

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 110

gtggcccca agtccggcc

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<210> SEQ ID NO 111
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 111
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gaggccccagg ccgggacctg 20

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<210> SEQ ID NO 112
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 112
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tgaggccca gccgggacct 20

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<210> SEQ ID NO 113
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 113
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gtgaggccca ggccgggacc 20

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<210> SEQ ID NO 114
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 114
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tggagggtga ggcccaggcc 20

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<210> SEQ ID NO 115
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 115
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ctggagggtc aggcccaggc 20

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<210> SEQ ID NO 116
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 116

gcgactggag ggtgaggccc

20

<210> SEQ ID NO 117
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 117

cggtcagcga ctggagggtg

20

<210> SEQ ID NO 118
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 118

gttcacggtc agcgactgga

20

<210> SEQ ID NO 119
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 119

cgttcacggc cagcgactgg

20

<210> SEQ ID NO 120
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 120

tatcgttcac ggtcagcgac

20

<210> SEQ ID NO 121
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 121

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tcgctgaccg tgaacgatac	20
<210> SEQ ID NO 122	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<221> NAME/KEY: source	
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> SEQUENCE: 122	
cgctgaccgt gaacgataca	20
<210> SEQ ID NO 123	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<221> NAME/KEY: source	
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> SEQUENCE: 123	
gctgaccgtg aacgatacacag	20
<210> SEQ ID NO 124	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<221> NAME/KEY: source	
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> SEQUENCE: 124	
gtactccctc gtatcggtca	20
<210> SEQ ID NO 125	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<221> NAME/KEY: source	
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> SEQUENCE: 125	
atctatcaca cctaccctga	20
<210> SEQ ID NO 126	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<221> NAME/KEY: source	
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
<400> SEQUENCE: 126	
tctatcacac ctaccctgat	20
<210> SEQ ID NO 127	
<211> LENGTH: 20	
<212> TYPE: DNA	

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 127

taccctgatg ggacgtacac

20

<210> SEQ ID NO 128
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 128

accctgatgg gacgtacact

20

<210> SEQ ID NO 129
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 129

agtgtacgtc ccatcagggt

20

<210> SEQ ID NO 130
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 130

tcccagtgt a cgtccatca

20

<210> SEQ ID NO 131
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 131

ctccccagtgt acgtccatca

20

<210> SEQ ID NO 132
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 132
gtacacgtggg agaatcttcc 20

<210> SEQ ID NO 133
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 133
cactgggaga atcttcctgg 20

<210> SEQ ID NO 134
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 134
ctgagcttcc taggacacctc 20

<210> SEQ ID NO 135
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 135
aggttccaga ttccattgct 20

<210> SEQ ID NO 136
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 136
aagcaatggaa 20

<210> SEQ ID NO 137
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 137
gattccattg cttggagcca 20

<210> SEQ ID NO 138

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 138

tggctccaag caatggaaatc

20

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<210> SEQ ID NO 139
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 139

gcggccatgg ctccaaagcaa

20

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<210> SEQ ID NO 140
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 140

tggagccatg gccgcgacgc

20

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<210> SEQ ID NO 141
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 141

agccatggcc gcgacgctgg

20

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<210> SEQ ID NO 142
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 142

gaccaccaggc gtcgcggcca

20

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<210> SEQ ID NO 143
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 143

gcagatgacc accagcgtcg

20

<210> SEQ ID NO 144

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 144

catctgcaca gcagtcatcg

20

<210> SEQ ID NO 145

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 145

ctgcacagca gtcatcggtgg

20

<210> SEQ ID NO 146

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 146

agccctcaga atccattctg

20

<210> SEQ ID NO 147

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 147

ctcagaatcc attctgtgga

20

<210> SEQ ID NO 148

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 148

ttccacagaa tggattctga

20

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<210> SEQ ID NO 149
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 149

cttccacaga atggattctg

20

<210> SEQ ID NO 150
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 150

attctgtgga aggtgacctc

20

<210> SEQ ID NO 151
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 151

tgaggtcacc ttccacagaa

20

<210> SEQ ID NO 152
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 152

gacctcagga gaaaatcagc

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<210> SEQ ID NO 153
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 153

caggagaaaa tcagctggac

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<210> SEQ ID NO 154
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 154

gtccagctga ttttctcctg

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<210> SEQ ID NO 155
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 155

gagaaaaatca gctggacagg

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<210> SEQ ID NO 156
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 156

aatcagctgg acaggaggaa

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<210> SEQ ID NO 157
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<212> TYPE: DNA
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 157

cccaagtgtc cctcaccccc

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<210> SEQ ID NO 158
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<212> TYPE: DNA
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 158

ctgggggtga gggagcactg

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<210> SEQ ID NO 159
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<212> TYPE: DNA
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<220> FEATURE:
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cctgggggtg agggagcac 20

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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 160

tcctgggggt gaggagcac 20

<210> SEQ ID NO 161
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<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 161

acacagttc ctgggggtga 20

<210> SEQ ID NO 162
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 162

gacacagttt cctgggggtg 20

<210> SEQ ID NO 163
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 163

accccccagga agctgtgtcc 20

<210> SEQ ID NO 164
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<220> FEATURE:
<221> NAME/KEY: source
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<400> SEQUENCE: 164

gcctggacac agcttcctgg 20

<210> SEQ ID NO 165
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<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 165

tgcctggaca cagcttcctg

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<210> SEQ ID NO 166
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<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 166

ctgcctggac acagcttcct

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<210> SEQ ID NO 167
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<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 167

tctgcctgga cacagttcc

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<210> SEQ ID NO 168
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 168

caggcagaag ctgcacctgc

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<210> SEQ ID NO 169
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 169

aggcagaagc tgcacctgct

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<210> SEQ ID NO 170
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 170
cagcagggtgc agcttctgcc 20

<210> SEQ ID NO 171
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<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 171
gctgcacatcg ctgggctctg 20

<210> SEQ ID NO 172
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 172
tgctctccac agagccccagc 20

<210> SEQ ID NO 173
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 173
ctgggctctg tggagagcag 20

<210> SEQ ID NO 174
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 174
tgggctctgt ggagagcagc 20

<210> SEQ ID NO 175
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 175
gggctctgtg gagagcagc 20

<210> SEQ ID NO 176

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 176

cgttggagag cagcggggag

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<210> SEQ ID NO 177
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 177

attgaagtag tcatgcagct

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<210> SEQ ID NO 178
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 178

tgtcctgagt tacagaagcc

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<210> SEQ ID NO 179
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 179

gtcctgagtt acagaaggct

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<210> SEQ ID NO 180
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 180

taccaggct tctgttaactc

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<210> SEQ ID NO 181
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 181

tgaagaagct gcagttaccc

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<210> SEQ ID NO 182

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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 182

tgcagcttct tcacagagac

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<210> SEQ ID NO 183

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 183

gttgtttcta ttgtgcctgt

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<210> SEQ ID NO 184

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 184

cgttgtttct atttgtgcctg

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<210> SEQ ID NO 185

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 185

ccgttgtttc tatttgtgcct

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<210> SEQ ID NO 186

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 186

ccacggcaca agtgacccag

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<210> SEQ ID NO 187
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 187

agttgacctg ggtcacttgt

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<210> SEQ ID NO 188
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 188

aagtccat tacaaatggc

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<210> SEQ ID NO 189
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 189

catccttcaa ggatcgagt

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<210> SEQ ID NO 190
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 190

atccttcaag gatcgagtgg

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<210> SEQ ID NO 191
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 191

aggatcgagt ggccccaggt

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<210> SEQ ID NO 192
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 192

aggccccggc ctgggcctca

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<210> SEQ ID NO 193
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 193

ggcctgggcc tcaccctcca

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<210> SEQ ID NO 194
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 194

cggtcagcga ctggagggtg

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<210> SEQ ID NO 195
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 195

gtcgctgacc gtgaacgata

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<210> SEQ ID NO 196
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 196

tgtatcgttc acggtcagcg

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<210> SEQ ID NO 197
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 197

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ctgtatcggtt cacggtcagc 20

<210> SEQ ID NO 198
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 198

atcagggttag gtgtgataga 20

<210> SEQ ID NO 199
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 199

agtgtacgtc ccatcagggt 20

<210> SEQ ID NO 200
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 200

ggaagattct cccagtgtac 20

<210> SEQ ID NO 201
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 201

tggaggctt agaaagctca 20

<210> SEQ ID NO 202
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 202

agcaatggaa tctggAACCT 20

<210> SEQ ID NO 203
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 203

agattccatt gcttggagcc

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<210> SEQ ID NO 204
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 204

gattccattg cttggagcca

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<210> SEQ ID NO 205
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 205

attgcttggaa gccatggcccg

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<210> SEQ ID NO 206
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 206

ttgcttggag ccatggccgc

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<210> SEQ ID NO 207
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 207

cagaatggat tctgagggt

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<210> SEQ ID NO 208
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 208
acagaatgga ttctgagggc 20

<210> SEQ ID NO 209
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 209
ttctgtggaa ggtgaccta 20

<210> SEQ ID NO 210
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 210
gctgatttc tcctgaggc 20

<210> SEQ ID NO 211
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 211
tcctgtccag ctgatttct 20

<210> SEQ ID NO 212
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 212
ttcctcttgt ccagctgatt 20

<210> SEQ ID NO 213
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 213
tgggggtgag ggagcactgg 20

<210> SEQ ID NO 214

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 214

agtgctccct caccggcagg

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<210> SEQ ID NO 215
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 215

tcaccccccag gaagctgtgt

20

<210> SEQ ID NO 216
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 216

caggaagctg tgtccaggca

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<210> SEQ ID NO 217
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 217

aggaagctgt gtccaggcag

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<210> SEQ ID NO 218
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 218

ggcagaagct gcacctgctg

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<210> SEQ ID NO 219
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 219

cagagcccaag cagggtgcagc

20

<210> SEQ ID NO 220

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 220

gctgctctcc acagagccca

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<210> SEQ ID NO 221

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 221

cgctgctctc cacagagccc

20

<210> SEQ ID NO 222

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 222

atgtcctgag ttacagaagc

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<210> SEQ ID NO 223

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 223

gagcacaccc actgcgtatgt

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<210> SEQ ID NO 224

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 224

gatggccagg agactgaaga

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<210> SEQ ID NO 225
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 225

ctgctcaccg gagcgaggatg

20

<210> SEQ ID NO 226
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 226

gtctgtggcc atgccccatca

20

<210> SEQ ID NO 227
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 227

tcacccggagc gggatgcgga

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<210> SEQ ID NO 228
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 228

gtggcaggca gcgcagaacc

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<210> SEQ ID NO 229
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 229

agcacacccag cacattgcc

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<210> SEQ ID NO 230
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 230

caggttgctg ttgagccaca

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<210> SEQ ID NO 231
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 231

cttcattgcc tgcttcgtcc

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<210> SEQ ID NO 232
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 232

gtacacccgag gagcccatga

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<210> SEQ ID NO 233
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 233

gatggcaatg tagcggtcaa

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<210> SEQ ID NO 234
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 234

ctccttcggtg tacatcacgg

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<210> SEQ ID NO 235
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 235

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cgaggagccc atgatgggca 20

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 236

gggctcctcg gtgtacatca 20

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<210> SEQ ID NO 237
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 237

cttttgtggtg tcactggccg 20

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<210> SEQ ID NO 238
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 238

ccgcctccgt gagcagggcc 20

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<210> SEQ ID NO 239
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 239

gggttctgctg ctgcctgcca 20

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 240

ggacgaagca ggcaatgaag 20

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<210> SEQ ID NO 241
<211> LENGTH: 20
<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 241

gtgctgatgg tgatggcaaa

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<210> SEQ ID NO 242
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 242

agcgcagaac ccgggtgctga

20

<210> SEQ ID NO 243
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 243

gagctccatc ttcaagtctcc

20

<210> SEQ ID NO 244
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 244

tgctgatggt gatggcaaag

20

<210> SEQ ID NO 245
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 245

ggcgccggcc gacatcgcaag

20

<210> SEQ ID NO 246
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 246

aatgaagagg cagccgtggc

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<210> SEQ ID NO 247
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 247

gggcaatgtg ctggtgtgct

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<210> SEQ ID NO 248
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 248

catgccccatc atgggctcct

20

<210> SEQ ID NO 249
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 249

aatgttagcgg tcaatggcgaa

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<210> SEQ ID NO 250
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 250

agttagttgggt gacgttctgc

20

<210> SEQ ID NO 251
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 251

agcgggtcaat ggcgatggcc

20

<210> SEQ ID NO 252

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 252

cgcacatcccgca tccgggtgagc

20

<210> SEQ ID NO 253
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 253

gcacatcccgctt ccgggtgagca

20

<210> SEQ ID NO 254
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 254

tgggcaatgt gctgggtgtgc

20

<210> SEQ ID NO 255
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 255

caactactttt gtgggtgtcac

20

<210> SEQ ID NO 256
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 256

cgttccggtg agcaggggccg

20

<210> SEQ ID NO 257
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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Synthetic oligonucleotide"

<400> SEQUENCE: 257
gatggtgatg gcaaaggaga 20

<210> SEQ ID NO 258
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 258
ggtgtacatc acggtgagac 20

<210> SEQ ID NO 259
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 259
gaacgtcacc aactactttg 20

<210> SEQ ID NO 260
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 260
cagtgacacc acaaagtagt 20

<210> SEQ ID NO 261
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 261
ggccatcctg ggcaatgtgc 20

<210> SEQ ID NO 262
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 262
ccccggccctg ctcacccggag 20

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<210> SEQ ID NO 263
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 263

caccagcaca ttgccccagga

20

<210> SEQ ID NO 264
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 264

tttgccatca ccatcagcac

20

<210> SEQ ID NO 265
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 265

ctccacccgtg atgtacaccg

20

<210> SEQ ID NO 266
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 266

ggagctggcc attgctgtgc

20

<210> SEQ ID NO 267
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 267

caggatggcc agcacagcaa

20

<210> SEQ ID NO 268
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 268

gaacccggtg ctgatggtga

20

<210> SEQ ID NO 269
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 269

tggagctctg cgtgaggacc

20

<210> SEQ ID NO 270
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 270

cccgctccgg tgagcagggc

20

<210> SEQ ID NO 271
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 271

aggcaatgaa gaggcagccg

20

<210> SEQ ID NO 272
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 272

cgggccctgc tcaccggagc

20

<210> SEQ ID NO 273
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 273

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gcggcgccg acatcgcagt 20

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<210> SEQ ID NO 274
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 274

ggtgctgatg gtgatggcaa 20

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<210> SEQ ID NO 275
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 275

ctactttgtg gtgtcactgg 20

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<210> SEQ ID NO 276
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 276

tacaccgagg agcccatgat 20

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<210> SEQ ID NO 277
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 277

tctgtggcca tgcccatcat 20

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<210> SEQ ID NO 278
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 278

attgctgtgc tggccatcct 20

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<210> SEQ ID NO 279
<211> LENGTH: 20
<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 279

cgtgaggacc aggacgaagc

20

<210> SEQ ID NO 280
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 280

ttgccatcac catcagcacc

20

<210> SEQ ID NO 281
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 281

ggatgcggat ggcaatgtag

20

<210> SEQ ID NO 282
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 282

ttgccatccg catcccgctc

20

<210> SEQ ID NO 283
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 283

tgaagatgga gctctgcgtg

20

<210> SEQ ID NO 284
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 284
cattgctgtg ctggccatcc 20

<210> SEQ ID NO 285
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 285
tgctggtgtg ctggggcg 20

<210> SEQ ID NO 286
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 286
ggcttcctcg g tgtacatcac 21

<210> SEQ ID NO 287
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 287
gagctctgcg tgaggaccag g 21

<210> SEQ ID NO 288
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 288
gatggagctc tgcgtgagga c 21

<210> SEQ ID NO 289
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 289
ccagcacacc agcacattgc c 21

<210> SEQ ID NO 290

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 290
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aggaccagga cgaaggcaggc a
```

21

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<210> SEQ ID NO 291
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 291
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```
tgcacatccgc atcccgctcc g
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21

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<210> SEQ ID NO 292
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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```
<400> SEQUENCE: 292
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```
gtgtggctca acagcaacct g
```

21

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<210> SEQ ID NO 293
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 293
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```
agctccaccg tgatgtacac c
```

21

```
<210> SEQ ID NO 294
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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```
<400> SEQUENCE: 294
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```
gttagcggtca atggcgatgg c
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21

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<210> SEQ ID NO 295
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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"Synthetic oligonucleotide"

<400> SEQUENCE: 295

cggtgctgat ggtgatggca a

21

<210> SEQ ID NO 296

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 296

ccctgctcac cggagcgaaa t

21

<210> SEQ ID NO 297

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 297

gtgacgttct gcagggtgct g

21

<210> SEQ ID NO 298

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 298

gctccaccgt gatgtacacc g

21

<210> SEQ ID NO 299

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 299

actgaagatg gagctctgcg t

21

<210> SEQ ID NO 300

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 300

ccagctccac cgtgatgtac a

21

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<210> SEQ ID NO 301
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 301

cctttgcccattaccatcagc a

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<210> SEQ ID NO 302
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 302

ccgggtgttgcatttgtatggc a

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<210> SEQ ID NO 303
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 303

cctggggcaatgtgttgtgtt g

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<210> SEQ ID NO 304
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 304

aggcagccgttggcaggcagc g

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<210> SEQ ID NO 305
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 305

ggcatggcca ggagactgaa g

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<210> SEQ ID NO 306
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 306

cgatggccag gagactgaag a

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<210> SEQ ID NO 307
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 307

tcccgctccg gtgagcaggc c

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<210> SEQ ID NO 308
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 308

tgtttcgtcc tggcctcac g

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<210> SEQ ID NO 309
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 309

accaggacg agcaggcaat g

21

<210> SEQ ID NO 310
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 310

atgtacacccg aggagcccat g

21

<210> SEQ ID NO 311
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 311

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tcgtctgtgg ccatgccccat c 21

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 312

tcaatggcga tggccaggag a 21

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<210> SEQ ID NO 313
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 313

ggtgctgatg gtgatggcaa a 21

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<210> SEQ ID NO 314
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 314

tagcggtaaa tggcgatggc c 21

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<210> SEQ ID NO 315
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 315

tccgcattcc gctccggtaa g 21

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<210> SEQ ID NO 316
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 316

ctggcgccgg ccgacatcgc a 21

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<210> SEQ ID NO 317
<211> LENGTH: 21
<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 317

gccattgctg tgctggccat c

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<210> SEQ ID NO 318
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 318

atccccgtcc ggtgagcagg g

21

<210> SEQ ID NO 319
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 319

agactgaaga tggagctcg c

21

<210> SEQ ID NO 320
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 320

cccccggccct gtcaccgga g

21

<210> SEQ ID NO 321
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 321

atggtgatgg caaaggggat g

21

<210> SEQ ID NO 322
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 322
gctcctcggt gtacatcacg g 21

<210> SEQ ID NO 323
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 323
tgtcgatggc aatagccaag 20

<210> SEQ ID NO 324
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 324
agaagtttgtt gacgttctgc 20

<210> SEQ ID NO 325
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 325
ttcgccatca ccatcagcac 20

<210> SEQ ID NO 326
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 326
gaagaagagg cagccatggc 20

<210> SEQ ID NO 327
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 327
cacaaggcacg ttacccagga 20

<210> SEQ ID NO 328

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 328

caacttcttc gtggtatctc

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<210> SEQ ID NO 329
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 329

caggatggcc agcacagcaa

20

<210> SEQ ID NO 330
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 330

aattccactc cggtagccaa

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<210> SEQ ID NO 331
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 331

agcgccagaag ccagtgtctga

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<210> SEQ ID NO 332
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 332

tggtgtatgg tgatggcgaa

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<210> SEQ ID NO 333
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 333

ggagctggcc attgctgtgc

20

<210> SEQ ID NO 334

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 334

aatagccaag aggctgaaga

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<210> SEQ ID NO 335

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 335

ctcctcggtg tacatcatgg

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<210> SEQ ID NO 336

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 336

ggacaaagca ggcgaagaag

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<210> SEQ ID NO 337

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 337

tctggcgccg gctgacatcg

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<210> SEQ ID NO 338

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 338

tggtaaacgt gtttgtgtgc

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<210> SEQ ID NO 339
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 339

gatgtacacc gaggagccca

20

<210> SEQ ID NO 340
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 340

taaccctctgg ctcacccggag

20

<210> SEQ ID NO 341
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 341

tcaccggagt ggaattcggaa

20

<210> SEQ ID NO 342
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 342

cgccgcggctg acatcgcggt

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<210> SEQ ID NO 343
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 343

gatgggtatg gcgaatggga

20

<210> SEQ ID NO 344
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 344

ggcttctgcg ctgcctgccaa

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<210> SEQ ID NO 345
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 345

attccactcc ggtgagccag

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<210> SEQ ID NO 346
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 346

ggtgtacatc atggtaggagc

20

<210> SEQ ID NO 347
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 347

attgctgtgc tggccatcct

20

<210> SEQ ID NO 348
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 348

ctccaccatcg atgtacacccg

20

<210> SEQ ID NO 349
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 349

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ggcggcggt gacatcgccg 20

<210> SEQ ID NO 350
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 350

tacaccgagg agcccatggc 20

<210> SEQ ID NO 351
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 351

gggttaacgtg cttgtgtgct 20

<210> SEQ ID NO 352
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 352

caggttgctg ttgatccaca 20

<210> SEQ ID NO 353
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 353

tgaagatgga actctgcgtg 20

<210> SEQ ID NO 354
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 354

gatggcgatg tatctgtcga 20

<210> SEQ ID NO 355
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 355

cttcttcgcc tgctttgtcc

20

<210> SEQ ID NO 356
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 356

aggcgaagaa gaggcagcca

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<210> SEQ ID NO 357
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 357

tgcttgtgtg ctggggcggt

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<210> SEQ ID NO 358
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 358

gaagccagtg ctgatggta

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<210> SEQ ID NO 359
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 359

cgtgaggacc aggacaaagc

20

<210> SEQ ID NO 360
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 360
tggaactctg cgtgaggacc 20

<210> SEQ ID NO 361
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 361
cattgctgtg ctggccatcc 20

<210> SEQ ID NO 362
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 362
ttctcccgcc atgggctcct 20

<210> SEQ ID NO 363
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 363
tggctcaccc gagtggaaatt 20

<210> SEQ ID NO 364
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 364
tgctgatggt gatggcgaat 20

<210> SEQ ID NO 365
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 365
cttcgtggta tctctggcgg 20

<210> SEQ ID NO 366

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 366
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agcacacaaag cacgttacc
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20

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<210> SEQ ID NO 367
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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```
<400> SEQUENCE: 367
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```
gggctcctcg gtgtacatca
```

20

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<210> SEQ ID NO 368
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 368
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```
gtacacccgag gagccatgg
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20

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<210> SEQ ID NO 369
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 369
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```
gaacgtcacc aacttcttcg
```

20

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<210> SEQ ID NO 370
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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```
<400> SEQUENCE: 370
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```
tgcgccatccg aattccactc
```

20

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<210> SEQ ID NO 371
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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"Synthetic oligonucleotide"

<400> SEQUENCE: 371

gagttccatc ttcagcctct

20

<210> SEQ ID NO 372

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 372

gaattccact ccggtgagcc

20

<210> SEQ ID NO 373

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 373

cagagataacc acgaagaagt

20

<210> SEQ ID NO 374

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 374

cttcttcgtg gtagtctctgg

20

<210> SEQ ID NO 375

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 375

cagtgcgtat ggtgtatggcg a

21

<210> SEQ ID NO 376

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 376

cgaattccac tccggtgagc c

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<210> SEQ ID NO 377
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 377

ccgaattcca ctccggtgag c

21

<210> SEQ ID NO 378
<211> LENGTH: 21
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Synthetic oligonucleotide"

<400> SEQUENCE: 378

gctgaagatg gaaactctgcg t

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Synthetic oligonucleotide"

<400> SEQUENCE: 379

cgtgcttgtg tgctggccg t

21

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<400> SEQUENCE: 380

gtgaggacca ggacaaaagca g

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 381

tcgatggcaa tagccaagag g

21

<210> SEQ ID NO 382
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 382

catcgacaga tacatcgcca t

21

<210> SEQ ID NO 383
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 383

gtacaccgag gagcccatgg c

21

<210> SEQ ID NO 384
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<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 384

gctccaccat gatgtacacc g

21

<210> SEQ ID NO 385
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Synthetic oligonucleotide"

<400> SEQUENCE: 385

aagccagtgc tgatggat g

21

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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 386

caccgcgatg tcagccgccg c

21

<210> SEQ ID NO 387
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Synthetic oligonucleotide"

<400> SEQUENCE: 387

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aggctgaaga tggaactctg c 21

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<220> FEATURE:
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Synthetic oligonucleotide"

<400> SEQUENCE: 388

ggccggccca gagataccac g 21

<210> SEQ ID NO 389
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<220> FEATURE:
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<400> SEQUENCE: 389

agctccacca tcatgtacac c 21

<210> SEQ ID NO 390
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 390

aggcagccat ggcaggcagc g 21

<210> SEQ ID NO 391
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 391

cctggctcac cgagtgaa t 21

<210> SEQ ID NO 392
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 392

ccagctccac catgatgtac a 21

<210> SEQ ID NO 393
<211> LENGTH: 21
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 393

accaggacaa agcaggcgaa g

21

<210> SEQ ID NO 394
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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<400> SEQUENCE: 394

cctgggtaac gtgcttgtgt g

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<210> SEQ ID NO 395
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 395

aggaccagga caaaggcaggc g

21

<210> SEQ ID NO 396
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 396

tca gccgcgc ccagagatac c

21

<210> SEQ ID NO 397
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 397

ggctccctcggtgtacatcat g

21

<210> SEQ ID NO 398
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 398

ctggcgccgg ctgacatcgc g

21

<210> SEQ ID NO 399
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 399

gatggaaactc tgcgtgagga c

21

<210> SEQ ID NO 400
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 400

gctcctcggt gtacatcatg g

21

<210> SEQ ID NO 401
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 401

tgtacaccga ggagccatg g

21

<210> SEQ ID NO 402
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 402

gccattgctg tgctggccat c

21

<210> SEQ ID NO 403
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 403

caatagccaa gaggtgaag a

21

<210> SEQ ID NO 404

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 404
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atgggtgatgg cgaatgggat g
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21

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<210> SEQ ID NO 405
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 405
```

```
atgtacaccg aggagcccat g
```

21

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<210> SEQ ID NO 406
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

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<400> SEQUENCE: 406
```

```
gtgtggatca acagcaacct g
```

21

```
<210> SEQ ID NO 407
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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```
<400> SEQUENCE: 407
```

```
tgtttgtcc tggcctcac g
```

21

```
<210> SEQ ID NO 408
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 408
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```
gtaacccctg gtcaccgga g
```

21

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<210> SEQ ID NO 409
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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"Synthetic oligonucleotide"

<400> SEQUENCE: 409

ccagcacaca agcacgttac c

21

<210> SEQ ID NO 410

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 410

tatctgtcga tggcaatagc c

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<210> SEQ ID NO 411

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 411

gcaatagcca agaggctgaa g

21

<210> SEQ ID NO 412

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 412

agtgctgatg gtgatggcg a

21

<210> SEQ ID NO 413

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 413

acaccgagga gcccatggcg g

21

<210> SEQ ID NO 414

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 414

cgcctatccga attccactcc g

21

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<210> SEQ ID NO 415
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 415

tggtgtcact ggccggggcc

20

<210> SEQ ID NO 416
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 416

ccatcaccat cagcacccggg

20

<210> SEQ ID NO 417
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 417

ccatcggtct gactccccatg

20

<210> SEQ ID NO 418
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 418

gctgaccgcgca gttgttccaa

20

<210> SEQ ID NO 419
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 419

aggatgtggc ccccatgaac

20

<210> SEQ ID NO 420
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 420

cctgtgtgct ggtggccctg

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<210> SEQ ID NO 421
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 421

cggatcttcc tggcgccgcg

20

<210> SEQ ID NO 422
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 422

ccctctgctg gctggcccta

20

<210> SEQ ID NO 423
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 423

ttctgccccg actgcagcca

20

<210> SEQ ID NO 424
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 424

aaggcagctg gcaccagtgc

20

<210> SEQ ID NO 425
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 425

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taaggccatc attgccatct g 21

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 426

cggcctgact cccatgctag g 21

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 427

gcagttgttc caacctagca t 21

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 428

ccgcagtgtt tccaaacctag c 21

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 429

caagaaccac tcccagggt g 21

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 430

cttggccctc cccgcagccc t 21

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<210> SEQ ID NO 431
<211> LENGTH: 21
<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 431

cacttggccc tccccgcagc c

21

<210> SEQ ID NO 432
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 432

ggcccaagtgg cctgtctctt t

21

<210> SEQ ID NO 433
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 433

tccatggggg ccacatcctc a

21

<210> SEQ ID NO 434
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 434

tgaagtacac catgttagttc a

21

<210> SEQ ID NO 435
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 435

ctggtgcccc tgctgctcat g

21

<210> SEQ ID NO 436
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 436

gctcatgtg ggtgttatt t

21

<210> SEQ ID NO 437

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 437

tttcagctgt cgtcgccg c

21

<210> SEQ ID NO 438

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

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<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 438

cgcgacgaca gctgaaggcag a

21

<210> SEQ ID NO 439

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 439

gatggagagc cagcctctgc c

21

<210> SEQ ID NO 440

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 440

gcgtggctgc agtcggggca g

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<210> SEQ ID NO 441

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 441

acgatggcca ggtacatgag c

21

<210> SEQ ID NO 442

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 442
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ctctcccaaca ccaattcggt t
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21

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<210> SEQ ID NO 443
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 443
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gattcacaac cgaattggtg t
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21

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<210> SEQ ID NO 444
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 444
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gggattcaca accgaattgg t
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21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 445
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cgtagatgaa gggattcaca a
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21

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<210> SEQ ID NO 446
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 446
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ggatacggta ggcgttagatg a
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21

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<210> SEQ ID NO 447
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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Synthetic oligonucleotide"

<400> SEQUENCE: 447

tcatctacgc ctaccgtatc c

21

<210> SEQ ID NO 448

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 448

cggatacggt aggcgttagat g

21

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<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 449

gcggaaggtc tggcggact c

21

<210> SEQ ID NO 450

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 450

aatgatcttg cgaaaggctc g

21

<210> SEQ ID NO 451

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 451

gacgtggctg cgaatgatct t

21

<210> SEQ ID NO 452

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 452

ttgctgcctc aggacgtggc t

21

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<210> SEQ ID NO 453
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 453

caaggcagct ggcaccagt c

21

<210> SEQ ID NO 454
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 454

cgggcactgg tgccagctgc c

21

<210> SEQ ID NO 455
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 455

cttggcagct catggcagtg a

21

<210> SEQ ID NO 456
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 456

ccgtctcaac ggccacccgc c

21

<210> SEQ ID NO 457
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 457

cacactcctg gcgggtggcc g

21

<210> SEQ ID NO 458
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 458

tgcgttggc ccacactcct g

21

<210> SEQ ID NO 459
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 459

ccattggccc tccgctcagg g

21

<210> SEQ ID NO 460
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 460

catagccatt gggcctccgc t

21

<210> SEQ ID NO 461
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 461

aatggctatg ccctggggct g

21

<210> SEQ ID NO 462
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 462

atgccctggg gctggtgagt g

21

<210> SEQ ID NO 463
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<212> TYPE: DNA
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 463

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gccctggggc tggtagtgg a 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 464

tggtagtgg agggagtgcc c 21

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<210> SEQ ID NO 465
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 465

gagggagtgcc ccaagagtcc c 21

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<210> SEQ ID NO 466
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 466

aggagagtgc caagagtccc a 21

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<210> SEQ ID NO 467
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 467

gtctgggagg cccgtttcc c 21

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 468

catggctaag gagctccacg t 21

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<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 469

gagctcccta gccatgagct c

21

<210> SEQ ID NO 470
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 470

gctccttagc catgagctca a

21

<210> SEQ ID NO 471
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 471

ggccttagtg accccctggc c

21

<210> SEQ ID NO 472
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 472

ccccctggcc caggatggag c

21

<210> SEQ ID NO 473
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 473

ctcctgtccc atcctgggcc a

21

<210> SEQ ID NO 474
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 474

ccgtgatgta caccgaggag

20

<210> SEQ ID NO 475

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 475

cttgccatc accatcagca

20

<210> SEQ ID NO 476

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 476

ttagccatca ccatcagcac

20

<210> SEQ ID NO 477

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 477

ttgcctgctt cgtcctggtc

20

<210> SEQ ID NO 478

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 478

tcctggctt cacgcagacg

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<210> SEQ ID NO 479

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 479

tcttcagtct cctggccatc

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<210> SEQ ID NO 480

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 480

gtctcctggc catcgccatt

20

<210> SEQ ID NO 481
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 481

accttagcatg ggagtcaggc

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<210> SEQ ID NO 482
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 482

aaccttagcat gggagtcaagg

20

<210> SEQ ID NO 483
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 483

atgcttaggtt ggaacaactg

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<210> SEQ ID NO 484
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 484

gcagccctgg gagtggttct

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<210> SEQ ID NO 485
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 485

cgcagccctg ggagtggttc

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<210> SEQ ID NO 486

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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 486

agggctgccc ggagggccaa

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<210> SEQ ID NO 487

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 487

tggggaccac atcctcaaag

20

<210> SEQ ID NO 488

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 488

catgaactac atgggtgact

20

<210> SEQ ID NO 489

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 489

atgaactaca tggtgtactt

20

<210> SEQ ID NO 490

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 490

acttctttgc ctgtgtgctg

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<210> SEQ ID NO 491
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 491

tgttgctcat gctgggtgtc

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<210> SEQ ID NO 492
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 492

caaatacgaca cccagcatga

20

<210> SEQ ID NO 493
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 493

gctgtcgtcg cgccgcagg

20

<210> SEQ ID NO 494
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 494

tggccgcgcg acgacagctg

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<210> SEQ ID NO 495
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 495

tctgcttcag ctgtcgtcgc

20

<210> SEQ ID NO 496
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 496

ggcagaggct ggctctccat

20

<210> SEQ ID NO 497
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 497

cggcagaggc tggctctcca

20

<210> SEQ ID NO 498
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 498

ccggcagagg ctggctctcc

20

<210> SEQ ID NO 499
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 499

cactgcagaa ggaggccat

20

<210> SEQ ID NO 500
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 500

tgctgccaag tcactggcca

20

<210> SEQ ID NO 501
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 501

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acaatgatgg ccagtgactt 20

<210> SEQ ID NO 502
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 502

tacacatcat caactgcttc 20

<210> SEQ ID NO 503
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 503

ctttcttctg ccccgactgc 20

<210> SEQ ID NO 504
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 504

gactgcagcc acggccctct 20

<210> SEQ ID NO 505
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 505

tctctggctc atgtacctgg 20

<210> SEQ ID NO 506
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 506

caaccgaatt ggtgtgggag 20

<210> SEQ ID NO 507
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 507

acaccaattc gggttgtaat

20

<210> SEQ ID NO 508
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 508

gttgtgaatc ctttcatctta

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<210> SEQ ID NO 509
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 509

ttcatctacg cctaccgtat

20

<210> SEQ ID NO 510
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 510

tctacgccta ccgttatccgc

20

<210> SEQ ID NO 511
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 511

cgagttccgc cagaccttcc

20

<210> SEQ ID NO 512
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 512
gccagacattt ccgcaagatc 20

<210> SEQ ID NO 513
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 513
ccagacaccttc cgcaagatca 20

<210> SEQ ID NO 514
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 514
gcaagatcat tcgcagccac 20

<210> SEQ ID NO 515
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 515
caagatcatt cgcagccacg 20

<210> SEQ ID NO 516
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 516
cagccacgtc ctgaggcagc 20

<210> SEQ ID NO 517
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 517
aggcagctgg caccagtgcc 20

<210> SEQ ID NO 518

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 518

tcaactgccc gagctgccaa

20

<210> SEQ ID NO 519
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 519

tctcaacggc caccggccag

20

<210> SEQ ID NO 520
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 520

ctcagggtgg ggagcactgc

20

<210> SEQ ID NO 521
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 521

caccctgagc ggaggcccaa

20

<210> SEQ ID NO 522
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 522

accctgagcg gaggcccaa

20

<210> SEQ ID NO 523
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 523

agggcatacg cattgggcct

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<210> SEQ ID NO 524

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<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 524

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<210> SEQ ID NO 525

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 525

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<210> SEQ ID NO 526

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 526

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<210> SEQ ID NO 527

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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 527

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<210> SEQ ID NO 528

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 528

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<210> SEQ ID NO 529
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Synthetic oligonucleotide"

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aggggaacac gggcctccca

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<210> SEQ ID NO 530
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 530

cgtctgggag gcccggttcc

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<210> SEQ ID NO 531
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 531

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<210> SEQ ID NO 532
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 532

ttgagctcat ggctaaggag

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<210> SEQ ID NO 533
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<212> TYPE: DNA
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 533

ctggcctaga tgacccccctg

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<210> SEQ ID NO 534
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<212> TYPE: DNA
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 534

tggcctagat gaccccttgg

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<210> SEQ ID NO 535
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<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 535

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<210> SEQ ID NO 536
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<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 536

ctggcccagg atggagcagg

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<210> SEQ ID NO 537
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 537

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<210> SEQ ID NO 538
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 538

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<210> SEQ ID NO 539
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ccctggggct ggtgagtgga 20

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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 540

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<210> SEQ ID NO 541
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
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<400> SEQUENCE: 541

accgcacgtt cagaagtccgg 20

<210> SEQ ID NO 542
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 542

acaactgtgt aaatttttgt 20

<210> SEQ ID NO 543
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 543

caactgtgtta aattttgtga 20

<210> SEQ ID NO 544
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 544

acctgtgaca accagaaatc 20

<210> SEQ ID NO 545
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<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 545

cctgtgacaa ccagaaatcc

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<210> SEQ ID NO 546
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 546

tgtggcttct cacagatgga

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<210> SEQ ID NO 547
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 547

tctgtgagaa gccacaggaa

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<210> SEQ ID NO 548
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 548

aagctccccc accatgactt

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<210> SEQ ID NO 549
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 549

gaataaaagtcaatggtaggggg

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<210> SEQ ID NO 550
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 550
agaataaaagt catggtaggg 20

<210> SEQ ID NO 551
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 551
ctaccatgac tttattctgg 20

<210> SEQ ID NO 552
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: S
ynthetic oligonucleotide"

<400> SEQUENCE: 552
taccatgact ttattctgg 20

<210> SEQ ID NO 553
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 553
taatgcacctt tggagaagca 20

<210> SEQ ID NO 554
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 554
ttcataatgc actttggaga 20

<210> SEQ ID NO 555
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 555
aagtgcatta tgaaggaaaa 20

<210> SEQ ID NO 556

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 556

tgtgttctg tagcttgat

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<210> SEQ ID NO 557
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 557

tgttagctcg atgagtgc当地

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<210> SEQ ID NO 558
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 558

agtgacaggc atcagccccc

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<210> SEQ ID NO 559
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 559

agtgggtggca ggaggctgat

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<210> SEQ ID NO 560
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 560

aggttgaact cagcttctgc

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<210> SEQ ID NO 561
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 561

caggttgaac tcagttctg

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<210> SEQ ID NO 562

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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 562

acctggaaa ccggcaagac

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<210> SEQ ID NO 563

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 563

cgtcttgccg gtttcccagg

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<210> SEQ ID NO 564

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 564

gcgtcttgcc ggtttcccag

20

<210> SEQ ID NO 565

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 565

tgagcttccg cgtcttgccg

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<210> SEQ ID NO 566

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 566

gcgagcactg tgccatcatc

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<210> SEQ ID NO 567
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 567

ggatgatggc acagtgtcg

20

<210> SEQ ID NO 568
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 568

aggatgatgg cacagtgc

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<210> SEQ ID NO 569
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 569

cgtgtgccaa caacatcaac

20

<210> SEQ ID NO 570
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 570

gctcaatggg cagcagctct

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<210> SEQ ID NO 571
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 571

accagggtgtt ccagctaat

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<210> SEQ ID NO 572
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 572

caccagggtg tccagctaa

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<210> SEQ ID NO 573
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 573

ccaccagggt gtccagctca

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<210> SEQ ID NO 574
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 574

gcttggcctt atagaccta

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<210> SEQ ID NO 575
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 575

gagcagttt agacagtggc

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<210> SEQ ID NO 576
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 576

agaggcatac tcctcatagg

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<210> SEQ ID NO 577
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 577

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ctatgaggag tatgcctctt 20

<210> SEQ ID NO 578
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 578

aagaggcata ctcctcatag 20

<210> SEQ ID NO 579
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 579

tatgaggagt atgcctcttg 20

<210> SEQ ID NO 580
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 580

gattgatgtc tgagaagatg 20

<210> SEQ ID NO 581
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 581

ctcctcagcc gtcaggaact 20

<210> SEQ ID NO 582
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 582

gttcctgacg gctgaggagc 20

<210> SEQ ID NO 583
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 583

gctcctcagc cgtcaggAAC

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<210> SEQ ID NO 584
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 584

tgacggctga ggAGCggAAg

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<210> SEQ ID NO 585
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 585

tcttccgctc ctcAGCCGTC

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<210> SEQ ID NO 586
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 586

aactccgtct tccgctcCTC

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<210> SEQ ID NO 587
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 587

caactccgtc ttccgctcCT

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<210> SEQ ID NO 588
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 588
ccaaactccgt cttccgctcc 20

<210> SEQ ID NO 589
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 589
acgccaaggg caacctacag 20

<210> SEQ ID NO 590
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 590
cgcccaagggc aacctacagg 20

<210> SEQ ID NO 591
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 591
agctgatgac atgcccgcgtc 20

<210> SEQ ID NO 592
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 592
gggcgaggga gctgcccagc 20

<210> SEQ ID NO 593
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 593
cgggcgaggg agctgcccag 20

<210> SEQ ID NO 594

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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cggggcgagg gagctgcccc
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 595
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tgcggccgggg gattgtcac
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<210> SEQ ID NO 596
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 596
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acatggagtg tgatcactgt
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20

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<210> SEQ ID NO 597
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 597
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cagtgtatcac actccatgtg
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20

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<210> SEQ ID NO 598
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 598
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tgtggggaggc ccaagatgcc
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<400> SEQUENCE: 599

tgtgcacgat gggcatcttg

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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<212> TYPE: DNA

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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

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gacgcaggaa aagcccaaag

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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

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cagacagagt agggtccaga

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gcccagcacga tccccaccgca

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aaggaaaaaa aaaaggctgg

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acaccagcaa tcctgacttg

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<400> SEQUENCE: 609

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<221> NAME/KEY: source
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gcaactccca gtgggtggcag

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<400> SEQUENCE: 611

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Synthetic oligonucleotide"

<400> SEQUENCE: 612

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<210> SEQ ID NO 613
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<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 613

aggccaagct gaagcagaac

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<210> SEQ ID NO 614
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<221> NAME/KEY: source
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<400> SEQUENCE: 614

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cctcttgaa gacagagaag 20

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ttctcatgt tcagattgat 20

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<400> SEQUENCE: 617

ctcgtgaaga acgaccta 20

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Synthetic oligonucleotide"

<400> SEQUENCE: 618

ggccgtcgca catcgctc 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 619

gcggggtctg ccatgggtcg 20

<210> SEQ ID NO 620
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 620

agttgctcat gcaggattc 20

<210> SEQ ID NO 621
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<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 621

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<210> SEQ ID NO 622
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<212> TYPE: DNA
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 622

ccccctaccat gactttattc

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<212> TYPE: DNA
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 623

aagtcatggt aggggagctt

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<210> SEQ ID NO 624
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<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 624

agtcatggta ggggagctt

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<210> SEQ ID NO 625
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 625

attgcactca tcagagctac

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<210> SEQ ID NO 626
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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<400> SEQUENCE: 626
cctagagtga agagattcat 20

<210> SEQ ID NO 627
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 627
ccaatgaatc ttttactct 20

<210> SEQ ID NO 628
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 628
aaagtcatgg taggggagct 20

<210> SEQ ID NO 629
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 629
gtgagcaatc ccccgccgca 20

<210> SEQ ID NO 630
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<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 630
gtcggttttc acgaggatat 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 631
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<211> LENGTH: 20
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 632

gacgcggcat gtcatcagct

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<210> SEQ ID NO 633
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 633

gcttctgctg ccggtaacg

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<210> SEQ ID NO 634
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 634

gtggatgacc tggctaacag

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<210> SEQ ID NO 635
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 635

tgatcacac tccatgtggg

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<210> SEQ ID NO 636
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 636

gccccatttag ctggacaccc

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<210> SEQ ID NO 637
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 637

gcggtcatct tccaggatga

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<210> SEQ ID NO 638

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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 638

gggagctgcc cagcttgcgc

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<210> SEQ ID NO 639

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 639

gttgatgttg ttggcacacg

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<210> SEQ ID NO 640

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 640

ggcatcttgg gcctccccaca

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<210> SEQ ID NO 641

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 641

gcggcatgtc atcagctggg

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<210> SEQ ID NO 642

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 642

gctcctcagc cgtcaggaac

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<210> SEQ ID NO 643
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 643

gctgggttta tattctgatg

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<210> SEQ ID NO 644
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 644

ccgacttctg aacgtgcgggt

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<210> SEQ ID NO 645
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 645

tgctggcgtt acgcgtccac

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<210> SEQ ID NO 646
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 646

cccgacttctt gaacgtgcgg

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<210> SEQ ID NO 647
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 647

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<210> SEQ ID NO 648
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 648

taccccgact tctgaacgtg

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<210> SEQ ID NO 649
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 649

cccaccgcac gttcagaagt

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<210> SEQ ID NO 650
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 650

cggcggcgcc ggtctgccat

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<210> SEQ ID NO 651
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 651

acgagcagcg gggctgtccca

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<210> SEQ ID NO 652
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 652

agcggttctt gccatgggtc

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<210> SEQ ID NO 653
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 653

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cctgagcagc ccccgaccca

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<210> SEQ ID NO 654
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 654

ccatgggtcg ggggctgctc

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<210> SEQ ID NO 655
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 655

aacgtgcgggt gggatcggtc

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<210> SEQ ID NO 656
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 656

ggacgtatgtc cagcgccac

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<210> SEQ ID NO 657
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 657

gtccacagga cgatgtcag

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<210> SEQ ID NO 658
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 658

catgggtcg gggctgctca

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<210> SEQ ID NO 659
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 659

cagcggggtc tgccatgggt

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<210> SEQ ID NO 660
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 660

atgggtcggt ggctgctcag

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<210> SEQ ID NO 661
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 661

cggggtctgc catgggtcgg

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<210> SEQ ID NO 662
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 662

aggaagtctg tgtggctgta

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<210> SEQ ID NO 663
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 663

ctccatctgt gagaagccac

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<210> SEQ ID NO 664
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 664

atgatagtca ctgacaacaa

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<210> SEQ ID NO 665

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 665

gatgctgcag ttgctcatgc

20

<210> SEQ ID NO 666

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 666

acagccacac agacttcctg

20

<210> SEQ ID NO 667

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 667

gaagccacag gaagtctgtg

20

<210> SEQ ID NO 668

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 668

ttcctgtggc ttctcacaga

20

<210> SEQ ID NO 669

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 669

ctgtggcttc tcacagatgg

20

<210> SEQ ID NO 670

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 670

tcacaaaatt tacacagttg

20

<210> SEQ ID NO 671
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 671

gacaacatca tcttctcaga

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<210> SEQ ID NO 672
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 672

tccagaataa agtcatggta

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<210> SEQ ID NO 673
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<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 673

ggtaggggag cttgggtca

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<210> SEQ ID NO 674
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 674

ttctccaaag tgcattatga

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<210> SEQ ID NO 675
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<212> TYPE: DNA
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<221> NAME/KEY: source
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"Synthetic oligonucleotide"

<400> SEQUENCE: 675

catcttccag aataaaagtca

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<210> SEQ ID NO 676

<211> LENGTH: 20

<212> TYPE: DNA

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<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 676

cacatgaaga aagtctcacc

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<210> SEQ ID NO 677

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 677

ttccagaata aagtcatggg

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<210> SEQ ID NO 678

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 678

tttccttca taatgcactt

20

<210> SEQ ID NO 679

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 679

cacagttgtg gaaaccttgac

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<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 680

cccaactccg tcttccgctc

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<210> SEQ ID NO 681
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 681

ggtttccct gcgtctggac 20

<210> SEQ ID NO 682
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 682

ctgagggtcta taaggccaag 20

<210> SEQ ID NO 683
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 683

tgatgtgaga ttttccacct 20

<210> SEQ ID NO 684
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 684

cctatgagga gtatgcctct 20

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<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 685

aagtgacagg catcagcctc 20

<210> SEQ ID NO 686
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 686

ccatgacccc aagctccccct

20

<210> SEQ ID NO 687
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 687

tttcataatg cactttggag

20

<210> SEQ ID NO 688
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 688

ttcatgtgtt cctgttagctc

20

<210> SEQ ID NO 689
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 689

ttctggaaga tgctgtttct

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<210> SEQ ID NO 690
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 690

cccacccagg gg tgcgtttttt

20

<210> SEQ ID NO 691
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 691

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agacagtggc agtcaagatc 20

<210> SEQ ID NO 692
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 692

cctgcgtctg gaccctactc 20

<210> SEQ ID NO 693
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 693

cacaactgtg taaattttgt 20

<210> SEQ ID NO 694
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 694

gagaaggcgc atcttccaga 20

<210> SEQ ID NO 695
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 695

tggttgtcac aggtggaaaa 20

<210> SEQ ID NO 696
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 696

ccaggttgaa ctcagttct 20

<210> SEQ ID NO 697
<211> LENGTH: 21
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 697

atcacaaaat ttacacagtt g

21

<210> SEQ ID NO 698
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 698

ggcatcagcc tcctgccacc a

21

<210> SEQ ID NO 699
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 699

gttagccagg tcataccacag a

21

<210> SEQ ID NO 700
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 700

gctgggcagc tccctcgccc g

21

<210> SEQ ID NO 701
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 701

caggaggctg atgcctgtca c

21

<210> SEQ ID NO 702
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 702

gaggagcgga agacggagtt g

21

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<210> SEQ ID NO 703
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 703

cgtctggacc ctactctgtc t

21

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<210> SEQ ID NO 704
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 704

ttttcccttc ataatgcact t

21

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<210> SEQ ID NO 705
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 705

ccattgagct ggacaccctg g

21

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<210> SEQ ID NO 706
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 706

cttctccaaa gtgcattatg a

21

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<210> SEQ ID NO 707
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 707

gcccaagatg cccatcgatc a

21

<210> SEQ ID NO 708

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 708
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```
tcatgtgttc ctgttagctct g
```

```
21
```

```
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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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```
<400> SEQUENCE: 709
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```
gtgatgctgc agttgctcat g
```

```
21
```

```
<210> SEQ ID NO 710
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 710
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tctcatgctt cagattgatg t
```

```
21
```

```
<210> SEQ ID NO 711
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 711
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```
tcccttatgag gagtagtgcc t
```

```
21
```

```
<210> SEQ ID NO 712
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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```
<400> SEQUENCE: 712
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```
catcacaaaa ttacacagt t
```

```
21
```

```
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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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"Synthetic oligonucleotide"

<400> SEQUENCE: 713

attgagctgg acaccctgg g

21

<210> SEQ ID NO 714

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 714

cagtcaagat ctttccctat g

21

<210> SEQ ID NO 715

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 715

aggatttctg gttgtcacag g

21

<210> SEQ ID NO 716

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 716

tccacacgtga tcacactcca t

21

<210> SEQ ID NO 717

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 717

agcagaacac ttcatcgatc t

21

<210> SEQ ID NO 718

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 718

ccggcaagac gcggaaagctc a

21

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<210> SEQ ID NO 719
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 719

gatgtcagag cggcatctt c

21

<210> SEQ ID NO 720
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 720

tcattgcact catcagagct a

21

<210> SEQ ID NO 721
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 721

ttcccagaat aaagtcatgg t

21

<210> SEQ ID NO 722
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 722

agattttcca cctgtgacaa c

21

<210> SEQ ID NO 723
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 723

actgcagcat cacctccatc t

21

<210> SEQ ID NO 724
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 724

agctgggcag ctcctcgcc c

21

<210> SEQ ID NO 725
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 725

tgacggctga ggagcggaaag a

21

<210> SEQ ID NO 726
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 726

cattgagctg gacaccctgg t

21

<210> SEQ ID NO 727
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 727

agcaaagcga cttttccca c

21

<210> SEQ ID NO 728
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 728

cgcgttaacc ggcagcagaa g

21

<210> SEQ ID NO 729
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 729

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gaaaatatgac tagcaacaag t 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 730

agacagagta gggtccagac g 21

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<210> SEQ ID NO 731
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 731

caggatttct ggttgtcaca g 21

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<210> SEQ ID NO 732
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 732

ctcctgttagg ttgcccttgg c 21

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<210> SEQ ID NO 733
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 733

acagagttagg gtccagacgc a 21

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<210> SEQ ID NO 734
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 734

gcttctccaa agtgcattat g 21

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<210> SEQ ID NO 735
<211> LENGTH: 21
<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 735

gcagcagaag ctgagttcaa c

21

<210> SEQ ID NO 736
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 736

tgaggagcgg aagacggagt t

21

<210> SEQ ID NO 737
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 737

cttggagaa gcagcatctt c

21

<210> SEQ ID NO 738
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 738

ctccccctacc atgactttat t

21

<210> SEQ ID NO 739
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 739

gacagagtag ggtccagacg c

21

<210> SEQ ID NO 740
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 740

ctgaggagcg gaagacggag t

21

<210> SEQ ID NO 741
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 741

gggcatcttg ggcctccac a

21

<210> SEQ ID NO 742
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 742

ccaagaggca tactcctcat a

21

<210> SEQ ID NO 743
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 743

agaatgacga gaacataaca c

21

<210> SEQ ID NO 744
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 744

cctgacgccc catgtcatca g

21

<210> SEQ ID NO 745
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 745

agcgagcact gtgccatcat c

21

<210> SEQ ID NO 746

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 746
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gcagggttagg tcgttttca c
```

21

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<210> SEQ ID NO 747
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 747
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acctccatct gtgagaagcc a
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21

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<210> SEQ ID NO 748
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 748
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taaaagtcatg gtaggggagc t
```

21

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<210> SEQ ID NO 749
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 749
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```
tcagagactc aggaacacat g
```

21

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<210> SEQ ID NO 750
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 750
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tctcagacat caatctgaag c
```

21

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<210> SEQ ID NO 751
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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"Synthetic oligonucleotide"

<400> SEQUENCE: 751

catcagcctc ctgccaccac t

21

<210> SEQ ID NO 752

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 752

cgtccctca g cggtaggaa c

21

<210> SEQ ID NO 753

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 753

aacctggaa accggcaaga c

21

<210> SEQ ID NO 754

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 754

tccacgcaa gggcaaccta c

21

<210> SEQ ID NO 755

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 755

gagggtgagca atccccccggg c

21

<210> SEQ ID NO 756

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 756

cagcagaagc tgagttcaac c

21

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<210> SEQ ID NO 757
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 757

tccaaaggc atactcctca t

21

<210> SEQ ID NO 758
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 758

agcagaagct gagttcaacc t

21

<210> SEQ ID NO 759
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 759

ccagttcctg acggctgagg a

21

<210> SEQ ID NO 760
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 760

aggagtatgc ctcttggaaag a

21

<210> SEQ ID NO 761
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 761

tccaaaggc catactcctc a

21

<210> SEQ ID NO 762
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 762

caactgtgta aattttgtga t

21

<210> SEQ ID NO 763
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 763

tgaaggaaaa aaaaaagcct g

21

<210> SEQ ID NO 764
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 764

cgtcttccgc tcctcagccg t

21

<210> SEQ ID NO 765
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 765

ccaggtcatc cacagacaga g

21

<210> SEQ ID NO 766
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 766

gccttagatg aagagattca t

21

<210> SEQ ID NO 767
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 767

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gttctccaaa gtgcattatg a 21

<210> SEQ ID NO 768
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 768

gcatcttcca gaataaaagtc a 21

<210> SEQ ID NO 769
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 769

caaccgtctg gtggccgacg 20

<210> SEQ ID NO 770
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 770

caggatcggg gctgtcgctt 20

<210> SEQ ID NO 771
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 771

tcgggcctcg ctggccgtaa 20

<210> SEQ ID NO 772
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 772

gaggtagtcg gccatgcgcc 20

<210> SEQ ID NO 773
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 773

cagggttgtt cgggcctcgc

20

<210> SEQ ID NO 774
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 774

ggaggttagtc ggccatgcgc

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<210> SEQ ID NO 775
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 775

ggcatactca atgcgtacat

20

<210> SEQ ID NO 776
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 776

ccgccttgtc atcaaccgtc

20

<210> SEQ ID NO 777
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 777

aggatcgggg ctgtcgcttc

20

<210> SEQ ID NO 778
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 778
ccttgtcatc aaccgtctgg 20

<210> SEQ ID NO 779
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 779
tactcaatgc gtacattgg 20

<210> SEQ ID NO 780
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 780
gggttccatt acggccagcg 20

<210> SEQ ID NO 781
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 781
ggcactgott ctgcgtacaa 20

<210> SEQ ID NO 782
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 782
ggtgatgac aaggcgac 20

<210> SEQ ID NO 783
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 783
tgctggggcc ttcctcgagg 20

<210> SEQ ID NO 784

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 784

ttgctggctg tggagggac

20

<210> SEQ ID NO 785
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 785

tttccttacc ttcgaaaatc

20

<210> SEQ ID NO 786
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 786

gactggcttg ggcagttcca

20

<210> SEQ ID NO 787
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 787

catgcagccc ttgcctgctg

20

<210> SEQ ID NO 788
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 788

agcaaaggac gaggtctaga

20

<210> SEQ ID NO 789
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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Synthetic oligonucleotide"

<400> SEQUENCE: 789
gcctgctggg gccttcctcg 20

<210> SEQ ID NO 790
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 790
cagactcacc agattccccga 20

<210> SEQ ID NO 791
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 791
acctcgtcct ttgctggctg 20

<210> SEQ ID NO 792
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 792
ctcaccagat tcccgaaagg 20

<210> SEQ ID NO 793
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 793
tacgcagaag cagtccccgc 20

<210> SEQ ID NO 794
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 794
aggtgtacag cagtggctgg 20

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<210> SEQ ID NO 795
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 795

ggtgtacagc agtggctgg

20

<210> SEQ ID NO 796
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 796

cggatgtgg cagccttgt

20

<210> SEQ ID NO 797
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 797

cactgacagc gtgaacaggt

20

<210> SEQ ID NO 798
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 798

actgacagcg tgaacaggt

20

<210> SEQ ID NO 799
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 799

gctcaacttc tgtctgggt

20

<210> SEQ ID NO 800
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 800

ctggctgtgg agcggactgg

20

<210> SEQ ID NO 801
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 801

gctctgactg tacggggcaa

20

<210> SEQ ID NO 802
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 802

agctctgact gtacggggca

20

<210> SEQ ID NO 803
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 803

acagtacccc ttccagctct

20

<210> SEQ ID NO 804
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 804

cgtcgccac cagacggttt

20

<210> SEQ ID NO 805
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 805

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ccagccactg ctgtacacct 20

<210> SEQ ID NO 806
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 806

accccgcccc tgcctatgcc 20

<210> SEQ ID NO 807
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 807

ggtatcagca gtgcaggagg 20

<210> SEQ ID NO 808
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 808

gatgtggtca gccttgtca 20

<210> SEQ ID NO 809
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 809

ggatgtggtc agccttgtc 20

<210> SEQ ID NO 810
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 810

ggccacgcat cctggcctt 20

<210> SEQ ID NO 811
<211> LENGTH: 20
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 811

gaaaggccag gatgcgtggc

20

<210> SEQ ID NO 812
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 812

actgcttgc caggccacgc

20

<210> SEQ ID NO 813
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 813

tctggactcc aactgcttg

20

<210> SEQ ID NO 814
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 814

gtctggactc caactgcttg

20

<210> SEQ ID NO 815
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 815

gcttcgtct ggactccaac

20

<210> SEQ ID NO 816
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 816
gacggaaagct ggagtccggca 20

<210> SEQ ID NO 817
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 817
cgctgtcagt gaaaaccact 20

<210> SEQ ID NO 818
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 818
ctgacacgcgt gaacaggtag 20

<210> SEQ ID NO 819
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 819
ttacggccag cgaggccccga 20

<210> SEQ ID NO 820
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 820
attacggcca gcgaggccccg 20

<210> SEQ ID NO 821
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 821
ggaatctgggt gagtctgagg 20

<210> SEQ ID NO 822

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<211> LENGTH: 20
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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ccctcagact caccagattc

20

<210> SEQ ID NO 823
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

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cgaaggtagg agaaggcttt

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<210> SEQ ID NO 824
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<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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gaaggtagga gaaggctttg

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<210> SEQ ID NO 825
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<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 825

gcaccttgg ctcaactctct

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<210> SEQ ID NO 826
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<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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tcgaggaggt ggcagagggt

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<210> SEQ ID NO 827
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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"Synthetic oligonucleotide"

<400> SEQUENCE: 827

tggaaactgcc caagccagtc

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<210> SEQ ID NO 828

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 828

agggacgggg cccacagggg

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<210> SEQ ID NO 829

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 829

gggacggggc ccacaggggc

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<210> SEQ ID NO 830

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 830

ctccacagcc agcaaaggac

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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 831

cagccagcaa aggacgaggt

20

<210> SEQ ID NO 832

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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 832

ctgccttcta gacctcgatcc

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<210> SEQ ID NO 833
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 833

cctaaggagg atgcgcctag

20

<210> SEQ ID NO 834
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 834

tggcctctg cactgtgtat

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<210> SEQ ID NO 835
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 835

agcagtgcag gaggccacat

20

<210> SEQ ID NO 836
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 836

ccgactccag cttccgtctg

20

<210> SEQ ID NO 837
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 837

ggggttccat tacggccagc

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<210> SEQ ID NO 838
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 838

cacagcagat ctcctcttgg

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<210> SEQ ID NO 839
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 839

attgccccgt acagtcagag

20

<210> SEQ ID NO 840
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 840

cccgtagt cagagcttga

20

<210> SEQ ID NO 841
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 841

tggtgaggaa gcaggcagt

20

<210> SEQ ID NO 842
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 842

tccttaggca taggcaggc

20

<210> SEQ ID NO 843
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 843

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cggccctgcc tatgcctaag 20

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<212> TYPE: DNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 844

taggcataagg caggggccggg 20

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 845

aggcaggggcc ggggtgggag 20

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 846

gcaggatcg ggctgtcgct 20

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<210> SEQ ID NO 847
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 847

ctgcacaagg ctgaccacat 20

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<210> SEQ ID NO 848
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 848

tgccacaaggc tgaccacatc 20

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<210> SEQ ID NO 849
<211> LENGTH: 20
<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 849

ctgaccacat cccggaaaggc

20

<210> SEQ ID NO 850
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 850

ggccacgcgtt cctggccttt

20

<210> SEQ ID NO 851
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 851

gcgtggccttg gacaaggcagt

20

<210> SEQ ID NO 852
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 852

gacaaggcagt tggagtcag

20

<210> SEQ ID NO 853
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 853

gttggagtcc agacggaagc

20

<210> SEQ ID NO 854
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 854
atgcgtacat tgggtgggccc 20

<210> SEQ ID NO 855
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 855
tggccccacc aatgtacgca 20

<210> SEQ ID NO 856
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 856
gctacctgtt cacgctgtca 20

<210> SEQ ID NO 857
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 857
tgacagcgta aacaggttagc 20

<210> SEQ ID NO 858
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 858
gtcgggcctc gtcggccgta 20

<210> SEQ ID NO 859
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 859
gcacttgcct aggctggtat 20

<210> SEQ ID NO 860

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 860

g g g a a t c t g g t g a g t c t g a g

20

<210> SEQ ID NO 861
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 861

c t c a c c a g a t t c c c g a a g g t

20

<210> SEQ ID NO 862
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 862

c t c c t a c c t t c g g g a a t c t g

20

<210> SEQ ID NO 863
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 863

c a a g a c c t t c t c t a c c t t c

20

<210> SEQ ID NO 864
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 864

c c a a g a c c t t c t c t a c c t t c

20

<210> SEQ ID NO 865
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 865

gccaaagacct ttccttaccc

20

<210> SEQ ID NO 866

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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 866

tatgcacagc agatcctcct

20

<210> SEQ ID NO 867

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 867

caaagggtgct ggaccaggag

20

<210> SEQ ID NO 868

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 868

ggctcaactct ctgtctgggc

20

<210> SEQ ID NO 869

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 869

agggtacccc agccccagaca

20

<210> SEQ ID NO 870

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 870

agagggtacc ccagccccaga

20

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<210> SEQ ID NO 871
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 871

gtaccctctg ccacccctc

20

<210> SEQ ID NO 872
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 872

ccttcctcgaa ggagggtggca

20

<210> SEQ ID NO 873
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 873

atgactggct tgggcagttc

20

<210> SEQ ID NO 874
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 874

ggccccctgtggcccccgtcc

20

<210> SEQ ID NO 875
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 875

aggacgaggtt ctagaaggca

20

<210> SEQ ID NO 876
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 876

tataagtgga ggcgtcgcg

20

<210> SEQ ID NO 877
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 877

gggcacgcgt ttaatataag

20

<210> SEQ ID NO 878
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 878

actcacgctg gatagcctcc

20

<210> SEQ ID NO 879
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 879

ggccgagatg tctcgctccg

20

<210> SEQ ID NO 880
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 880

cacgcgttta atataagtgg

20

<210> SEQ ID NO 881
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 881

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aagtggaggc gtcgcgtgg 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 882

gagtagcgcg agcacagcta 20

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<210> SEQ ID NO 883
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 883

agtggaggcg tcgcgtggc 20

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<210> SEQ ID NO 884
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 884

gcccgaaatgc tgtcagcttc 20

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<210> SEQ ID NO 885
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 885

cgcgagcaca gctaaggcca 20

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<210> SEQ ID NO 886
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 886

ctcgcgtac tctcttttc 20

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<210> SEQ ID NO 887
<211> LENGTH: 20
<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 887

ggccacggag cgagacatct

20

<210> SEQ ID NO 888
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 888

cgtgagtaaa cctgaatctt

20

<210> SEQ ID NO 889
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 889

agtcacatgg ttcacacggc

20

<210> SEQ ID NO 890
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 890

aagtcaacctt caatgtcgga

20

<210> SEQ ID NO 891
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 891

cagtaagtca acttcaatgt

20

<210> SEQ ID NO 892
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 892
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<213> ORGANISM: Artificial Sequence
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<210> SEQ ID NO 896
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

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18

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<221> NAME/KEY: source
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19

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<221> NAME/KEY: source
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Synthetic oligonucleotide"
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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21

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22

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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 904

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23

<210> SEQ ID NO 905

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<212> TYPE: RNA

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<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 905

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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

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<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 906

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<210> SEQ ID NO 907

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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

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<221> NAME/KEY: source

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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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acuuuuccauu cucugcugga u

21

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Synthetic oligonucleotide"

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22

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 911

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23

<210> SEQ ID NO 912
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 912

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24

<210> SEQ ID NO 913
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Synthetic oligonucleotide"

<400> SEQUENCE: 913

agcaaggacu ggucuuuc

18

<210> SEQ ID NO 914
<211> LENGTH: 19
<212> TYPE: RNA
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 914

agcaaggacu ggucuuucu

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<210> SEQ ID NO 915
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

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<210> SEQ ID NO 916
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 916

agcaaggacu ggucuuucua u

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<210> SEQ ID NO 917
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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Synthetic oligonucleotide"

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<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 918

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23

<210> SEQ ID NO 919
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 919

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agcaaggacu ggucuuucua ucuc 24

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 920

agugggggug aaucagu 18

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 921

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 922

agugggggug aaucagugu 20

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 923

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 924

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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 925

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23

<210> SEQ ID NO 926
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 926

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 927

auccauccga cauugaag

18

<210> SEQ ID NO 928
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 928

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19

<210> SEQ ID NO 929
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 929

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<210> SEQ ID NO 930
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

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<400> SEQUENCE: 930
auccauccga cauugaaguu g 21

<210> SEQ ID NO 931
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 931
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<210> SEQ ID NO 932
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 932
auccauccga cauugaaguu gac 23

<210> SEQ ID NO 933
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 933
auccauccga cauugaaguu gacu 24

<210> SEQ ID NO 934
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 934
caauucucuc uccauuuu 18

<210> SEQ ID NO 935
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 935
caauucucuc uccauuuu 19

<210> SEQ ID NO 936

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<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 936

caauucucuc uccauuucuuc

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<210> SEQ ID NO 937
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 937

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21

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<210> SEQ ID NO 938
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 938

caauucucuc uccauuucuuc ag

22

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<210> SEQ ID NO 939
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 939

caauucucuc uccauuucuuc agu

23

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<210> SEQ ID NO 940
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 940

caauucucuc uccauuucuuc agua

24

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<210> SEQ ID NO 941
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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Synthetic oligonucleotide"

<400> SEQUENCE: 941

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18

<210> SEQ ID NO 942

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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 942

caguggggggu gaauucagu

19

<210> SEQ ID NO 943

<211> LENGTH: 20

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 943

caguggggggu gaauucagug

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<210> SEQ ID NO 944

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 944

caguggggggu gaauucagug u

21

<210> SEQ ID NO 945

<211> LENGTH: 22

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 945

caguggggggu gaauucagug ua

22

<210> SEQ ID NO 946

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 946

caguggggggu gaauucagug uag

23

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<210> SEQ ID NO 947
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 947

cagugggggu gaaucagug uagu

24

<210> SEQ ID NO 948
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 948

cauucucugc uggaugac

18

<210> SEQ ID NO 949
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 949

cauucucugc uggaugacg

19

<210> SEQ ID NO 950
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 950

cauucucugc uggaugacgu

20

<210> SEQ ID NO 951
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 951

cauucucugc uggaugacgu g

21

<210> SEQ ID NO 952
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 952

cauucucugc uggaugacgu ga

22

<210> SEQ ID NO 953
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 953

cauucucugc uggaugacgu gag

23

<210> SEQ ID NO 954
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 954

cauucucugc uggaugacgu gagu

24

<210> SEQ ID NO 955
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 955

cccgauauuc cucaggua

18

<210> SEQ ID NO 956
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 956

cccgauauuc cucaggua

19

<210> SEQ ID NO 957
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 957

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cccgauauuc cucagguacu

20

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<210> SEQ ID NO 958
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 958
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cccgauauuc cucagguacu c

21

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<210> SEQ ID NO 959
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 959
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cccgauauuc cucagguacu cc

22

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<210> SEQ ID NO 960
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 960
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cccgauauuc cucagguacu cca

23

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<210> SEQ ID NO 961
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 961
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cccgauauuc cucagguacu ccaa

24

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<210> SEQ ID NO 962
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 962
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ccgauauucc ucagguac

18

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<210> SEQ ID NO 963
<211> LENGTH: 19
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 963

ccgauauucc ucagguacu

19

<210> SEQ ID NO 964
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<212> TYPE: RNA

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<212> TYPE: RNA

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<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

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<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 984

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<400> SEQUENCE: 985

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<400> SEQUENCE: 986

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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 989

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<210> SEQ ID NO 990
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 990

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<210> SEQ ID NO 991
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
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<400> SEQUENCE: 991

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 992

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 993

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 994

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<210> SEQ ID NO 995
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 996

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 998

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<212> TYPE: RNA
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 999

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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Synthetic oligonucleotide"

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1004

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18

<210> SEQ ID NO 1005
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1005

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<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 1006
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1007
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<210> SEQ ID NO 1008
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
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<210> SEQ ID NO 1009
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<212> TYPE: RNA
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<220> FEATURE:
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<212> TYPE: RNA
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<220> FEATURE:
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<220> FEATURE:
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<220> FEATURE:
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19

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<210> SEQ ID NO 1014
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<210> SEQ ID NO 1015
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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22

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<210> SEQ ID NO 1016
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<212> TYPE: RNA
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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23

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<210> SEQ ID NO 1017
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<212> TYPE: RNA
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<221> NAME/KEY: source
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<210> SEQ ID NO 1018

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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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18

<210> SEQ ID NO 1019

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 1019

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<210> SEQ ID NO 1020

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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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21

<210> SEQ ID NO 1022

<211> LENGTH: 22

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 1022

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<210> SEQ ID NO 1023
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 1023

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23

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<211> LENGTH: 24
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<212> TYPE: RNA
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<400> SEQUENCE: 1025

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<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
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<400> SEQUENCE: 1026

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Synthetic oligonucleotide"

<400> SEQUENCE: 1027

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<211> LENGTH: 21
<212> TYPE: RNA
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<220> FEATURE:

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<221> NAME/KEY: source
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<400> SEQUENCE: 1028

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<210> SEQ ID NO 1030
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<212> TYPE: RNA
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<221> NAME/KEY: source
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Synthetic oligonucleotide"

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<221> NAME/KEY: source
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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<210> SEQ ID NO 1033
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<220> FEATURE:
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 1034

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<210> SEQ ID NO 1035
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 1035

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<210> SEQ ID NO 1036
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<212> TYPE: RNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1036

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<210> SEQ ID NO 1037
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 1037

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<210> SEQ ID NO 1038
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1038

cauagaucga gacauguaag cagc 24

<210> SEQ ID NO 1039
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<220> FEATURE:
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Synthetic oligonucleotide"

<400> SEQUENCE: 1039

cuccacuguc uuuuuucau

18

<210> SEQ ID NO 1040
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<221> NAME/KEY: source
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<400> SEQUENCE: 1040

cuccacuguc uuuuuucaua

19

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Synthetic oligonucleotide"

<400> SEQUENCE: 1041

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20

<210> SEQ ID NO 1042
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<212> TYPE: RNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1042

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21

<210> SEQ ID NO 1043
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1043

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22

<210> SEQ ID NO 1044
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 1044
cuccacuguc uuuuucauag auc 23

<210> SEQ ID NO 1045
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1045
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<210> SEQ ID NO 1046
<211> LENGTH: 18
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 1046
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<210> SEQ ID NO 1047
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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Synthetic oligonucleotide"

<400> SEQUENCE: 1047
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<210> SEQ ID NO 1048
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<212> TYPE: RNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1048
ucauagaucg agacauguaa 20

<210> SEQ ID NO 1049
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1049
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<210> SEQ ID NO 1050

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<211> LENGTH: 22
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1050

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ucauagaucg agacauguaa gc

22

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<210> SEQ ID NO 1051
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<212> TYPE: RNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1051

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ucauagaucg agacauguaa gca

23

```

<210> SEQ ID NO 1052
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<212> TYPE: RNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1052

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ucauagaucg agacauguaa gcag

24

```

<210> SEQ ID NO 1053
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1053

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uccacugucu uuuucaua

18

```

<210> SEQ ID NO 1054
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1054

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uccacugucu uuuucauag

19

```

<210> SEQ ID NO 1055
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

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"Synthetic oligonucleotide"

<400> SEQUENCE: 1055

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<210> SEQ ID NO 1056

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<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1056

uccacugucu uuuucauaga u

21

<210> SEQ ID NO 1057

<211> LENGTH: 22

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1057

uccacugucu uuuucauaga uc

22

<210> SEQ ID NO 1058

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1058

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23

<210> SEQ ID NO 1059

<211> LENGTH: 24

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1059

uccacugucu uuuucauaga ucga

24

<210> SEQ ID NO 1060

<211> LENGTH: 18

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1060

ucuccacugu cuuuuuca

18

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<210> SEQ ID NO 1061
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1061
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ucuccacugu cuuuuucau
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19

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<210> SEQ ID NO 1062
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1062
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```
ucuccacugu cuuuuucaua
```

20

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<210> SEQ ID NO 1063
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1063
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```
ucuccacugu cuuuuucaua g
```

21

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<210> SEQ ID NO 1064
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1064
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```
ucuccacugu cuuuuucaua ga
```

22

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<210> SEQ ID NO 1065
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1065
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```
ucuccacugu cuuuuucaua gau
```

23

```
<210> SEQ ID NO 1066
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 1066

ucuccacugu cuuuuucaua gauc

24

<210> SEQ ID NO 1067
 <211> LENGTH: 18
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic oligonucleotide"

<400> SEQUENCE: 1067

uucuccacug ucuuuuuc

18

<210> SEQ ID NO 1068
 <211> LENGTH: 19
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic oligonucleotide"

<400> SEQUENCE: 1068

uucuccacug ucuuuuuca

19

<210> SEQ ID NO 1069
 <211> LENGTH: 20
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic oligonucleotide"

<400> SEQUENCE: 1069

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20

<210> SEQ ID NO 1070
 <211> LENGTH: 21
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic oligonucleotide"

<400> SEQUENCE: 1070

uucuccacug ucuuuuuucau a

21

<210> SEQ ID NO 1071
 <211> LENGTH: 22
 <212> TYPE: RNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic oligonucleotide"

<400> SEQUENCE: 1071

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uucuccacug ucuuuuucau ag 22

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<211> LENGTH: 23
<212> TYPE: RNA
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1072

uucuccacug ucuuuuucau aga 23

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<210> SEQ ID NO 1073
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1073

uucuccacug ucuuuuucau agau 24

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<210> SEQ ID NO 1074
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1074

uuucuccacu gucuuuuu 18

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<210> SEQ ID NO 1075
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1075

uuucuccacu gucuuuuuc 19

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<210> SEQ ID NO 1076
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1076

uuucuccacu gucuuuuuca 20

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<210> SEQ ID NO 1077
<211> LENGTH: 21
<212> TYPE: RNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1077

uuucuccacu gucuuuuuca u

21

<210> SEQ ID NO 1078
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1078

uuucuccacu gucuuuuuca ua

22

<210> SEQ ID NO 1079
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1079

uuucuccacu gucuuuuuca uag

23

<210> SEQ ID NO 1080
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1080

uuucuccacu gucuuuuuca uaga

24

<210> SEQ ID NO 1081
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1081

uuuucuccac uguuuuuu

18

<210> SEQ ID NO 1082
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 1082

uuuuucuccac ugucuuuuuu

19

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<210> SEQ ID NO 1083
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1083

uuuuucuccac ugucuuuuuuc

20

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<210> SEQ ID NO 1084
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1084

uuuuucuccac ugucuuuuuuc a

21

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<210> SEQ ID NO 1085
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1085

uuuuucuccac ugucuuuuuuc au

22

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<210> SEQ ID NO 1086
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1086

uuuuucuccac ugucuuuuuuc aua

23

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<210> SEQ ID NO 1087
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1087

uuuuucuccac ugucuuuuuuc auag

24

<210> SEQ ID NO 1088

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1088
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gaggttaaagg gtttgattt g
```

21

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<210> SEQ ID NO 1089
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1089
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```
cctctaaagg ttatgtttac a
```

21

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<210> SEQ ID NO 1090
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1090
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agtgcattt cttgttagcac t
```

21

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<210> SEQ ID NO 1091
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1091
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cttggtagcac tgccacatgtt a
```

21

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<210> SEQ ID NO 1092
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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<400> SEQUENCE: 1092
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tccattacat gataaaaagac t
```

21

```
<210> SEQ ID NO 1093
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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"Synthetic oligonucleotide"

<400> SEQUENCE: 1093

ctcccattaca ggataaaaga c

21

<210> SEQ ID NO 1094

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1094

tctccattac aggataaaag a

21

<210> SEQ ID NO 1095

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1095

atcctgtaat ggagaaaaat c

21

<210> SEQ ID NO 1096

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1096

tcctgtatg gagaaaaatc c

21

<210> SEQ ID NO 1097

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1097

aaacatgagt aagttgtttt g

21

<210> SEQ ID NO 1098

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1098

gctttcaaac atgagtaagt t

21

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<210> SEQ ID NO 1099
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1099
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```
aaagccaaac cattcattgt c 21
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```
<210> SEQ ID NO 1100
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1100
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```
gttaacagcag tcatcatcca t 21
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```
<210> SEQ ID NO 1101
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1101
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```
accatcctca tggattggtg t 21
```

```
<210> SEQ ID NO 1102
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1102
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tgtccatcat ttcaccatcc t 21
```

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<210> SEQ ID NO 1103
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1103
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gaaatttctg tccatcattt c 21
```

```
<210> SEQ ID NO 1104
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1104

agaaaatttct gtccatcatt t

21

<210> SEQ ID NO 1105
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1105

tttttagaaat ttctgtccat c

21

<210> SEQ ID NO 1106
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1106

cttttttagaaa tttctgtcca t

21

<210> SEQ ID NO 1107
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1107

ttttttttta gaaatttctg t

21

<210> SEQ ID NO 1108
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1108

taaaagaaaa gaaagaattt t

21

<210> SEQ ID NO 1109
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1109

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aaacat tt ac atcttaccat t	21
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<210> SEQ ID NO 1110 <211> LENGTH: 21 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
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<400> SEQUENCE: 1110	
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catcttacca tttcttcttc a	21
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<210> SEQ ID NO 1111 <211> LENGTH: 21 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
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<400> SEQUENCE: 1111	
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tatagataat gaagaagaaa t	21
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<210> SEQ ID NO 1112 <211> LENGTH: 21 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
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<400> SEQUENCE: 1112	
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ttcttcatta tctatagaaa g	21
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<210> SEQ ID NO 1113 <211> LENGTH: 21 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
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<400> SEQUENCE: 1113	
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ctggcctgta ctgcgaagaa c	21
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<210> SEQ ID NO 1114 <211> LENGTH: 21 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
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<400> SEQUENCE: 1114	
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cttaccaatg tagtaacaac t	21
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<210> SEQ ID NO 1115 <211> LENGTH: 21 <212> TYPE: DNA	
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1115

gcacgtcatt gtggccattg t

21

<210> SEQ ID NO 1116
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1116

ttagcacgt cattgtggcc a

21

<210> SEQ ID NO 1117
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1117

ccatcagctc cagagaagct c

21

<210> SEQ ID NO 1118
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1118

tctccctgca gatttaccat c

21

<210> SEQ ID NO 1119
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1119

aatgcttta ctttgca g

21

<210> SEQ ID NO 1120
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

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<400> SEQUENCE: 1120
aatgcttac ctttgactg a 21

<210> SEQ_ID NO 1121
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1121
ccttgact gataggttt g 21

<210> SEQ_ID NO 1122
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1122
cagtgtatgg ttttgtcatt c 21

<210> SEQ_ID NO 1123
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1123
aagggaatga caaaacctat c 21

<210> SEQ_ID NO 1124
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1124
caaggaaatg acaaaaccta t 21

<210> SEQ_ID NO 1125
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1125
gtcattccct tgaaaaatcct g 21

<210> SEQ_ID NO 1126
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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 1126
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```
tcattccctt gaaaatcctg a
```

21

```
<210> SEQ ID NO 1127
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 1127
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```
tgaagggtta attccgcata g
```

21

```
<210> SEQ ID NO 1128
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 1128
```

```
gaaggttaa ttccgcata g
```

21

```
<210> SEQ ID NO 1129
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 1129
```

```
aagggttaat tccgcatagg t
```

21

```
<210> SEQ ID NO 1130
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
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```
<400> SEQUENCE: 1130
```

```
attccgcata ggttatttcc t
```

21

```
<210> SEQ ID NO 1131
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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"Synthetic oligonucleotide"

<400> SEQUENCE: 1131

gcaactgaac aggaaataac c

21

<210> SEQ ID NO 1132

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1132

agcaactgaa cagggaaataa c

21

<210> SEQ ID NO 1133

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1133

ctgttcagtt gctaaaatgg a

21

<210> SEQ ID NO 1134

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1134

tattgccttt aggtttcgt t

21

<210> SEQ ID NO 1135

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1135

atgccttta gggtttcggtt g

21

<210> SEQ ID NO 1136

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1136

ttgcctttag gttttcggtt c

21

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<210> SEQ ID NO 1137
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 1137
```

```
ggtttgcgtt gctgcctctt t
```

```
21
```

```
<210> SEQ ID NO 1138
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 1138
```

```
cgttgctgcc tctttgggtt t
```

```
21
```

```
<210> SEQ ID NO 1139
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 1139
```

```
gttgctgctt ctgggggtt g
```

```
21
```

```
<210> SEQ ID NO 1140
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 1140
```

```
ggtttgggg cagattcagg t
```

```
21
```

```
<210> SEQ ID NO 1141
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"
```

```
<400> SEQUENCE: 1141
```

```
ggggcagatt caggctcgag t
```

```
21
```

```
<210> SEQ ID NO 1142
<211> LENGTH: 1334
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 1142

Met Gly His His His His His Gly Ser Thr Gln Phe Glu Gly Phe
1           5          10          15

Thr Asn Leu Tyr Gln Val Ser Lys Thr Leu Arg Phe Glu Leu Ile Pro
20          25          30

Gln Gly Lys Thr Leu Lys His Ile Gln Glu Gln Gly Phe Ile Glu Glu
35          40          45

Asp Lys Ala Arg Asn Asp His Tyr Lys Glu Leu Lys Pro Ile Ile Asp
50          55          60

Arg Ile Tyr Lys Thr Tyr Ala Asp Gln Cys Leu Gln Leu Val Gln Leu
65          70          75          80

Asp Trp Glu Asn Leu Ser Ala Ala Ile Asp Ser Tyr Arg Lys Glu Lys
85          90          95

Thr Glu Glu Thr Arg Asn Ala Leu Ile Glu Glu Gln Ala Thr Tyr Arg
100         105         110

Asn Ala Ile His Asp Tyr Phe Ile Gly Arg Thr Asp Asn Leu Thr Asp
115         120         125

Ala Ile Asn Lys Arg His Ala Glu Ile Tyr Lys Gly Leu Phe Lys Ala
130         135         140

Glu Leu Phe Asn Gly Lys Val Leu Lys Gln Leu Gly Thr Val Thr Thr
145         150         155         160

Thr Glu His Glu Asn Ala Leu Leu Arg Ser Phe Asp Lys Phe Thr Thr
165         170         175

Tyr Phe Ser Gly Phe Tyr Glu Asn Arg Lys Asn Val Phe Ser Ala Glu
180         185         190

Asp Ile Ser Thr Ala Ile Pro His Arg Ile Val Gln Asp Asn Phe Pro
195         200         205

Lys Phe Lys Glu Asn Cys His Ile Phe Thr Arg Leu Ile Thr Ala Val
210         215         220

Pro Ser Leu Arg Glu His Phe Glu Asn Val Lys Lys Ala Ile Gly Ile
225         230         235         240

Phe Val Ser Thr Ser Ile Glu Glu Val Phe Ser Phe Pro Phe Tyr Asn
245         250         255

Gln Leu Leu Thr Gln Thr Gln Ile Asp Leu Tyr Asn Gln Leu Leu Gly
260         265         270

Gly Ile Ser Arg Glu Ala Gly Thr Glu Lys Ile Lys Gly Leu Asn Glu
275         280         285

Val Leu Asn Leu Ala Ile Gln Lys Asn Asp Glu Thr Ala His Ile Ile
290         295         300

Ala Ser Leu Pro His Arg Phe Ile Pro Leu Phe Lys Gln Ile Leu Ser
305         310         315         320

Asp Arg Asn Thr Leu Ser Phe Ile Leu Glu Glu Phe Lys Ser Asp Glu
325         330         335

Glu Val Ile Gln Ser Phe Cys Lys Tyr Lys Thr Leu Leu Arg Asn Glu
340         345         350

Asn Val Leu Glu Thr Ala Glu Ala Leu Phe Asn Glu Leu Asn Ser Ile
355         360         365

Asp Leu Thr His Ile Phe Ile Ser His Lys Lys Leu Glu Thr Ile Ser

```

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370	375	380
Ser Ala Leu Cys Asp His Trp Asp Thr Leu Arg Asn Ala Leu Tyr Glu		
385	390	395
		400
Arg Arg Ile Ser Glu Leu Thr Gly Lys Ile Thr Lys Ser Ala Lys Glu		
405	410	415
Lys Val Gln Arg Ser Leu Lys His Glu Asp Ile Asn Leu Gln Glu Ile		
420	425	430
Ile Ser Ala Ala Gly Lys Glu Leu Ser Glu Ala Phe Lys Gln Lys Thr		
435	440	445
Ser Glu Ile Leu Ser His Ala His Ala Ala Leu Asp Gln Pro Leu Pro		
450	455	460
Thr Thr Leu Lys Lys Gln Glu Glu Lys Glu Ile Leu Lys Ser Gln Leu		
465	470	475
		480
Asp Ser Leu Leu Gly Leu Tyr His Leu Leu Asp Trp Phe Ala Val Asp		
485	490	495
Glu Ser Asn Glu Val Asp Pro Glu Phe Ser Ala Arg Leu Thr Gly Ile		
500	505	510
Lys Leu Glu Met Glu Pro Ser Leu Ser Phe Tyr Asn Lys Ala Arg Asn		
515	520	525
Tyr Ala Thr Lys Lys Pro Tyr Ser Val Glu Lys Phe Lys Leu Asn Phe		
530	535	540
Gln Met Pro Thr Leu Ala Ser Gly Trp Asp Val Asn Lys Glu Lys Asn		
545	550	555
		560
Asn Gly Ala Ile Leu Phe Val Lys Asn Gly Leu Tyr Tyr Leu Gly Ile		
565	570	575
Met Pro Lys Gln Lys Gly Arg Tyr Lys Ala Leu Ser Phe Glu Pro Thr		
580	585	590
Glu Lys Thr Ser Glu Gly Phe Asp Lys Met Tyr Tyr Asp Tyr Phe Pro		
595	600	605
Asp Ala Ala Lys Met Ile Pro Lys Cys Ser Thr Gln Leu Lys Ala Val		
610	615	620
Thr Ala His Phe Gln Thr His Thr Pro Ile Leu Leu Ser Asn Asn		
625	630	635
		640
Phe Ile Glu Pro Leu Glu Ile Thr Lys Glu Ile Tyr Asp Leu Asn Asn		
645	650	655
Pro Glu Lys Glu Pro Lys Lys Phe Gln Thr Ala Tyr Ala Lys Lys Thr		
660	665	670
Gly Asp Gln Lys Gly Tyr Arg Glu Ala Leu Cys Lys Trp Ile Asp Phe		
675	680	685
Thr Arg Asp Phe Leu Ser Lys Tyr Thr Lys Thr Ser Ile Asp Leu		
690	695	700
Ser Ser Leu Arg Pro Ser Ser Gln Tyr Lys Asp Leu Gly Glu Tyr Tyr		
705	710	715
		720
Ala Glu Leu Asn Pro Leu Leu Tyr His Ile Ser Phe Gln Arg Ile Ala		
725	730	735
Glu Lys Glu Ile Met Asp Ala Val Glu Thr Gly Lys Leu Tyr Leu Phe		
740	745	750
Gln Ile Tyr Asn Lys Asp Phe Ala Lys Gly His His Gly Lys Pro Asn		
755	760	765
Leu His Thr Leu Tyr Trp Thr Gly Leu Phe Ser Pro Glu Asn Leu Ala		
770	775	780

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Lys Thr Ser Ile Lys Leu Asn Gly Gln Ala Glu Leu Phe Tyr Arg Pro
785 790 795 800

Lys Ser Arg Met Lys Arg Met Ala Ala Arg Leu Gly Glu Lys Met Leu
805 810 815

Asn Lys Lys Leu Lys Asp Gln Lys Thr Pro Ile Pro Asp Thr Leu Tyr
820 825 830

Gln Glu Leu Tyr Asp Tyr Val Asn His Arg Leu Ser His Asp Leu Ser
835 840 845

Asp Glu Ala Arg Ala Leu Leu Pro Asn Val Ile Thr Lys Glu Val Ser
850 855 860

His Glu Ile Ile Lys Asp Arg Arg Phe Thr Ser Asp Lys Phe Phe Phe
865 870 875 880

His Val Pro Ile Thr Leu Asn Tyr Gln Ala Ala Asn Ser Pro Ser Lys
885 890 895

Phe Asn Gln Arg Val Asn Ala Tyr Leu Lys Glu His Pro Glu Thr Pro
900 905 910

Ile Ile Gly Ile Asp Arg Gly Glu Arg Asn Leu Ile Tyr Ile Thr Val
915 920 925

Ile Asp Ser Thr Gly Lys Ile Leu Glu Gln Arg Ser Leu Asn Thr Ile
930 935 940

Gln Gln Phe Asp Tyr Gln Lys Lys Leu Asp Asn Arg Glu Lys Glu Arg
945 950 955 960

Val Ala Ala Arg Gln Ala Trp Ser Val Val Gly Thr Ile Lys Asp Leu
965 970 975

Lys Gln Gly Tyr Leu Ser Gln Val Ile His Glu Ile Val Asp Leu Met
980 985 990

Ile His Tyr Gln Ala Val Val Val Leu Glu Asn Leu Asn Phe Gly Phe
995 1000 1005

Lys Ser Lys Arg Thr Gly Ile Ala Glu Lys Ala Val Tyr Gln Gln
1010 1015 1020

Phe Glu Lys Met Leu Ile Asp Lys Leu Asn Cys Leu Val Leu Lys
1025 1030 1035

Asp Tyr Pro Ala Glu Lys Val Gly Gly Val Leu Asn Pro Tyr Gln
1040 1045 1050

Leu Thr Asp Gln Phe Thr Ser Phe Ala Lys Met Gly Thr Gln Ser
1055 1060 1065

Gly Phe Leu Phe Tyr Val Pro Ala Pro Tyr Thr Ser Lys Ile Asp
1070 1075 1080

Pro Leu Thr Gly Phe Val Asp Pro Phe Val Trp Lys Thr Ile Lys
1085 1090 1095

Asn His Glu Ser Arg Lys His Phe Leu Glu Gly Phe Asp Phe Leu
1100 1105 1110

His Tyr Asp Val Lys Thr Gly Asp Phe Ile Leu His Phe Lys Met
1115 1120 1125

Asn Arg Asn Leu Ser Phe Gln Arg Gly Leu Pro Gly Phe Met Pro
1130 1135 1140

Ala Trp Asp Ile Val Phe Glu Lys Asn Glu Thr Gln Phe Asp Ala
1145 1150 1155

Lys Gly Thr Pro Phe Ile Ala Gly Lys Arg Ile Val Pro Val Ile
1160 1165 1170

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Glu	Asn	His	Arg	Phe	Thr	Gly	Arg	Tyr	Arg	Asp	Leu	Tyr	Pro	Ala
1175						1180					1185			
Asn	Glu	Leu	Ile	Ala	Leu	Leu	Glu	Glu	Lys	Gly	Ile	Val	Phe	Arg
1190						1195					1200			
Asp	Gly	Ser	Asn	Ile	Leu	Pro	Lys	Leu	Leu	Glu	Asn	Asp	Asp	Ser
1205						1210					1215			
His	Ala	Ile	Asp	Thr	Met	Val	Ala	Leu	Ile	Arg	Ser	Val	Leu	Gln
1220						1225					1230			
Met	Arg	Asn	Ser	Asn	Ala	Ala	Thr	Gly	Glu	Asp	Tyr	Ile	Asn	Ser
1235						1240					1245			
Pro	Val	Arg	Asp	Leu	Asn	Gly	Val	Cys	Phe	Asp	Ser	Arg	Phe	Gln
1250						1255					1260			
Asn	Pro	Glu	Trp	Pro	Met	Asp	Ala	Asp	Ala	Asn	Gly	Ala	Tyr	His
1265						1270					1275			
Ile	Ala	Leu	Lys	Gly	Gln	Leu	Leu	Leu	Asn	His	Leu	Lys	Glu	Ser
1280						1285					1290			
Lys	Asp	Leu	Lys	Leu	Gln	Asn	Gly	Ile	Ser	Asn	Gln	Asp	Trp	Leu
1295						1300					1305			
Ala	Tyr	Ile	Gln	Glu	Leu	Arg	Asn	Gly	Ser	Pro	Lys	Lys	Lys	Arg
1310						1315					1320			
Lys	Val	Gly	Ser	Pro	Lys	Lys	Lys	Arg	Lys	Val				
1325						1330								

<210> SEQ ID NO 1143
 <211> LENGTH: 1363
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <221> NAME/KEY: source
 <223> OTHER INFORMATION: /note="Description of Artificial Sequence:
 Synthetic polypeptide"

<400> SEQUENCE: 1143

Met	Thr	Gln	Phe	Glu	Gly	Phe	Thr	Asn	Leu	Tyr	Gln	Val	Ser	Lys	Thr
1			5			10					15				
Leu	Arg	Phe	Glu	Leu	Ile	Pro	Gln	Gly	Lys	Thr	Leu	Lys	His	Ile	Gln
						20					25			30	
Glu	Gln	Gly	Phe	Ile	Glu	Glu	Asp	Lys	Ala	Arg	Asn	Asp	His	Tyr	Lys
						35					40			45	
Glu	Leu	Lys	Pro	Ile	Ile	Asp	Arg	Ile	Tyr	Lys	Thr	Tyr	Ala	Asp	Gln
						50					55			60	
Cys	Leu	Gln	Leu	Val	Gln	Leu	Asp	Trp	Glu	Asn	Leu	Ser	Ala	Ala	Ile
						65					70			80	
Asp	Ser	Tyr	Arg	Lys	Glu	Lys	Thr	Glu	Glu	Thr	Arg	Asn	Ala	Leu	Ile
						85					90			95	
Glu	Glu	Gln	Ala	Thr	Tyr	Arg	Asn	Ala	Ile	His	Asp	Tyr	Phe	Ile	Gly
						100					105			110	
Arg	Thr	Asp	Asn	Leu	Thr	Asp	Ala	Ile	Asn	Lys	Arg	His	Ala	Glu	Ile
						115					120			125	
Tyr	Lys	Gly	Leu	Phe	Lys	Ala	Glu	Leu	Phe	Asn	Gly	Lys	Val	Leu	Lys
						130					135			140	
Gln	Leu	Gly	Thr	Val	Thr	Thr	Asn	Glu	Asn	Ala	Leu	Leu	Arg		
						145					150			155	
Ser	Phe	Asp	Lys	Phe	Thr	Thr	Tyr	Phe	Ser	Gly	Phe	Tyr	Glu	Asn	Arg

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165	170	175
Lys Asn Val Phe Ser Ala Glu Asp Ile Ser Thr Ala Ile Pro His Arg		
180	185	190
Ile Val Gln Asp Asn Phe Pro Lys Phe Lys Glu Asn Cys His Ile Phe		
195	200	205
Thr Arg Leu Ile Thr Ala Val Pro Ser Leu Arg Glu His Phe Glu Asn		
210	215	220
Val Lys Lys Ala Ile Gly Ile Phe Val Ser Thr Ser Ile Glu Glu Val		
225	230	235
Phe Ser Phe Pro Phe Tyr Asn Gln Leu Leu Thr Gln Thr Gln Ile Asp		
245	250	255
Leu Tyr Asn Gln Leu Leu Gly Gly Ile Ser Arg Glu Ala Gly Thr Glu		
260	265	270
Lys Ile Lys Gly Leu Asn Glu Val Leu Asn Leu Ala Ile Gln Lys Asn		
275	280	285
Asp Glu Thr Ala His Ile Ile Ala Ser Leu Pro His Arg Phe Ile Pro		
290	295	300
Leu Phe Lys Gln Ile Leu Ser Asp Arg Asn Thr Leu Ser Phe Ile Leu		
305	310	315
Glu Glu Phe Lys Ser Asp Glu Glu Val Ile Gln Ser Phe Cys Lys Tyr		
325	330	335
Lys Thr Leu Leu Arg Asn Glu Asn Val Leu Glu Thr Ala Glu Ala Leu		
340	345	350
Phe Asn Glu Leu Asn Ser Ile Asp Leu Thr His Ile Phe Ile Ser His		
355	360	365
Lys Lys Leu Glu Thr Ile Ser Ser Ala Leu Cys Asp His Trp Asp Thr		
370	375	380
Leu Arg Asn Ala Leu Tyr Glu Arg Arg Ile Ser Glu Leu Thr Gly Lys		
385	390	395
Ile Thr Lys Ser Ala Lys Glu Lys Val Gln Arg Ser Leu Lys His Glu		
405	410	415
Asp Ile Asn Leu Gln Glu Ile Ile Ser Ala Ala Gly Lys Glu Leu Ser		
420	425	430
Glu Ala Phe Lys Gln Lys Thr Ser Glu Ile Leu Ser His Ala His Ala		
435	440	445
Ala Leu Asp Gln Pro Leu Pro Thr Thr Leu Lys Lys Gln Glu Glu Lys		
450	455	460
Glu Ile Leu Lys Ser Gln Leu Asp Ser Leu Leu Gly Leu Tyr His Leu		
465	470	475
Leu Asp Trp Phe Ala Val Asp Glu Ser Asn Glu Val Asp Pro Glu Phe		
485	490	495
Ser Ala Arg Leu Thr Gly Ile Lys Leu Glu Met Glu Pro Ser Leu Ser		
500	505	510
Phe Tyr Asn Lys Ala Arg Asn Tyr Ala Thr Lys Lys Pro Tyr Ser Val		
515	520	525
Glu Lys Phe Lys Leu Asn Phe Gln Arg Pro Thr Leu Ala Ser Gly Trp		
530	535	540
Asp Val Asn Lys Glu Lys Asn Asn Gly Ala Ile Leu Phe Val Lys Asn		
545	550	555
Gly Leu Tyr Tyr Leu Gly Ile Met Pro Lys Gln Lys Gly Arg Tyr Lys		
565	570	575

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Ala Leu Ser Phe Glu Pro Thr Glu Lys Thr Ser Glu Gly Phe Asp Lys
 580 585 590
 Met Tyr Tyr Asp Tyr Phe Pro Asp Ala Ala Lys Met Ile Pro Lys Cys
 595 600 605
 Ser Thr Gln Leu Lys Ala Val Thr Ala His Phe Gln Thr His Thr Thr
 610 615 620
 Pro Ile Leu Leu Ser Asn Asn Phe Ile Glu Pro Leu Glu Ile Thr Lys
 625 630 635 640
 Glu Ile Tyr Asp Leu Asn Asn Pro Glu Lys Glu Pro Lys Lys Phe Gln
 645 650 655
 Thr Ala Tyr Ala Lys Lys Thr Gly Asp Gln Lys Gly Tyr Arg Glu Ala
 660 665 670
 Leu Cys Lys Trp Ile Asp Phe Thr Arg Asp Phe Leu Ser Lys Tyr Thr
 675 680 685
 Lys Thr Thr Ser Ile Asp Leu Ser Ser Leu Arg Pro Ser Ser Gln Tyr
 690 695 700
 Lys Asp Leu Gly Glu Tyr Tyr Ala Glu Leu Asn Pro Leu Leu Tyr His
 705 710 715 720
 Ile Ser Phe Gln Arg Ile Ala Glu Lys Glu Ile Met Asp Ala Val Glu
 725 730 735
 Thr Gly Lys Leu Tyr Leu Phe Gln Ile Tyr Asn Lys Asp Phe Ala Lys
 740 745 750
 Gly His His Gly Lys Pro Asn Leu His Thr Leu Tyr Trp Thr Gly Leu
 755 760 765
 Phe Ser Pro Glu Asn Leu Ala Lys Thr Ser Ile Lys Leu Asn Gly Gln
 770 775 780
 Ala Glu Leu Phe Tyr Arg Pro Lys Ser Arg Met Lys Arg Met Ala His
 785 790 795 800
 Arg Leu Gly Glu Lys Met Leu Asn Lys Lys Leu Lys Asp Gln Lys Thr
 805 810 815
 Pro Ile Pro Asp Thr Leu Tyr Gln Glu Leu Tyr Asp Tyr Val Asn His
 820 825 830
 Arg Leu Ser His Asp Leu Ser Asp Glu Ala Arg Ala Leu Leu Pro Asn
 835 840 845
 Val Ile Thr Lys Glu Val Ser His Glu Ile Ile Lys Asp Arg Arg Phe
 850 855 860
 Thr Ser Asp Lys Phe Leu Phe His Val Pro Ile Thr Leu Asn Tyr Gln
 865 870 875 880
 Ala Ala Asn Ser Pro Ser Lys Phe Asn Gln Arg Val Asn Ala Tyr Leu
 885 890 895
 Lys Glu His Pro Glu Thr Pro Ile Ile Gly Ile Asp Arg Gly Glu Arg
 900 905 910
 Asn Leu Ile Tyr Ile Thr Val Ile Asp Ser Thr Gly Lys Ile Leu Glu
 915 920 925
 Gln Arg Ser Leu Asn Thr Ile Gln Gln Phe Asp Tyr Gln Lys Lys Leu
 930 935 940
 Asp Asn Arg Glu Lys Glu Arg Val Ala Ala Arg Gln Ala Trp Ser Val
 945 950 955 960
 Val Gly Thr Ile Lys Asp Leu Lys Gln Gly Tyr Leu Ser Gln Val Ile
 965 970 975

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His	Glu	Ile	Val	Asp	Leu	Met	Ile	His	Tyr	Gln	Ala	Val	Val	Val	Leu
980								985							990
<hr/>															
Glu	Asn	Leu	Asn	Phe	Gly	Phe	Lys	Ser	Lys	Arg	Thr	Gly	Ile	Ala	Glu
995								1000							1005
<hr/>															
Lys	Ala	Val	Tyr	Gln	Gln	Phe	Glu	Lys	Met	Leu	Ile	Asp	Lys	Leu	
1010									1015						1020
<hr/>															
Asn	Cys	Leu	Val	Leu	Lys	Asp	Tyr	Pro	Ala	Glu	Lys	Val	Gly	Gly	
1025									1030						1035
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Val	Leu	Asn	Pro	Tyr	Gln	Leu	Thr	Asp	Gln	Phe	Thr	Ser	Phe	Ala	
1040									1045						1050
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Lys	Met	Gly	Thr	Gln	Ser	Gly	Phe	Leu	Phe	Tyr	Val	Pro	Ala	Pro	
1055									1060						1065
<hr/>															
Tyr	Thr	Ser	Lys	Ile	Asp	Pro	Leu	Thr	Gly	Phe	Val	Asp	Pro	Phe	
1070									1075						1080
<hr/>															
Val	Trp	Lys	Thr	Ile	Lys	Asn	His	Glu	Ser	Arg	Lys	His	Phe	Leu	
1085									1090						1095
<hr/>															
Glu	Gly	Phe	Asp	Phe	Leu	His	Tyr	Asp	Val	Lys	Thr	Gly	Asp	Phe	
1100									1105						1110
<hr/>															
Ile	Leu	His	Phe	Lys	Met	Asn	Arg	Asn	Leu	Ser	Phe	Gln	Arg	Gly	
1115									1120						1125
<hr/>															
Leu	Pro	Gly	Phe	Met	Pro	Ala	Trp	Asp	Ile	Val	Phe	Glu	Lys	Asn	
1130									1135						1140
<hr/>															
Glu	Thr	Gln	Phe	Asp	Ala	Lys	Gly	Thr	Pro	Phe	Ile	Ala	Gly	Lys	
1145									1150						1155
<hr/>															
Arg	Ile	Val	Pro	Val	Ile	Glu	Asn	His	Arg	Phe	Thr	Gly	Arg	Tyr	
1160									1165						1170
<hr/>															
Arg	Asp	Leu	Tyr	Pro	Ala	Asn	Glu	Leu	Ile	Ala	Leu	Leu	Glu	Glu	
1175									1180						1185
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Lys	Gly	Ile	Val	Phe	Arg	Asp	Gly	Ser	Asn	Ile	Leu	Pro	Lys	Leu	
1190									1195						1200
<hr/>															
Leu	Glu	Asn	Asp	Asp	Ser	His	Ala	Ile	Asp	Thr	Met	Val	Ala	Leu	
1205									1210						1215
<hr/>															
Ile	Arg	Ser	Val	Leu	Gln	Met	Arg	Asn	Ser	Asn	Ala	Ala	Thr	Gly	
1220									1225						1230
<hr/>															
Glu	Asp	Tyr	Ile	Asn	Ser	Pro	Val	Arg	Asp	Leu	Asn	Gly	Val	Cys	
1235									1240						1245
<hr/>															
Phe	Asp	Ser	Arg	Phe	Gln	Asn	Pro	Glu	Trp	Pro	Met	Asp	Ala	Asp	
1250									1255						1260
<hr/>															
Ala	Asn	Gly	Ala	Tyr	His	Ile	Ala	Leu	Lys	Gly	Gln	Leu	Leu	Leu	
1265									1270						1275
<hr/>															
Asn	His	Leu	Lys	Glu	Ser	Lys	Asp	Leu	Lys	Leu	Gln	Asn	Gly	Ile	
1280									1285						1290
<hr/>															
Ser	Asn	Gln	Asp	Trp	Leu	Ala	Tyr	Ile	Gln	Glu	Leu	Arg	Asn	Gly	
1295									1300						1305
<hr/>															
Arg	Ser	Ser	Asp	Asp	Glu	Ala	Thr	Ala	Asp	Ser	Gln	His	Ala	Ala	
1310									1315						1320
<hr/>															
Pro	Pro	Lys	Lys	Lys	Arg	Lys	Val	Gly	Gly	Ser	Gly	Gly	Ser	Gly	
1325									1330						1335
<hr/>															
Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	
1340									1345						1350
<hr/>															
Gly	Ser	Leu	Glu	His	His	His	His	His	His	His	His				

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1355

1360

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<210> SEQ ID NO 1144
<211> LENGTH: 1363
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 1144

Met Thr Gln Phe Glu Gly Phe Thr Asn Leu Tyr Gln Val Ser Lys Thr
1           5          10          15

Leu Arg Phe Glu Leu Ile Pro Gln Gly Lys Thr Leu Lys His Ile Gln
20          25          30

Glu Gln Gly Phe Ile Glu Glu Asp Lys Ala Arg Asn Asp His Tyr Lys
35          40          45

Glu Leu Lys Pro Ile Ile Asp Arg Ile Tyr Lys Thr Tyr Ala Asp Gln
50          55          60

Cys Leu Gln Leu Val Gln Leu Asp Trp Glu Asn Leu Ser Ala Ala Ile
65          70          75          80

Asp Ser Tyr Arg Lys Glu Lys Thr Glu Glu Thr Arg Asn Ala Leu Ile
85          90          95

Glu Glu Gln Ala Thr Tyr Arg Asn Ala Ile His Asp Tyr Phe Ile Gly
100         105         110

Arg Thr Asp Asn Leu Thr Asp Ala Ile Asn Lys Arg His Ala Glu Ile
115         120         125

Tyr Lys Gly Leu Phe Lys Ala Glu Leu Phe Asn Gly Lys Val Leu Lys
130         135         140

Gln Leu Gly Thr Val Thr Thr Glu His Glu Asn Ala Leu Leu Arg
145         150         155         160

Ser Phe Asp Lys Phe Thr Thr Tyr Phe Ser Gly Phe Tyr Glu Asn Arg
165         170         175

Lys Asn Val Phe Ser Ala Glu Asp Ile Ser Thr Ala Ile Pro His Arg
180         185         190

Ile Val Gln Asp Asn Phe Pro Lys Phe Lys Glu Asn Cys His Ile Phe
195         200         205

Thr Arg Leu Ile Thr Ala Val Pro Ser Leu Arg Glu His Phe Glu Asn
210         215         220

Val Lys Lys Ala Ile Gly Ile Phe Val Ser Thr Ser Ile Glu Glu Val
225         230         235         240

Phe Ser Phe Pro Phe Tyr Asn Gln Leu Leu Thr Gln Thr Gln Ile Asp
245         250         255

Leu Tyr Asn Gln Leu Leu Gly Gly Ile Ser Arg Glu Ala Gly Thr Glu
260         265         270

Lys Ile Lys Gly Leu Asn Glu Val Leu Asn Leu Ala Ile Gln Lys Asn
275         280         285

Asp Glu Thr Ala His Ile Ile Ala Ser Leu Pro His Arg Phe Ile Pro
290         295         300

Leu Phe Lys Gln Ile Leu Ser Asp Arg Asn Thr Leu Ser Phe Ile Leu
305         310         315         320

Glu Glu Phe Lys Ser Asp Glu Glu Val Ile Gln Ser Phe Cys Lys Tyr
325         330         335

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Lys Thr Leu Leu Arg Asn Glu Asn Val Leu Glu Thr Ala Glu Ala Leu
340 345 350

Phe Asn Glu Leu Asn Ser Ile Asp Leu Thr His Ile Phe Ile Ser His
355 360 365

Lys Lys Leu Glu Thr Ile Ser Ser Ala Leu Cys Asp His Trp Asp Thr
370 375 380

Leu Arg Asn Ala Leu Tyr Glu Arg Arg Ile Ser Glu Leu Thr Gly Lys
385 390 395 400

Ile Thr Lys Ser Ala Lys Glu Lys Val Gln Arg Ser Leu Lys His Glu
405 410 415

Asp Ile Asn Leu Gln Glu Ile Ile Ser Ala Ala Gly Lys Glu Leu Ser
420 425 430

Glu Ala Phe Lys Gln Lys Thr Ser Glu Ile Leu Ser His Ala His Ala
435 440 445

Ala Leu Asp Gln Pro Leu Pro Thr Thr Leu Lys Lys Gln Glu Glu Lys
450 455 460

Glu Ile Leu Lys Ser Gln Leu Asp Ser Leu Leu Gly Leu Tyr His Leu
465 470 475 480

Leu Asp Trp Phe Ala Val Asp Glu Ser Asn Glu Val Asp Pro Glu Phe
485 490 495

Ser Ala Arg Leu Thr Gly Ile Lys Leu Glu Met Glu Pro Ser Leu Ser
500 505 510

Phe Tyr Asn Ala Arg Asn Tyr Ala Thr Lys Lys Pro Tyr Ser Val
515 520 525

Glu Lys Phe Lys Leu Asn Phe Gln Met Pro Thr Leu Ala Ser Gly Trp
530 535 540

Asp Val Asn Lys Glu Lys Asn Asn Gly Ala Ile Leu Phe Val Lys Asn
545 550 555 560

Gly Leu Tyr Tyr Leu Gly Ile Met Pro Lys Gln Lys Gly Arg Tyr Lys
565 570 575

Ala Leu Ser Phe Glu Pro Thr Glu Lys Thr Ser Glu Gly Phe Asp Lys
580 585 590

Met Tyr Tyr Asp Tyr Phe Pro Asp Ala Ala Lys Met Ile Pro Lys Cys
595 600 605

Ser Thr Gln Leu Lys Ala Val Thr Ala His Phe Gln Thr His Thr Thr
610 615 620

Pro Ile Leu Leu Ser Asn Asn Phe Ile Glu Pro Leu Glu Ile Thr Lys
625 630 635 640

Glu Ile Tyr Asp Leu Asn Asn Pro Glu Lys Glu Pro Lys Lys Phe Gln
645 650 655

Thr Ala Tyr Ala Lys Lys Thr Gly Asp Gln Lys Gly Tyr Arg Glu Ala
660 665 670

Leu Cys Lys Trp Ile Asp Phe Thr Arg Asp Phe Leu Ser Lys Tyr Thr
675 680 685

Lys Thr Thr Ser Ile Asp Leu Ser Ser Leu Arg Pro Ser Ser Gln Tyr
690 695 700

Lys Asp Leu Gly Glu Tyr Tyr Ala Glu Leu Asn Pro Leu Leu Tyr His
705 710 715 720

Ile Ser Phe Gln Arg Ile Ala Glu Lys Glu Ile Met Asp Ala Val Glu
725 730 735

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Thr	Gly	Lys	Leu	Tyr	Leu	Phe	Gln	Ile	Tyr	Asn	Lys	Asp	Phe	Ala	Lys
740															750
Gly	His	His	Gly	Lys	Pro	Asn	Leu	His	Thr	Leu	Tyr	Trp	Thr	Gly	Leu
755															765
Phe	Ser	Pro	Glu	Asn	Leu	Ala	Lys	Thr	Ser	Ile	Lys	Leu	Asn	Gly	Gln
770															780
Ala	Glu	Leu	Phe	Tyr	Arg	Pro	Lys	Ser	Arg	Met	Lys	Arg	Met	Ala	His
785															800
Arg	Leu	Gly	Glu	Lys	Met	Leu	Asn	Lys	Lys	Leu	Lys	Asp	Gln	Lys	Thr
805															815
Pro	Ile	Pro	Asp	Thr	Leu	Tyr	Gln	Glu	Leu	Tyr	Asp	Tyr	Val	Asn	His
820															830
Arg	Leu	Ser	His	Asp	Leu	Ser	Asp	Glu	Ala	Arg	Ala	Leu	Leu	Pro	Asn
835															845
Val	Ile	Thr	Lys	Glu	Val	Ser	His	Glu	Ile	Ile	Lys	Asp	Arg	Arg	Phe
850															860
Thr	Ser	Asp	Lys	Phe	Phe	His	Val	Pro	Ile	Thr	Leu	Asn	Tyr	Gln	
865															880
Ala	Ala	Asn	Ser	Pro	Ser	Lys	Phe	Asn	Gln	Arg	Val	Asn	Ala	Tyr	Leu
885															895
Lys	Glu	His	Pro	Glu	Thr	Pro	Ile	Ile	Gly	Ile	Asp	Arg	Gly	Glu	Arg
900															910
Asn	Leu	Ile	Tyr	Ile	Thr	Val	Ile	Asp	Ser	Thr	Gly	Lys	Ile	Leu	Glu
915															925
Gln	Arg	Ser	Leu	Asn	Thr	Ile	Gln	Gln	Phe	Asp	Tyr	Gln	Lys	Lys	Leu
930															940
Asp	Asn	Arg	Glu	Lys	Glu	Arg	Val	Ala	Ala	Arg	Gln	Ala	Trp	Ser	Val
945															960
Val	Gly	Thr	Ile	Lys	Asp	Leu	Lys	Gln	Gly	Tyr	Leu	Ser	Gln	Val	Ile
965															975
His	Glu	Ile	Val	Asp	Leu	Met	Ile	His	Tyr	Gln	Ala	Val	Val	Val	Leu
980															990
Glu	Asn	Leu	Asn	Phe	Gly	Phe	Lys	Ser	Lys	Arg	Thr	Gly	Ile	Ala	Glu
995															1005
Lys	Ala	Val	Tyr	Gln	Gln	Phe	Glu	Lys	Met	Leu	Ile	Asp	Lys	Leu	
1010															1020
Asn	Cys	Leu	Val	Leu	Lys	Asp	Tyr	Pro	Ala	Glu	Lys	Val	Gly	Gly	
1025															1035
Val	Leu	Asn	Pro	Tyr	Gln	Leu	Thr	Asp	Gln	Phe	Thr	Ser	Phe	Ala	
1040															1050
Lys	Met	Gly	Thr	Gln	Ser	Gly	Phe	Leu	Phe	Tyr	Val	Pro	Ala	Pro	
1055															1065
Tyr	Thr	Ser	Lys	Ile	Asp	Pro	Leu	Thr	Gly	Phe	Val	Asp	Pro	Phe	
1070															1080
Val	Trp	Lys	Thr	Ile	Lys	Asn	His	Glu	Ser	Arg	Lys	His	Phe	Leu	
1085															1095
Glu	Gly	Phe	Asp	Phe	Leu	His	Tyr	Asp	Val	Lys	Thr	Gly	Asp	Phe	
1100															1110
Ile	Leu	His	Phe	Lys	Met	Asn	Arg	Asn	Leu	Ser	Phe	Gln	Arg	Gly	
1115															1125
Leu	Pro	Gly	Phe	Met	Pro	Ala	Trp	Asp	Ile	Val	Phe	Glu	Lys	Asn	

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1130	1135	1140
Glu	Thr	Gln Phe Asp Ala Lys Gly Thr Pro Phe Ile Ala Gly Lys
1145	1150	1155
Arg	Ile	Val Pro Val Ile Glu Asn His Arg Phe Thr Gly Arg Tyr
1160	1165	1170
Arg	Asp	Leu Tyr Pro Ala Asn Glu Leu Ile Ala Leu Leu Glu Glu
1175	1180	1185
Lys	Gly	Ile Val Phe Arg Asp Gly Ser Asn Ile Leu Pro Lys Leu
1190	1195	1200
Leu	Glu	Asn Asp Asp Ser His Ala Ile Asp Thr Met Val Ala Leu
1205	1210	1215
Ile	Arg	Ser Val Leu Gln Met Arg Asn Ser Asn Ala Ala Thr Gly
1220	1225	1230
Glu	Asp	Tyr Ile Asn Ser Pro Val Arg Asp Leu Asn Gly Val Cys
1235	1240	1245
Phe	Asp	Ser Arg Phe Gln Asn Pro Glu Trp Pro Met Asp Ala Asp
1250	1255	1260
Ala	Asn	Gly Ala Tyr His Ile Ala Leu Lys Gly Gln Leu Leu Leu
1265	1270	1275
Asn	His	Leu Lys Glu Ser Lys Asp Leu Lys Leu Gln Asn Gly Ile
1280	1285	1290
Ser	Asn	Gln Asp Trp Leu Ala Tyr Ile Gln Glu Leu Arg Asn Gly
1295	1300	1305
Arg	Ser	Ser Asp Asp Glu Ala Thr Ala Asp Ser Gln His Ala Ala
1310	1315	1320
Pro	Pro	Lys Lys Lys Arg Lys Val Gly Gly Ser Gly Gly Ser Gly
1325	1330	1335
Gly	Ser	Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1340	1345	1350
Gly	Ser	Leu Glu His His His His His His His
1355	1360	

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<210> SEQ ID NO 1145
<211> LENGTH: 1363
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

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<400> SEQUENCE: 1145

Met	Thr	Gln Phe Glu Gly Phe Thr Asn Leu Tyr Gln Val Ser Lys Thr
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Leu	Arg	Phe Glu Leu Ile Pro Gln Gly Lys Thr Leu Lys His Ile Gln
		20 25 30
Glu	Gln	Gly Phe Ile Glu Glu Asp Lys Ala Arg Asn Asp His Tyr Lys
		35 40 45
Glu	Leu	Lys Pro Ile Ile Asp Arg Ile Tyr Lys Thr Tyr Ala Asp Gln
		50 55 60
Cys	Leu	Gln Leu Val Gln Leu Asp Trp Glu Asn Leu Ser Ala Ala Ile
65		70 75 80
Asp	Ser	Tyr Arg Lys Glu Lys Thr Glu Glu Thr Arg Asn Ala Leu Ile
		85 90 95

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Glu Glu Gln Ala Thr Tyr Arg Asn Ala Ile His Asp Tyr Phe Ile Gly
 100 105 110
 Arg Thr Asp Asn Leu Thr Asp Ala Ile Asn Lys Arg His Ala Glu Ile
 115 120 125
 Tyr Lys Gly Leu Phe Lys Ala Glu Leu Phe Asn Gly Lys Val Leu Lys
 130 135 140
 Gln Leu Gly Thr Val Thr Thr Glu His Glu Asn Ala Leu Leu Arg
 145 150 155 160
 Ser Phe Asp Lys Phe Thr Thr Tyr Phe Ser Gly Phe Tyr Glu Asn Arg
 165 170 175
 Lys Asn Val Phe Ser Ala Glu Asp Ile Ser Thr Ala Ile Pro His Arg
 180 185 190
 Ile Val Gln Asp Asn Phe Pro Lys Phe Lys Glu Asn Cys His Ile Phe
 195 200 205
 Thr Arg Leu Ile Thr Ala Val Pro Ser Leu Arg Glu His Phe Glu Asn
 210 215 220
 Val Lys Lys Ala Ile Gly Ile Phe Val Ser Thr Ser Ile Glu Glu Val
 225 230 235 240
 Phe Ser Phe Pro Phe Tyr Asn Gln Leu Leu Thr Gln Thr Gln Ile Asp
 245 250 255
 Leu Tyr Asn Gln Leu Leu Gly Gly Ile Ser Arg Glu Ala Gly Thr Glu
 260 265 270
 Lys Ile Lys Gly Leu Asn Glu Val Leu Asn Leu Ala Ile Gln Lys Asn
 275 280 285
 Asp Glu Thr Ala His Ile Ile Ala Ser Leu Pro His Arg Phe Ile Pro
 290 295 300
 Leu Phe Lys Gln Ile Leu Ser Asp Arg Asn Thr Leu Ser Phe Ile Leu
 305 310 315 320
 Glu Glu Phe Lys Ser Asp Glu Glu Val Ile Gln Ser Phe Cys Lys Tyr
 325 330 335
 Lys Thr Leu Leu Arg Asn Glu Asn Val Leu Glu Thr Ala Glu Ala Leu
 340 345 350
 Phe Asn Glu Leu Asn Ser Ile Asp Leu Thr His Ile Phe Ile Ser His
 355 360 365
 Lys Lys Leu Glu Thr Ile Ser Ser Ala Leu Cys Asp His Trp Asp Thr
 370 375 380
 Leu Arg Asn Ala Leu Tyr Glu Arg Arg Ile Ser Glu Leu Thr Gly Lys
 385 390 395 400
 Ile Thr Lys Ser Ala Lys Glu Lys Val Gln Arg Ser Leu Lys His Glu
 405 410 415
 Asp Ile Asn Leu Gln Glu Ile Ile Ser Ala Ala Gly Lys Glu Leu Ser
 420 425 430
 Glu Ala Phe Lys Gln Lys Thr Ser Glu Ile Leu Ser His Ala His Ala
 435 440 445
 Ala Leu Asp Gln Pro Leu Pro Thr Thr Leu Lys Lys Gln Glu Glu Lys
 450 455 460
 Glu Ile Leu Lys Ser Gln Leu Asp Ser Leu Leu Gly Leu Tyr His Leu
 465 470 475 480
 Leu Asp Trp Phe Ala Val Asp Glu Ser Asn Glu Val Asp Pro Glu Phe
 485 490 495

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Ser	Ala	Arg	Leu	Thr	Gly	Ile	Lys	Leu	Glu	Met	Glu	Pro	Ser	Leu	Ser
500								505						510	
Phe	Tyr	Asn	Lys	Ala	Arg	Asn	Tyr	Ala	Thr	Lys	Lys	Pro	Tyr	Ser	Val
515								520						525	
Glu	Lys	Phe	Lys	Leu	Asn	Phe	Gln	Arg	Pro	Thr	Leu	Ala	Ser	Gly	Trp
530							535				540				
Asp	Val	Asn	Lys	Glu	Lys	Asn	Asn	Gly	Ala	Ile	Leu	Phe	Val	Lys	Asn
545							550			555			560		
Gly	Leu	Tyr	Tyr	Leu	Gly	Ile	Met	Pro	Lys	Gln	Lys	Gly	Arg	Tyr	Lys
565							570			575					
Ala	Leu	Ser	Phe	Glu	Pro	Thr	Glu	Lys	Thr	Ser	Glu	Gly	Phe	Asp	Lys
580							585				590				
Met	Tyr	Tyr	Asp	Tyr	Phe	Pro	Asp	Ala	Ala	Lys	Met	Ile	Pro	Lys	Cys
595							600				605				
Ser	Thr	Gln	Leu	Lys	Ala	Val	Thr	Ala	His	Phe	Gln	Thr	His	Thr	Thr
610							615			620					
Pro	Ile	Leu	Leu	Ser	Asn	Asn	Phe	Ile	Glu	Pro	Leu	Glu	Ile	Thr	Lys
625							630			635			640		
Glu	Ile	Tyr	Asp	Leu	Asn	Asn	Pro	Glu	Lys	Glu	Pro	Lys	Lys	Phe	Gln
645							650			655					
Thr	Ala	Tyr	Ala	Lys	Lys	Thr	Gly	Asp	Gln	Lys	Gly	Tyr	Arg	Glu	Ala
660							665			670					
Leu	Cys	Lys	Trp	Ile	Asp	Phe	Thr	Arg	Asp	Phe	Leu	Ser	Lys	Tyr	Thr
675							680			685					
Lys	Thr	Thr	Ser	Ile	Asp	Leu	Ser	Ser	Leu	Arg	Pro	Ser	Ser	Gln	Tyr
690							695			700					
Lys	Asp	Leu	Gly	Glu	Tyr	Tyr	Ala	Glu	Leu	Asn	Pro	Leu	Leu	Tyr	His
705							710			715			720		
Ile	Ser	Phe	Gln	Arg	Ile	Ala	Glu	Lys	Glu	Ile	Met	Asp	Ala	Val	Glu
725							730			735					
Thr	Gly	Lys	Leu	Tyr	Leu	Phe	Gln	Ile	Tyr	Asn	Lys	Asp	Phe	Ala	Lys
740							745			750					
Gly	His	His	Gly	Lys	Pro	Asn	Leu	His	Thr	Leu	Tyr	Trp	Thr	Gly	Leu
755							760			765					
Phe	Ser	Pro	Glu	Asn	Leu	Ala	Lys	Thr	Ser	Ile	Lys	Leu	Asn	Gly	Gln
770							775			780					
Ala	Glu	Leu	Phe	Tyr	Arg	Pro	Lys	Ser	Arg	Met	Lys	Arg	Met	Ala	Ala
785							790			795			800		
Arg	Leu	Gly	Glu	Lys	Met	Leu	Asn	Lys	Leu	Lys	Asp	Gln	Lys	Thr	
805							810			815					
Pro	Ile	Pro	Asp	Thr	Leu	Tyr	Gln	Glu	Leu	Tyr	Asp	Tyr	Val	Asn	His
820							825			830					
Arg	Leu	Ser	His	Asp	Leu	Ser	Asp	Glu	Ala	Arg	Ala	Leu	Leu	Pro	Asn
835							840			845					
Val	Ile	Thr	Lys	Glu	Val	Ser	His	Glu	Ile	Ile	Lys	Asp	Arg	Arg	Phe
850							855			860					
Thr	Ser	Asp	Lys	Phe	Leu	Phe	His	Val	Pro	Ile	Thr	Leu	Asn	Tyr	Gln
865							870			875			880		
Ala	Ala	Asn	Ser	Pro	Ser	Lys	Phe	Asn	Gln	Arg	Val	Asn	Ala	Tyr	Leu
885							890			895					
Lys	Glu	His	Pro	Glu	Thr	Pro	Ile	Ile	Gly	Ile	Asp	Arg	Gly	Glu	Arg

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900	905	910
Asn Leu Ile Tyr Ile Thr Val Ile Asp Ser Thr Gly Lys Ile Leu Glu		
915	920	925
Gln Arg Ser Leu Asn Thr Ile Gln Gln Phe Asp Tyr Gln Lys Lys Leu		
930	935	940
Asp Asn Arg Glu Lys Glu Arg Val Ala Ala Arg Gln Ala Trp Ser Val		
945	950	955
Val Gly Thr Ile Lys Asp Leu Lys Gln Gly Tyr Leu Ser Gln Val Ile		
965	970	975
His Glu Ile Val Asp Leu Met Ile His Tyr Gln Ala Val Val Val Leu		
980	985	990
Glu Asn Leu Asn Phe Gly Phe Lys Ser Lys Arg Thr Gly Ile Ala Glu		
995	1000	1005
Lys Ala Val Tyr Gln Gln Phe Glu Lys Met Leu Ile Asp Lys Leu		
1010	1015	1020
Asn Cys Leu Val Leu Lys Asp Tyr Pro Ala Glu Lys Val Gly Gly		
1025	1030	1035
Val Leu Asn Pro Tyr Gln Leu Thr Asp Gln Phe Thr Ser Phe Ala		
1040	1045	1050
Lys Met Gly Thr Gln Ser Gly Phe Leu Phe Tyr Val Pro Ala Pro		
1055	1060	1065
Tyr Thr Ser Lys Ile Asp Pro Leu Thr Gly Phe Val Asp Pro Phe		
1070	1075	1080
Val Trp Lys Thr Ile Lys Asn His Glu Ser Arg Lys His Phe Leu		
1085	1090	1095
Glu Gly Phe Asp Phe Leu His Tyr Asp Val Lys Thr Gly Asp Phe		
1100	1105	1110
Ile Leu His Phe Lys Met Asn Arg Asn Leu Ser Phe Gln Arg Gly		
1115	1120	1125
Leu Pro Gly Phe Met Pro Ala Trp Asp Ile Val Phe Glu Lys Asn		
1130	1135	1140
Glu Thr Gln Phe Asp Ala Lys Gly Thr Pro Phe Ile Ala Gly Lys		
1145	1150	1155
Arg Ile Val Pro Val Ile Glu Asn His Arg Phe Thr Gly Arg Tyr		
1160	1165	1170
Arg Asp Leu Tyr Pro Ala Asn Glu Leu Ile Ala Leu Leu Glu Glu		
1175	1180	1185
Lys Gly Ile Val Phe Arg Asp Gly Ser Asn Ile Leu Pro Lys Leu		
1190	1195	1200
Leu Glu Asn Asp Asp Ser His Ala Ile Asp Thr Met Val Ala Leu		
1205	1210	1215
Ile Arg Ser Val Leu Gln Met Arg Asn Ser Asn Ala Ala Thr Gly		
1220	1225	1230
Glu Asp Tyr Ile Asn Ser Pro Val Arg Asp Leu Asn Gly Val Cys		
1235	1240	1245
Phe Asp Ser Arg Phe Gln Asn Pro Glu Trp Pro Met Asp Ala Asp		
1250	1255	1260
Ala Asn Gly Ala Tyr His Ile Ala Leu Lys Gly Gln Leu Leu Leu		
1265	1270	1275
Asn His Leu Lys Glu Ser Lys Asp Leu Lys Leu Gln Asn Gly Ile		
1280	1285	1290

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Ser	Asn	Gln	Asp	Trp	Leu	Ala	Tyr	Ile	Gln	Glu	Leu	Arg	Asn	Gly
1295					1300				1305					
Arg	Ser	Ser	Asp	Asp	Glu	Ala	Thr	Ala	Asp	Ser	Gln	His	Ala	Ala
1310					1315				1320					
Pro	Pro	Lys	Lys	Lys	Arg	Lys	Val	Gly	Gly	Ser	Gly	Gly	Ser	Gly
1325					1330				1335					
Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly
1340					1345				1350					
Gly	Ser	Leu	Glu	His	His	His	His	His	His	His	His			
1355					1360									

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<210> SEQ_ID NO 1146
<211> LENGTH: 1331
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 1146

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Met	Thr	Gln	Phe	Glu	Gly	Phe	Thr	Asn	Leu	Tyr	Gln	Val	Ser	Lys	Thr
1			5			10				15					

Leu	Arg	Phe	Glu	Leu	Ile	Pro	Gln	Gly	Lys	Thr	Leu	Lys	His	Ile	Gln
		20			25				30						

Glu	Gln	Gly	Phe	Ile	Glu	Glu	Asp	Lys	Ala	Arg	Asn	Asp	His	Tyr	Lys
		35			40				45						

Glu	Leu	Lys	Pro	Ile	Ile	Asp	Arg	Ile	Tyr	Lys	Thr	Tyr	Ala	Asp	Gln
		50			55				60						

Cys	Leu	Gln	Leu	Val	Gln	Leu	Asp	Trp	Glu	Asn	Leu	Ser	Ala	Ala	Ile
		65			70			75			80				

Asp	Ser	Tyr	Arg	Lys	Glu	Lys	Thr	Glu	Glu	Thr	Arg	Asn	Ala	Leu	Ile
		85			90				95						

Glu	Glu	Gln	Ala	Thr	Tyr	Arg	Asn	Ala	Ile	His	Asp	Tyr	Phe	Ile	Gly
		100			105				110						

Arg	Thr	Asp	Asn	Leu	Thr	Asp	Ala	Ile	Asn	Lys	Arg	His	Ala	Glu	Ile
		115			120				125						

Tyr	Lys	Gly	Leu	Phe	Lys	Ala	Glu	Leu	Phe	Asn	Gly	Lys	Val	Leu	Lys
		130			135				140						

Gln	Leu	Gly	Thr	Val	Thr	Thr	Glu	His	Glu	Asn	Ala	Leu	Leu	Arg
		145			150			155			160			

Ser	Phe	Asp	Lys	Phe	Thr	Thr	Tyr	Phe	Ser	Gly	Phe	Tyr	Glu	Asn	Arg
		165			170			175							

Lys	Asn	Val	Phe	Ser	Ala	Glu	Asp	Ile	Ser	Thr	Ala	Ile	Pro	His	Arg
		180			185				190						

Ile	Val	Gln	Asp	Asn	Phe	Pro	Lys	Phe	Lys	Glu	Asn	Cys	His	Ile	Phe
		195			200				205						

Thr	Arg	Leu	Ile	Thr	Ala	Val	Pro	Ser	Leu	Arg	Glu	His	Phe	Glu	Asn
		210			215				220						

Val	Lys	Lys	Ala	Ile	Gly	Ile	Phe	Val	Ser	Thr	Ser	Ile	Glu	Glu	Val
		225			230			235			240				

Phe	Ser	Phe	Pro	Phe	Tyr	Asn	Gln	Leu	Leu	Thr	Gln	Thr	Gln	Ile	Asp
		245			250				255						

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Leu	Tyr	Asn	Gln	Leu	Leu	Gly	Gly	Ile	Ser	Arg	Glu	Ala	Gly	Thr	Glu
260				265							270				
Lys	Ile	Lys	Gly	Leu	Asn	Glu	Val	Leu	Asn	Leu	Ala	Ile	Gln	Lys	Asn
275				280							285				
Asp	Glu	Thr	Ala	His	Ile	Ile	Ala	Ser	Leu	Pro	His	Arg	Phe	Ile	Pro
290					295						300				
Leu	Phe	Lys	Gln	Ile	Leu	Ser	Asp	Arg	Asn	Thr	Leu	Ser	Phe	Ile	Leu
305					310				315				320		
Glu	Glu	Phe	Lys	Ser	Asp	Glu	Glu	Val	Ile	Gln	Ser	Phe	Cys	Lys	Tyr
325						330				335					
Lys	Thr	Leu	Leu	Arg	Asn	Glu	Asn	Val	Leu	Glu	Thr	Ala	Glu	Ala	Leu
					340				345				350		
Phe	Asn	Glu	Leu	Asn	Ser	Ile	Asp	Leu	Thr	His	Ile	Phe	Ile	Ser	His
						355		360			365				
Lys	Lys	Leu	Glu	Thr	Ile	Ser	Ser	Ala	Leu	Cys	Asp	His	Trp	Asp	Thr
						370		375			380				
Leu	Arg	Asn	Ala	Leu	Tyr	Glu	Arg	Arg	Ile	Ser	Glu	Leu	Thr	Gly	Lys
385						390			395				400		
Ile	Thr	Lys	Ser	Ala	Lys	Glu	Lys	Val	Gln	Arg	Ser	Leu	Lys	His	Glu
							405		410			415			
Asp	Ile	Asn	Leu	Gln	Glu	Ile	Ile	Ser	Ala	Ala	Gly	Lys	Glu	Leu	Ser
						420			425			430			
Glu	Ala	Phe	Lys	Gln	Lys	Thr	Ser	Glu	Ile	Leu	Ser	His	Ala	His	Ala
						435		440			445				
Ala	Leu	Asp	Gln	Pro	Leu	Pro	Thr	Thr	Leu	Lys	Lys	Gln	Glu	Glu	Lys
						450			455			460			
Glu	Ile	Leu	Lys	Ser	Gln	Leu	Asp	Ser	Leu	Leu	Gly	Leu	Tyr	His	Leu
465						470			475				480		
Leu	Asp	Trp	Phe	Ala	Val	Asp	Glu	Ser	Asn	Glu	Val	Asp	Pro	Glu	Phe
						485			490			495			
Ser	Ala	Arg	Leu	Thr	Gly	Ile	Lys	Leu	Glu	Met	Glu	Pro	Ser	Leu	Ser
						500			505			510			
Phe	Tyr	Asn	Ala	Arg	Asn	Tyr	Ala	Thr	Lys	Lys	Pro	Tyr	Ser	Val	
						515		520			525				
Glu	Lys	Phe	Lys	Leu	Asn	Phe	Gln	Arg	Pro	Thr	Leu	Ala	Ser	Gly	Trp
						530		535			540				
Asp	Val	Asn	Lys	Glu	Lys	Asn	Asn	Gly	Ala	Ile	Leu	Phe	Val	Lys	Asn
545							550			555			560		
Gly	Leu	Tyr	Tyr	Leu	Gly	Ile	Met	Pro	Lys	Gln	Lys	Gly	Arg	Tyr	Lys
						565			570			575			
Ala	Leu	Ser	Phe	Glu	Pro	Thr	Glu	Lys	Thr	Ser	Glu	Gly	Phe	Asp	Lys
						580			585			590			
Met	Tyr	Tyr	Asp	Tyr	Phe	Pro	Asp	Ala	Ala	Lys	Met	Ile	Pro	Lys	Cys
						595			600			605			
Ser	Thr	Gln	Leu	Lys	Ala	Val	Thr	Ala	His	Phe	Gln	Thr	His	Thr	Thr
						610		615			620				
Pro	Ile	Leu	Leu	Ser	Asn	Asn	Phe	Ile	Glu	Pro	Leu	Glu	Ile	Thr	Lys
						625		630			635			640	
Glu	Ile	Tyr	Asp	Leu	Asn	Asn	Pro	Glu	Lys	Glu	Pro	Lys	Lys	Phe	Gln
							645		650				655		
Thr	Ala	Tyr	Ala	Lys	Lys	Thr	Gly	Asp	Gln	Lys	Gly	Tyr	Arg	Glu	Ala

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660	665	670
Leu Cys Lys Trp Ile Asp Phe Thr Arg Asp Phe Leu Ser Lys Tyr Thr		
675	680	685
Lys Thr Thr Ser Ile Asp Leu Ser Ser Leu Arg Pro Ser Ser Gln Tyr		
690	695	700
Lys Asp Leu Gly Glu Tyr Tyr Ala Glu Leu Asn Pro Leu Leu Tyr His		
705	710	715
Ile Ser Phe Gln Arg Ile Ala Glu Lys Glu Ile Met Asp Ala Val Glu		
725	730	735
Thr Gly Lys Leu Tyr Leu Phe Gln Ile Tyr Asn Lys Asp Phe Ala Lys		
740	745	750
Gly His His Gly Lys Pro Asn Leu His Thr Leu Tyr Trp Thr Gly Leu		
755	760	765
Phe Ser Pro Glu Asn Leu Ala Lys Thr Ser Ile Lys Leu Asn Gly Gln		
770	775	780
Ala Glu Leu Phe Tyr Arg Pro Lys Ser Arg Met Lys Arg Met Ala Ala		
785	790	795
Arg Leu Gly Glu Lys Met Leu Asn Lys Lys Leu Lys Asp Gln Lys Thr		
805	810	815
Pro Ile Pro Asp Thr Leu Tyr Gln Glu Leu Tyr Asp Tyr Val Asn His		
820	825	830
Arg Leu Ser His Asp Leu Ser Asp Glu Ala Arg Ala Leu Leu Pro Asn		
835	840	845
Val Ile Thr Lys Glu Val Ser His Glu Ile Ile Lys Asp Arg Arg Phe		
850	855	860
Thr Ser Asp Lys Phe Leu Phe His Val Pro Ile Thr Leu Asn Tyr Gln		
865	870	875
Ala Ala Asn Ser Pro Ser Lys Phe Asn Gln Arg Val Asn Ala Tyr Leu		
885	890	895
Lys Glu His Pro Glu Thr Pro Ile Ile Gly Ile Asp Arg Gly Glu Arg		
900	905	910
Asn Leu Ile Tyr Ile Thr Val Ile Asp Ser Thr Gly Lys Ile Leu Glu		
915	920	925
Gln Arg Ser Leu Asn Thr Ile Gln Gln Phe Asp Tyr Gln Lys Lys Leu		
930	935	940
Asp Asn Arg Glu Lys Glu Arg Val Ala Ala Arg Gln Ala Trp Ser Val		
945	950	955
Val Gly Thr Ile Lys Asp Leu Lys Gln Gly Tyr Leu Ser Gln Val Ile		
965	970	975
His Glu Ile Val Asp Leu Met Ile His Tyr Gln Ala Val Val Val Leu		
980	985	990
Glu Asn Leu Asn Phe Gly Phe Lys Ser Lys Arg Thr Gly Ile Ala Glu		
995	1000	1005
Lys Ala Val Tyr Gln Gln Phe Glu Lys Met Leu Ile Asp Lys Leu		
1010	1015	1020
Asn Cys Leu Val Leu Lys Asp Tyr Pro Ala Glu Lys Val Gly Gly		
1025	1030	1035
Val Leu Asn Pro Tyr Gln Leu Thr Asp Gln Phe Thr Ser Phe Ala		
1040	1045	1050
Lys Met Gly Thr Gln Ser Gly Phe Leu Phe Tyr Val Pro Ala Pro		
1055	1060	1065

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Tyr Thr Ser Lys Ile Asp Pro Leu Thr Gly Phe Val Asp Pro Phe
1070 1075 1080

Val Trp Lys Thr Ile Lys Asn His Glu Ser Arg Lys His Phe Leu
1085 1090 1095

Glu Gly Phe Asp Phe Leu His Tyr Asp Val Lys Thr Gly Asp Phe
1100 1105 1110

Ile Leu His Phe Lys Met Asn Arg Asn Leu Ser Phe Gln Arg Gly
1115 1120 1125

Leu Pro Gly Phe Met Pro Ala Trp Asp Ile Val Phe Glu Lys Asn
1130 1135 1140

Glu Thr Gln Phe Asp Ala Lys Gly Thr Pro Phe Ile Ala Gly Lys
1145 1150 1155

Arg Ile Val Pro Val Ile Glu Asn His Arg Phe Thr Gly Arg Tyr
1160 1165 1170

Arg Asp Leu Tyr Pro Ala Asn Glu Leu Ile Ala Leu Leu Glu Glu
1175 1180 1185

Lys Gly Ile Val Phe Arg Asp Gly Ser Asn Ile Leu Pro Lys Leu
1190 1195 1200

Leu Glu Asn Asp Asp Ser His Ala Ile Asp Thr Met Val Ala Leu
1205 1210 1215

Ile Arg Ser Val Leu Gln Met Arg Asn Ser Asn Ala Ala Thr Gly
1220 1225 1230

Glu Asp Tyr Ile Asn Ser Pro Val Arg Asp Leu Asn Gly Val Cys
1235 1240 1245

Phe Asp Ser Arg Phe Gln Asn Pro Glu Trp Pro Met Asp Ala Asp
1250 1255 1260

Ala Asn Gly Ala Tyr His Ile Ala Leu Lys Gly Gln Leu Leu Leu
1265 1270 1275

Asn His Leu Lys Glu Ser Lys Asp Leu Lys Leu Gln Asn Gly Ile
1280 1285 1290

Ser Asn Gln Asp Trp Leu Ala Tyr Ile Gln Glu Leu Arg Asn Gly
1295 1300 1305

Arg Ser Ser Asp Asp Glu Ala Thr Ala Asp Ser Gln His Ala Ala
1310 1315 1320

Pro Pro Lys Lys Arg Lys Val
1325 1330

<210> SEQ ID NO 1147
<211> LENGTH: 1331
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 1147

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Leu Arg Phe Glu Leu Ile Pro Gln Gly Lys Thr Leu Lys His Ile Gln
20 25 30

Glu Gln Gly Phe Ile Glu Glu Asp Lys Ala Arg Asn Asp His Tyr Lys
35 40 45

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Glu	Leu	Lys	Pro	Ile	Ile	Asp	Arg	Ile	Tyr	Lys	Thr	Tyr	Tyr	Ala	Asp	Gln
50						55				60						
Cys	Leu	Gln	Leu	Val	Gln	Leu	Asp	Trp	Glu	Asn	Leu	Ser	Ala	Ala	Ile	
65						70			75						80	
Asp	Ser	Tyr	Arg	Lys	Glu	Lys	Thr	Glu	Glu	Thr	Arg	Asn	Ala	Leu	Ile	
						85			90					95		
Glu	Glu	Gln	Ala	Thr	Tyr	Arg	Asn	Ala	Ile	His	Asp	Tyr	Phe	Ile	Gly	
						100			105				110			
Arg	Thr	Asp	Asn	Leu	Thr	Asp	Ala	Ile	Asn	Lys	Arg	His	Ala	Glu	Ile	
						115			120				125			
Tyr	Lys	Gly	Leu	Phe	Lys	Ala	Glu	Leu	Phe	Asn	Gly	Lys	Val	Leu	Lys	
						130			135			140				
Gln	Leu	Gly	Thr	Val	Thr	Thr	Glu	His	Glu	Asn	Ala	Leu	Leu	Arg		
						145			150			155			160	
Ser	Phe	Asp	Lys	Phe	Thr	Thr	Tyr	Phe	Ser	Gly	Phe	Tyr	Glu	Asn	Arg	
						165			170			175				
Lys	Asn	Val	Phe	Ser	Ala	Glu	Asp	Ile	Ser	Thr	Ala	Ile	Pro	His	Arg	
						180			185			190				
Ile	Val	Gln	Asp	Asn	Phe	Pro	Lys	Phe	Lys	Glu	Asn	Cys	His	Ile	Phe	
						195			200			205				
Thr	Arg	Leu	Ile	Thr	Ala	Val	Pro	Ser	Leu	Arg	Glu	His	Phe	Glu	Asn	
						210			215			220				
Val	Lys	Lys	Ala	Ile	Gly	Ile	Phe	Val	Ser	Thr	Ser	Ile	Glu	Glu	Val	
						225			230			235			240	
Phe	Ser	Phe	Pro	Phe	Tyr	Asn	Gln	Leu	Leu	Thr	Gln	Thr	Gln	Ile	Asp	
						245			250			255				
Leu	Tyr	Asn	Gln	Leu	Leu	Gly	Gly	Ile	Ser	Arg	Glu	Ala	Gly	Thr	Glu	
						260			265			270				
Lys	Ile	Lys	Gly	Leu	Asn	Glu	Val	Leu	Asn	Leu	Ala	Ile	Gln	Lys	Asn	
						275			280			285				
Asp	Glu	Thr	Ala	His	Ile	Ile	Ala	Ser	Leu	Pro	His	Arg	Phe	Ile	Pro	
						290			295			300				
Leu	Phe	Lys	Gln	Ile	Leu	Ser	Asp	Arg	Asn	Thr	Leu	Ser	Phe	Ile	Leu	
						305			310			315			320	
Glu	Glu	Phe	Lys	Ser	Asp	Glu	Glu	Val	Ile	Gln	Ser	Phe	Cys	Lys	Tyr	
						325			330			335				
Lys	Thr	Leu	Leu	Arg	Asn	Glu	Asn	Val	Leu	Glu	Thr	Ala	Glu	Ala	Leu	
						340			345			350				
Phe	Asn	Glu	Leu	Asn	Ser	Ile	Asp	Leu	Thr	His	Ile	Phe	Ile	Ser	His	
						355			360			365				
Lys	Lys	Leu	Glu	Thr	Ile	Ser	Ser	Ala	Leu	Cys	Asp	His	Trp	Asp	Thr	
						370			375			380				
Leu	Arg	Asn	Ala	Leu	Tyr	Glu	Arg	Arg	Ile	Ser	Glu	Leu	Thr	Gly	Lys	
						385			390			395			400	
Ile	Thr	Lys	Ser	Ala	Lys	Glu	Lys	Val	Gln	Arg	Ser	Leu	Lys	His	Glu	
						405			410			415				
Asp	Ile	Asn	Leu	Gln	Glu	Ile	Ile	Ser	Ala	Ala	Gly	Lys	Glu	Leu	Ser	
						420			425			430				
Glu	Ala	Phe	Lys	Gln	Lys	Thr	Ser	Glu	Ile	Leu	Ser	His	Ala	His	Ala	
						435			440			445				
Ala	Leu	Asp	Gln	Pro	Leu	Pro	Thr	Thr	Leu	Lys	Gln	Glu	Glu	Lys		

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450	455	460
Glu Ile Leu Lys Ser Gln Leu Asp Ser Leu Leu Gly Leu Tyr His Leu		
465	470	475
		480
Leu Asp Trp Phe Ala Val Asp Glu Ser Asn Glu Val Asp Pro Glu Phe		
485	490	495
Ser Ala Arg Leu Thr Gly Ile Lys Leu Glu Met Glu Pro Ser Leu Ser		
500	505	510
Phe Tyr Asn Lys Ala Arg Asn Tyr Ala Thr Lys Lys Pro Tyr Ser Val		
515	520	525
Glu Lys Phe Lys Leu Asn Phe Gln Arg Pro Thr Leu Ala Ser Gly Trp		
530	535	540
Asp Val Asn Lys Glu Lys Asn Asn Gly Ala Ile Leu Phe Val Lys Asn		
545	550	555
		560
Gly Leu Tyr Tyr Leu Gly Ile Met Pro Lys Gln Lys Gly Arg Tyr Lys		
565	570	575
Ala Leu Ser Phe Glu Pro Thr Glu Lys Thr Ser Glu Gly Phe Asp Lys		
580	585	590
Met Tyr Tyr Asp Tyr Phe Pro Asp Ala Ala Lys Met Ile Pro Lys Cys		
595	600	605
Ser Thr Gln Leu Lys Ala Val Thr Ala His Phe Gln Thr His Thr Thr		
610	615	620
Pro Ile Leu Leu Ser Asn Asn Phe Ile Glu Pro Leu Glu Ile Thr Lys		
625	630	635
		640
Glu Ile Tyr Asp Leu Asn Asn Pro Glu Lys Glu Pro Lys Lys Phe Gln		
645	650	655
Thr Ala Tyr Ala Lys Lys Thr Gly Asp Gln Lys Gly Tyr Arg Glu Ala		
660	665	670
Leu Cys Lys Trp Ile Asp Phe Thr Arg Asp Phe Leu Ser Lys Tyr Thr		
675	680	685
Lys Thr Thr Ser Ile Asp Leu Ser Ser Leu Arg Pro Ser Ser Gln Tyr		
690	695	700
Lys Asp Leu Gly Glu Tyr Tyr Ala Glu Leu Asn Pro Leu Leu Tyr His		
705	710	715
		720
Ile Ser Phe Gln Arg Ile Ala Glu Lys Glu Ile Met Asp Ala Val Glu		
725	730	735
Thr Gly Lys Leu Tyr Leu Phe Gln Ile Tyr Asn Lys Asp Phe Ala Lys		
740	745	750
Gly His His Gly Lys Pro Asn Leu His Thr Leu Tyr Trp Thr Gly Leu		
755	760	765
Phe Ser Pro Glu Asn Leu Ala Lys Thr Ser Ile Lys Leu Asn Gly Gln		
770	775	780
Ala Glu Leu Phe Tyr Arg Pro Lys Ser Arg Met Lys Arg Met Ala His		
785	790	795
		800
Arg Leu Gly Glu Lys Met Leu Asn Lys Lys Leu Lys Asp Gln Lys Thr		
805	810	815
Pro Ile Pro Asp Thr Leu Tyr Gln Glu Leu Tyr Asp Tyr Val Asn His		
820	825	830
Arg Leu Ser His Asp Leu Ser Asp Glu Ala Arg Ala Leu Leu Pro Asn		
835	840	845
Val Ile Thr Lys Glu Val Ser His Glu Ile Ile Lys Asp Arg Arg Phe		
850	855	860

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Thr Ser Asp Lys Phe Leu Phe His Val Pro Ile Thr Leu Asn Tyr Gln
 865 870 875 880
 Ala Ala Asn Ser Pro Ser Lys Phe Asn Gln Arg Val Asn Ala Tyr Leu
 885 890 895
 Lys Glu His Pro Glu Thr Pro Ile Ile Gly Ile Asp Arg Gly Glu Arg
 900 905 910
 Asn Leu Ile Tyr Ile Thr Val Ile Asp Ser Thr Gly Lys Ile Leu Glu
 915 920 925
 Gln Arg Ser Leu Asn Thr Ile Gln Gln Phe Asp Tyr Gln Lys Lys Leu
 930 935 940
 Asp Asn Arg Glu Lys Glu Arg Val Ala Ala Arg Gln Ala Trp Ser Val
 945 950 955 960
 Val Gly Thr Ile Lys Asp Leu Lys Gln Gly Tyr Leu Ser Gln Val Ile
 965 970 975
 His Glu Ile Val Asp Leu Met Ile His Tyr Gln Ala Val Val Val Leu
 980 985 990
 Glu Asn Leu Asn Phe Gly Phe Lys Ser Lys Arg Thr Gly Ile Ala Glu
 995 1000 1005
 Lys Ala Val Tyr Gln Gln Phe Glu Lys Met Leu Ile Asp Lys Leu
 1010 1015 1020
 Asn Cys Leu Val Leu Lys Asp Tyr Pro Ala Glu Lys Val Gly Gly
 1025 1030 1035
 Val Leu Asn Pro Tyr Gln Leu Thr Asp Gln Phe Thr Ser Phe Ala
 1040 1045 1050
 Lys Met Gly Thr Gln Ser Gly Phe Leu Phe Tyr Val Pro Ala Pro
 1055 1060 1065
 Tyr Thr Ser Lys Ile Asp Pro Leu Thr Gly Phe Val Asp Pro Phe
 1070 1075 1080
 Val Trp Lys Thr Ile Lys Asn His Glu Ser Arg Lys His Phe Leu
 1085 1090 1095
 Glu Gly Phe Asp Phe Leu His Tyr Asp Val Lys Thr Gly Asp Phe
 1100 1105 1110
 Ile Leu His Phe Lys Met Asn Arg Asn Leu Ser Phe Gln Arg Gly
 1115 1120 1125
 Leu Pro Gly Phe Met Pro Ala Trp Asp Ile Val Phe Glu Lys Asn
 1130 1135 1140
 Glu Thr Gln Phe Asp Ala Lys Gly Thr Pro Phe Ile Ala Gly Lys
 1145 1150 1155
 Arg Ile Val Pro Val Ile Glu Asn His Arg Phe Thr Gly Arg Tyr
 1160 1165 1170
 Arg Asp Leu Tyr Pro Ala Asn Glu Leu Ile Ala Leu Leu Glu Glu
 1175 1180 1185
 Lys Gly Ile Val Phe Arg Asp Gly Ser Asn Ile Leu Pro Lys Leu
 1190 1195 1200
 Leu Glu Asn Asp Asp Ser His Ala Ile Asp Thr Met Val Ala Leu
 1205 1210 1215
 Ile Arg Ser Val Leu Gln Met Arg Asn Ser Asn Ala Ala Thr Gly
 1220 1225 1230
 Glu Asp Tyr Ile Asn Ser Pro Val Arg Asp Leu Asn Gly Val Cys
 1235 1240 1245

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Phe	Asp	Ser	Arg	Phe	Gln	Asn	Pro	Glu	Trp	Pro	Met	Asp	Ala	Asp
1250				1255							1260			
Ala	Asn	Gly	Ala	Tyr	His	Ile	Ala	Leu	Lys	Gly	Gln	Leu	Leu	Leu
1265				1270							1275			
Asn	His	Leu	Lys	Glu	Ser	Lys	Asp	Leu	Lys	Leu	Gln	Asn	Gly	Ile
1280				1285							1290			
Ser	Asn	Gln	Asp	Trp	Leu	Ala	Tyr	Ile	Gln	Glu	Leu	Arg	Asn	Gly
1295				1300							1305			
Arg	Ser	Ser	Asp	Asp	Glu	Ala	Thr	Ala	Asp	Ser	Gln	His	Ala	Ala
1310				1315							1320			
Pro	Pro	Lys	Lys	Lys	Arg	Lys	Val							
1325				1330										

<210> SEQ ID NO 1148
<211> LENGTH: 1363
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 1148

Met	Thr	Gln	Phe	Glu	Gly	Phe	Thr	Asn	Leu	Tyr	Gln	Val	Ser	Lys	Thr
1				5					10					15	

Leu	Arg	Phe	Glu	Leu	Ile	Pro	Gln	Gly	Lys	Thr	Leu	Lys	His	Ile	Gln
				20				25					30		

Glu	Gln	Gly	Phe	Ile	Glu	Glu	Asp	Lys	Ala	Arg	Asn	Asp	His	Tyr	Lys
				35			40						45		

Glu	Leu	Lys	Pro	Ile	Ile	Asp	Arg	Ile	Tyr	Lys	Thr	Tyr	Ala	Asp	Gln
				50			55						60		

Cys	Leu	Gln	Leu	Val	Gln	Leu	Asp	Trp	Glu	Asn	Leu	Ser	Ala	Ala	Ile
				65				70					80		

Asp	Ser	Tyr	Arg	Lys	Glu	Lys	Thr	Glu	Glu	Thr	Arg	Asn	Ala	Leu	Ile
				85				90					95		

Glu	Glu	Gln	Ala	Thr	Tyr	Arg	Asn	Ala	Ile	His	Asp	Tyr	Phe	Ile	Gly
				100				105					110		

Arg	Thr	Asp	Asn	Leu	Thr	Asp	Ala	Ile	Asn	Lys	Arg	His	Ala	Glu	Ile
				115			120						125		

Tyr	Lys	Gly	Leu	Phe	Lys	Ala	Glu	Leu	Phe	Asn	Gly	Lys	Val	Leu	Lys
				130			135					140			

Gln	Leu	Gly	Thr	Val	Thr	Thr	Glu	His	Glu	Asn	Ala	Leu	Leu	Arg
				145			150					160		

Ser	Phe	Asp	Lys	Phe	Thr	Thr	Tyr	Phe	Ser	Gly	Phe	Tyr	Glu	Asn	Arg
				165			170					175			

Lys	Asn	Val	Phe	Ser	Ala	Glu	Asp	Ile	Ser	Thr	Ala	Ile	Pro	His	Arg
				180			185					190			

Ile	Val	Gln	Asp	Asn	Phe	Pro	Lys	Phe	Lys	Glu	Asn	Cys	His	Ile	Phe
				195			200					205			

Thr	Arg	Leu	Ile	Thr	Ala	Val	Pro	Ser	Leu	Arg	Glu	His	Phe	Glu	Asn
				210			215					220			

Val	Lys	Lys	Ala	Ile	Gly	Ile	Phe	Val	Ser	Thr	Ser	Ile	Glu	Glu	Val
				225			230					235			240

Phe Ser Phe Pro Phe Tyr Asn Gln Leu Leu Thr Gln Thr Gln Ile Asp

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245	250	255
Leu Tyr Asn Gln Leu Leu Gly Gly Ile Ser Arg Glu Ala Gly Thr Glu		
260	265	270
Lys Ile Lys Gly Leu Asn Glu Val Leu Asn Leu Ala Ile Gln Lys Asn		
275	280	285
Asp Glu Thr Ala His Ile Ile Ala Ser Leu Pro His Arg Phe Ile Pro		
290	295	300
Leu Phe Lys Gln Ile Leu Ser Asp Arg Asn Thr Leu Ser Phe Ile Leu		
305	310	315
Glu Glu Phe Lys Ser Asp Glu Glu Val Ile Gln Ser Phe Cys Lys Tyr		
325	330	335
Lys Thr Leu Leu Arg Asn Glu Asn Val Leu Glu Thr Ala Glu Ala Leu		
340	345	350
Phe Asn Glu Leu Asn Ser Ile Asp Leu Thr His Ile Phe Ile Ser His		
355	360	365
Lys Lys Leu Glu Thr Ile Ser Ser Ala Leu Cys Asp His Trp Asp Thr		
370	375	380
Leu Arg Asn Ala Leu Tyr Glu Arg Arg Ile Ser Glu Leu Thr Gly Lys		
385	390	395
Ile Thr Lys Ser Ala Lys Glu Lys Val Gln Arg Ser Leu Lys His Glu		
405	410	415
Asp Ile Asn Leu Gln Glu Ile Ile Ser Ala Ala Gly Lys Glu Leu Ser		
420	425	430
Glu Ala Phe Lys Gln Lys Thr Ser Glu Ile Leu Ser His Ala His Ala		
435	440	445
Ala Leu Asp Gln Pro Leu Pro Thr Thr Leu Lys Lys Gln Glu Glu Lys		
450	455	460
Glu Ile Leu Lys Ser Gln Leu Asp Ser Leu Leu Gly Leu Tyr His Leu		
465	470	475
Leu Asp Trp Phe Ala Val Asp Glu Ser Asn Glu Val Asp Pro Glu Phe		
485	490	495
Ser Ala Arg Leu Thr Gly Ile Lys Leu Glu Met Glu Pro Ser Leu Ser		
500	505	510
Phe Tyr Asn Lys Ala Arg Asn Tyr Ala Thr Lys Lys Pro Tyr Ser Val		
515	520	525
Glu Lys Phe Lys Leu Asn Phe Gln Arg Pro Thr Leu Ala Ser Gly Trp		
530	535	540
Asp Val Asn Lys Glu Lys Asn Asn Gly Ala Ile Leu Phe Val Lys Asn		
545	550	555
Gly Leu Tyr Tyr Leu Gly Ile Met Pro Lys Gln Lys Gly Arg Tyr Lys		
565	570	575
Ala Leu Ser Phe Glu Pro Thr Glu Lys Thr Ser Glu Gly Phe Asp Lys		
580	585	590
Met Tyr Tyr Asp Tyr Phe Pro Asp Ala Ala Lys Met Ile Pro Lys Cys		
595	600	605
Ser Thr Gln Leu Lys Ala Val Thr Ala His Phe Gln Thr His Thr Thr		
610	615	620
Pro Ile Leu Leu Ser Asn Asn Phe Ile Glu Pro Leu Glu Ile Thr Lys		
625	630	635
Glu Ile Tyr Asp Leu Asn Asn Pro Glu Lys Glu Pro Lys Lys Phe Gln		
645	650	655

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Thr Ala Tyr Ala Lys Lys Thr Gly Asp Gln Lys Gly Tyr Arg Glu Ala
 660 665 670
 Leu Cys Lys Trp Ile Asp Phe Thr Arg Asp Phe Leu Ser Lys Tyr Thr
 675 680 685
 Lys Thr Thr Ser Ile Asp Leu Ser Ser Leu Arg Pro Ser Ser Gln Tyr
 690 695 700
 Lys Asp Leu Gly Glu Tyr Tyr Ala Glu Leu Asn Pro Leu Leu Tyr His
 705 710 715 720
 Ile Ser Phe Gln Arg Ile Ala Glu Lys Ile Met Asp Ala Val Glu
 725 730 735
 Thr Gly Lys Leu Tyr Leu Phe Gln Ile Tyr Asn Lys Asp Phe Ala Lys
 740 745 750
 Gly His His Gly Lys Pro Asn Leu His Thr Leu Tyr Trp Thr Gly Leu
 755 760 765
 Phe Ser Pro Glu Asn Leu Ala Lys Thr Ser Ile Lys Leu Asn Gly Gln
 770 775 780
 Ala Glu Leu Phe Tyr Arg Pro Lys Ser Arg Met Lys Arg Met Ala His
 785 790 795 800
 Arg Leu Gly Glu Lys Met Leu Asn Lys Lys Leu Lys Asp Gln Lys Thr
 805 810 815
 Pro Ile Pro Asp Thr Leu Tyr Gln Glu Leu Tyr Asp Tyr Val Asn His
 820 825 830
 Arg Leu Ser His Asp Leu Ser Asp Glu Ala Arg Ala Leu Leu Pro Asn
 835 840 845
 Val Ile Thr Lys Glu Val Ser His Glu Ile Ile Lys Asp Arg Arg Phe
 850 855 860
 Thr Ser Asp Lys Phe Leu Phe His Val Pro Ile Thr Leu Asn Tyr Gln
 865 870 875 880
 Ala Ala Asn Ser Pro Ser Lys Phe Asn Gln Arg Val Asn Ala Tyr Leu
 885 890 895
 Lys Glu His Pro Glu Thr Pro Ile Ile Gly Ile Asp Arg Gly Glu Arg
 900 905 910
 Asn Leu Ile Tyr Ile Thr Val Ile Asp Ser Thr Gly Lys Ile Leu Glu
 915 920 925
 Gln Arg Ser Leu Asn Thr Ile Gln Gln Phe Asp Tyr Gln Lys Lys Leu
 930 935 940
 Asp Asn Arg Glu Lys Glu Arg Val Ala Ala Arg Gln Ala Trp Ser Val
 945 950 955 960
 Val Gly Thr Ile Lys Asp Leu Lys Gln Gly Tyr Leu Ser Gln Val Ile
 965 970 975
 His Glu Ile Val Asp Leu Met Ile His Tyr Gln Ala Val Val Val Leu
 980 985 990
 Glu Asn Leu Asn Phe Gly Phe Lys Ser Lys Arg Thr Gly Ile Ala Glu
 995 1000 1005
 Lys Ala Val Tyr Gln Gln Phe Glu Lys Met Leu Ile Asp Lys Leu
 1010 1015 1020
 Asn Cys Leu Val Leu Lys Asp Tyr Pro Ala Glu Lys Val Gly Gly
 1025 1030 1035
 Val Leu Asn Pro Tyr Gln Leu Thr Asp Gln Phe Thr Ser Phe Ala
 1040 1045 1050

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Lys	Met	Gly	Thr	Gln	Ser	Gly	Phe	Leu	Phe	Tyr	Val	Pro	Ala	Pro
1055					1060						1065			
Tyr	Thr	Ser	Lys	Ile	Asp	Pro	Leu	Thr	Gly	Phe	Val	Asp	Pro	Phe
1070						1075					1080			
Val	Trp	Lys	Thr	Ile	Lys	Asn	His	Glu	Ser	Arg	Lys	His	Phe	Leu
1085						1090					1095			
Glu	Gly	Phe	Asp	Phe	Leu	His	Tyr	Asp	Val	Lys	Thr	Gly	Asp	Phe
1100						1105					1110			
Ile	Leu	His	Phe	Lys	Met	Asn	Arg	Asn	Leu	Ser	Phe	Gln	Arg	Gly
1115						1120					1125			
Leu	Pro	Gly	Phe	Met	Pro	Ala	Trp	Asp	Ile	Val	Phe	Glu	Lys	Asn
1130						1135					1140			
Glu	Thr	Gln	Phe	Asp	Ala	Lys	Gly	Thr	Pro	Phe	Ile	Ala	Gly	Lys
1145						1150					1155			
Arg	Ile	Val	Pro	Val	Ile	Glu	Asn	His	Arg	Phe	Thr	Gly	Arg	Tyr
1160						1165					1170			
Arg	Asp	Leu	Tyr	Pro	Ala	Asn	Glu	Leu	Ile	Ala	Leu	Leu	Glu	Glu
1175						1180					1185			
Lys	Gly	Ile	Val	Phe	Arg	Asp	Gly	Ser	Asn	Ile	Leu	Pro	Lys	Leu
1190						1195					1200			
Leu	Glu	Asn	Asp	Asp	Ser	His	Ala	Ile	Asp	Thr	Met	Val	Ala	Leu
1205						1210					1215			
Ile	Arg	Ser	Val	Leu	Gln	Met	Arg	Asn	Ser	Asn	Ala	Ala	Thr	Gly
1220						1225					1230			
Glu	Asp	Tyr	Ile	Asn	Ser	Pro	Val	Arg	Asp	Leu	Asn	Gly	Val	Cys
1235						1240					1245			
Phe	Asp	Ser	Arg	Phe	Gln	Asn	Pro	Glu	Trp	Pro	Met	Asp	Ala	Asp
1250						1255					1260			
Ala	Asn	Gly	Ala	Tyr	His	Ile	Ala	Leu	Lys	Gly	Gln	Leu	Leu	Leu
1265						1270					1275			
Asn	His	Leu	Lys	Glu	Ser	Lys	Asp	Leu	Lys	Leu	Gln	Asn	Gly	Ile
1280						1285					1290			
Ser	Asn	Gln	Asp	Trp	Leu	Ala	Tyr	Ile	Gln	Glu	Leu	Arg	Asn	Gly
1295						1300					1305			
Arg	Ser	Ser	Asp	Asp	Glu	Ala	Thr	Ala	Asp	Ser	Gln	His	Ala	Ala
1310						1315					1320			
Pro	Pro	Lys	Lys	Lys	Arg	Lys	Val	Gly	Gly	Ser	Gly	Gly	Ser	Gly
1325						1330					1335			
Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly
1340						1345					1350			
Gly	Ser	Leu	Glu	His	His	His	His	His	His	His	His			
1355						1360								

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<210> SEQ ID NO 1149
<211> LENGTH: 1361
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"
<400> SEQUENCE: 1149

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Met Gly Arg Asp Pro Gly Lys Pro Ile Pro Asn Pro Leu Leu Gly Leu

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1	5	10	15
Asp Ser Thr Ala Pro Lys Lys Lys Arg Lys Val Gly Ile His Gly Val			
20	25	30	
Pro Ala Ala Thr Gln Phe Glu Gly Phe Thr Asn Leu Tyr Gln Val Ser			
35	40	45	
Lys Thr Leu Arg Phe Glu Leu Ile Pro Gln Gly Lys Thr Leu Lys His			
50	55	60	
Ile Gln Glu Gln Gly Phe Ile Glu Asp Lys Ala Arg Asn Asp His			
65	70	75	80
Tyr Lys Glu Leu Lys Pro Ile Ile Asp Arg Ile Tyr Lys Thr Tyr Ala			
85	90	95	
Asp Gln Cys Leu Gln Leu Val Gln Leu Asp Trp Glu Asn Leu Ser Ala			
100	105	110	
Ala Ile Asp Ser Tyr Arg Lys Glu Lys Thr Glu Glu Thr Arg Asn Ala			
115	120	125	
Leu Ile Glu Glu Gln Ala Thr Tyr Arg Asn Ala Ile His Asp Tyr Phe			
130	135	140	
Ile Gly Arg Thr Asp Asn Leu Thr Asp Ala Ile Asn Lys Arg His Ala			
145	150	155	160
Glu Ile Tyr Lys Gly Leu Phe Lys Ala Glu Leu Phe Asn Gly Lys Val			
165	170	175	
Leu Lys Gln Leu Gly Thr Val Thr Thr Glu His Glu Asn Ala Leu			
180	185	190	
Leu Arg Ser Phe Asp Lys Phe Thr Thr Tyr Phe Ser Gly Phe Tyr Glu			
195	200	205	
Asn Arg Lys Asn Val Phe Ser Ala Glu Asp Ile Ser Thr Ala Ile Pro			
210	215	220	
His Arg Ile Val Gln Asp Asn Phe Pro Lys Phe Lys Glu Asn Cys His			
225	230	235	240
Ile Phe Thr Arg Leu Ile Thr Ala Val Pro Ser Leu Arg Glu His Phe			
245	250	255	
Glu Asn Val Lys Lys Ala Ile Gly Ile Phe Val Ser Thr Ser Ile Glu			
260	265	270	
Glu Val Phe Ser Phe Pro Phe Tyr Asn Gln Leu Leu Thr Gln Thr Gln			
275	280	285	
Ile Asp Leu Tyr Asn Gln Leu Leu Gly Gly Ile Ser Arg Glu Ala Gly			
290	295	300	
Thr Glu Lys Ile Lys Gly Leu Asn Glu Val Leu Asn Leu Ala Ile Gln			
305	310	315	320
Lys Asn Asp Glu Thr Ala His Ile Ile Ala Ser Leu Pro His Arg Phe			
325	330	335	
Ile Pro Leu Phe Lys Gln Ile Leu Ser Asp Arg Asn Thr Leu Ser Phe			
340	345	350	
Ile Leu Glu Glu Phe Lys Ser Asp Glu Glu Val Ile Gln Ser Phe Cys			
355	360	365	
Lys Tyr Lys Thr Leu Leu Arg Asn Glu Asn Val Leu Glu Thr Ala Glu			
370	375	380	
Ala Leu Phe Asn Glu Leu Asn Ser Ile Asp Leu Thr His Ile Phe Ile			
385	390	395	400
Ser His Lys Lys Leu Glu Thr Ile Ser Ser Ala Leu Cys Asp His Trp			
405	410	415	

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Asp Thr Leu Arg Asn Ala Leu Tyr Glu Arg Arg Ile Ser Glu Leu Thr
 420 425 430
 Gly Lys Ile Thr Lys Ser Ala Lys Glu Lys Val Gln Arg Ser Leu Lys
 435 440 445
 His Glu Asp Ile Asn Leu Gln Glu Ile Ile Ser Ala Ala Gly Lys Glu
 450 455 460
 Leu Ser Glu Ala Phe Lys Gln Lys Thr Ser Glu Ile Leu Ser His Ala
 465 470 475 480
 His Ala Ala Leu Asp Gln Pro Leu Pro Thr Thr Leu Lys Lys Gln Glu
 485 490 495
 Glu Lys Glu Ile Leu Lys Ser Gln Leu Asp Ser Leu Leu Gly Leu Tyr
 500 505 510
 His Leu Leu Asp Trp Phe Ala Val Asp Glu Ser Asn Glu Val Asp Pro
 515 520 525
 Glu Phe Ser Ala Arg Leu Thr Gly Ile Lys Leu Glu Met Glu Pro Ser
 530 535 540
 Leu Ser Phe Tyr Asn Lys Ala Arg Asn Tyr Ala Thr Lys Lys Pro Tyr
 545 550 555 560
 Ser Val Glu Lys Phe Lys Leu Asn Phe Gln Met Pro Thr Leu Ala Ser
 565 570 575
 Gly Trp Asp Val Asn Lys Glu Lys Asn Asn Gly Ala Ile Leu Phe Val
 580 585 590
 Lys Asn Gly Leu Tyr Tyr Leu Gly Ile Met Pro Lys Gln Lys Gly Arg
 595 600 605
 Tyr Lys Ala Leu Ser Phe Glu Pro Thr Glu Lys Thr Ser Glu Gly Phe
 610 615 620
 Asp Lys Met Tyr Tyr Asp Tyr Phe Pro Asp Ala Ala Lys Met Ile Pro
 625 630 635 640
 Lys Cys Ser Thr Gln Leu Lys Ala Val Thr Ala His Phe Gln Thr His
 645 650 655
 Thr Thr Pro Ile Leu Leu Ser Asn Asn Phe Ile Glu Pro Leu Glu Ile
 660 665 670
 Thr Lys Glu Ile Tyr Asp Leu Asn Asn Pro Glu Lys Glu Pro Lys Lys
 675 680 685
 Phe Gln Thr Ala Tyr Ala Lys Lys Thr Gly Asp Gln Lys Gly Tyr Arg
 690 695 700
 Glu Ala Leu Cys Lys Trp Ile Asp Phe Thr Arg Asp Phe Leu Ser Lys
 705 710 715 720
 Tyr Thr Lys Thr Thr Ser Ile Asp Leu Ser Ser Leu Arg Pro Ser Ser
 725 730 735
 Gln Tyr Lys Asp Leu Gly Glu Tyr Tyr Ala Glu Leu Asn Pro Leu Leu
 740 745 750
 Tyr His Ile Ser Phe Gln Arg Ile Ala Glu Lys Glu Ile Met Asp Ala
 755 760 765
 Val Glu Thr Gly Lys Leu Tyr Leu Phe Gln Ile Tyr Asn Lys Asp Phe
 770 775 780
 Ala Lys Gly His His Gly Lys Pro Asn Leu His Thr Leu Tyr Trp Thr
 785 790 795 800
 Gly Leu Phe Ser Pro Glu Asn Leu Ala Lys Thr Ser Ile Lys Leu Asn
 805 810 815

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Gly	Gln	Ala	Glu	Leu	Phe	Tyr	Arg	Pro	Lys	Ser	Arg	Met	Lys	Arg	Met
820															830
Ala	His	Arg	Leu	Gly	Glu	Lys	Met	Leu	Asn	Lys	Lys	Leu	Lys	Asp	Gln
835															845
Lys	Thr	Pro	Ile	Pro	Asp	Thr	Leu	Tyr	Gln	Glu	Leu	Tyr	Asp	Tyr	Val
850															860
Asn	His	Arg	Leu	Ser	His	Asp	Leu	Ser	Asp	Glu	Ala	Arg	Ala	Leu	Leu
865															880
Pro	Asn	Val	Ile	Thr	Lys	Glu	Val	Ser	His	Glu	Ile	Ile	Lys	Asp	Arg
885															895
Arg	Phe	Thr	Ser	Asp	Lys	Phe	Phe	His	Val	Pro	Ile	Thr	Leu	Asn	
900															910
Tyr	Gln	Ala	Ala	Asn	Ser	Pro	Ser	Lys	Phe	Asn	Gln	Arg	Val	Asn	Ala
915															925
Tyr	Leu	Lys	Glu	His	Pro	Glu	Thr	Pro	Ile	Ile	Gly	Ile	Asp	Arg	Gly
930															940
Glu	Arg	Asn	Leu	Ile	Tyr	Ile	Thr	Val	Ile	Asp	Ser	Thr	Gly	Lys	Ile
945															960
Leu	Glu	Gln	Arg	Ser	Leu	Asn	Thr	Ile	Gln	Gln	Phe	Asp	Tyr	Gln	Lys
965															975
Lys	Leu	Asp	Asn	Arg	Glu	Lys	Glu	Arg	Val	Ala	Ala	Arg	Gln	Ala	Trp
980															990
Ser	Val	Val	Gly	Thr	Ile	Lys	Asp	Leu	Lys	Gln	Gly	Tyr	Leu	Ser	Gln
995															1005
Val	Ile	His	Glu	Ile	Val	Asp	Leu	Met	Ile	His	Tyr	Gln	Ala	Val	
1010															1020
Val	Val	Leu	Glu	Asn	Leu	Asn	Phe	Gly	Phe	Lys	Ser	Lys	Arg	Thr	
1025															1035
Gly	Ile	Ala	Glu	Lys	Ala	Val	Tyr	Gln	Gln	Phe	Glu	Lys	Met	Leu	
1040															1050
Ile	Asp	Lys	Leu	Asn	Cys	Leu	Val	Leu	Lys	Asp	Tyr	Pro	Ala	Glu	
1055															1065
Lys	Val	Gly	Gly	Val	Leu	Asn	Pro	Tyr	Gln	Leu	Thr	Asp	Gln	Phe	
1070															1080
Thr	Ser	Phe	Ala	Lys	Met	Gly	Thr	Gln	Ser	Gly	Phe	Leu	Phe	Tyr	
1085															1095
Val	Pro	Ala	Pro	Tyr	Thr	Ser	Lys	Ile	Asp	Pro	Leu	Thr	Gly	Phe	
1100															1110
Val	Asp	Pro	Phe	Val	Trp	Lys	Thr	Ile	Lys	Asn	His	Glu	Ser	Arg	
1115															1125
Lys	His	Phe	Leu	Glu	Gly	Phe	Asp	Phe	Leu	His	Tyr	Asp	Val	Lys	
1130															1140
Thr	Gly	Asp	Phe	Ile	Leu	His	Phe	Lys	Met	Asn	Arg	Asn	Leu	Ser	
1145															1155
Phe	Gln	Arg	Gly	Leu	Pro	Gly	Phe	Met	Pro	Ala	Trp	Asp	Ile	Val	
1160															1170
Phe	Glu	Lys	Asn	Glu	Thr	Gln	Phe	Asp	Ala	Lys	Gly	Thr	Pro	Phe	
1175															1185
Ile	Ala	Gly	Lys	Arg	Ile	Val	Pro	Val	Ile	Glu	Asn	His	Arg	Phe	
1190															1200
Thr	Gly	Arg	Tyr	Arg	Asp	Leu	Tyr	Pro	Ala	Asn	Glu	Leu	Ile	Ala	

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1205	1210	1215
Leu Leu Glu Glu Lys Gly Ile Val Phe Arg Asp Gly Ser Asn Ile		
1220	1225	1230
Leu Pro Lys Leu Leu Glu Asn Asp Asp Ser His Ala Ile Asp Thr		
1235	1240	1245
Met Val Ala Leu Ile Arg Ser Val Leu Gln Met Arg Asn Ser Asn		
1250	1255	1260
Ala Ala Thr Gly Glu Asp Tyr Ile Asn Ser Pro Val Arg Asp Leu		
1265	1270	1275
Asn Gly Val Cys Phe Asp Ser Arg Phe Gln Asn Pro Glu Trp Pro		
1280	1285	1290
Met Asp Ala Asp Ala Asn Gly Ala Tyr His Ile Ala Leu Lys Gly		
1295	1300	1305
Gln Leu Leu Leu Asn His Leu Lys Glu Ser Lys Asp Leu Lys Leu		
1310	1315	1320
Gln Asn Gly Ile Ser Asn Gln Asp Trp Leu Ala Tyr Ile Gln Glu		
1325	1330	1335
Leu Arg Asn Pro Lys Lys Arg Lys Val Lys Leu Ala Ala Ala		
1340	1345	1350
Leu Glu His His His His His		
1355	1360	

<210> SEQ ID NO 1150
<211> LENGTH: 1307
<212> TYPE: PRT
<213> ORGANISM: Acidaminococcus sp.

<400> SEQUENCE: 1150

Met Thr Gln Phe Glu Gly Phe Thr Asn Leu Tyr Gln Val Ser Lys Thr			
1	5	10	15
Leu Arg Phe Glu Leu Ile Pro Gln Gly Lys Thr Leu Lys His Ile Gln			
20	25	30	
Glu Gln Gly Phe Ile Glu Glu Asp Lys Ala Arg Asn Asp His Tyr Lys			
35	40	45	
Glu Leu Lys Pro Ile Ile Asp Arg Ile Tyr Lys Thr Tyr Ala Asp Gln			
50	55	60	
Cys Leu Gln Leu Val Gln Leu Asp Trp Glu Asn Leu Ser Ala Ala Ile			
65	70	75	80
Asp Ser Tyr Arg Lys Glu Lys Thr Glu Glu Thr Arg Asn Ala Leu Ile			
85	90	95	
Glu Glu Gln Ala Thr Tyr Arg Asn Ala Ile His Asp Tyr Phe Ile Gly			
100	105	110	
Arg Thr Asp Asn Leu Thr Asp Ala Ile Asn Lys Arg His Ala Glu Ile			
115	120	125	
Tyr Lys Gly Leu Phe Lys Ala Glu Leu Phe Asn Gly Lys Val Leu Lys			
130	135	140	
Gln Leu Gly Thr Val Thr Thr Glu His Glu Asn Ala Leu Leu Arg			
145	150	155	160
Ser Phe Asp Lys Phe Thr Thr Tyr Phe Ser Gly Phe Tyr Glu Asn Arg			
165	170	175	
Lys Asn Val Phe Ser Ala Glu Asp Ile Ser Thr Ala Ile Pro His Arg			
180	185	190	

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Ile	Val	Gln	Asp	Asn	Phe	Pro	Lys	Phe	Lys	Glu	Asn	Cys	His	Ile	Phe
195					200				205						
Thr	Arg	Leu	Ile	Thr	Ala	Val	Pro	Ser	Leu	Arg	Glu	His	Phe	Glu	Asn
210					215				220						
Val	Lys	Ala	Ile	Gly	Ile	Phe	Val	Ser	Thr	Ser	Ile	Glu	Glu	Val	
225					230				235						240
Phe	Ser	Phe	Pro	Phe	Tyr	Asn	Gln	Leu	Leu	Thr	Gln	Thr	Gln	Ile	Asp
					245			250							255
Leu	Tyr	Asn	Gln	Leu	Leu	Gly	Gly	Ile	Ser	Arg	Glu	Ala	Gly	Thr	Glu
					260			265							270
Lys	Ile	Lys	Gly	Leu	Asn	Glu	Val	Leu	Asn	Leu	Ala	Ile	Gln	Lys	Asn
					275			280							285
Asp	Glu	Thr	Ala	His	Ile	Ile	Ala	Ser	Leu	Pro	His	Arg	Phe	Ile	Pro
					290			295							300
Leu	Phe	Lys	Gln	Ile	Leu	Ser	Asp	Arg	Asn	Thr	Leu	Ser	Phe	Ile	Leu
					305			310							320
Glu	Glu	Phe	Lys	Ser	Asp	Glu	Glu	Val	Ile	Gln	Ser	Phe	Cys	Lys	Tyr
					325			330							335
Lys	Thr	Leu	Leu	Arg	Asn	Glu	Asn	Val	Leu	Glu	Thr	Ala	Glu	Ala	Leu
					340			345							350
Phe	Asn	Glu	Leu	Asn	Ser	Ile	Asp	Leu	Thr	His	Ile	Phe	Ile	Ser	His
					355			360							365
Lys	Lys	Leu	Glu	Thr	Ile	Ser	Ser	Ala	Leu	Cys	Asp	His	Trp	Asp	Thr
					370			375							380
Leu	Arg	Asn	Ala	Leu	Tyr	Glu	Arg	Arg	Ile	Ser	Glu	Leu	Thr	Gly	Lys
					385			390							400
Ile	Thr	Lys	Ser	Ala	Lys	Glu	Lys	Val	Gln	Arg	Ser	Leu	Lys	His	Glu
					405			410							415
Asp	Ile	Asn	Leu	Gln	Glu	Ile	Ile	Ser	Ala	Ala	Gly	Lys	Glu	Leu	Ser
					420			425							430
Glu	Ala	Phe	Lys	Gln	Lys	Thr	Ser	Glu	Ile	Leu	Ser	His	Ala	His	Ala
					435			440							445
Ala	Leu	Asp	Gln	Pro	Leu	Pro	Thr	Thr	Leu	Lys	Lys	Gln	Glu	Glu	Lys
					450			455							460
Glu	Ile	Leu	Lys	Ser	Gln	Leu	Asp	Ser	Leu	Leu	Gly	Leu	Tyr	His	Leu
					465			470							480
Leu	Asp	Trp	Phe	Ala	Val	Asp	Glu	Ser	Asn	Glu	Val	Asp	Pro	Glu	Phe
					485			490							495
Ser	Ala	Arg	Leu	Thr	Gly	Ile	Lys	Leu	Glu	Met	Glu	Pro	Ser	Leu	Ser
					500			505							510
Phe	Tyr	Asn	Lys	Ala	Arg	Asn	Tyr	Ala	Thr	Lys	Lys	Pro	Tyr	Ser	Val
					515			520							525
Glu	Lys	Phe	Lys	Leu	Asn	Phe	Gln	Met	Pro	Thr	Leu	Ala	Ser	Gly	Trp
					530			535							540
Asp	Val	Asn	Lys	Glu	Lys	Asn	Asn	Gly	Ala	Ile	Leu	Phe	Val	Lys	Asn
					545			550							560
Gly	Leu	Tyr	Tyr	Leu	Gly	Ile	Met	Pro	Lys	Gln	Lys	Gly	Arg	Tyr	Lys
					565			570							575
Ala	Leu	Ser	Phe	Glu	Pro	Thr	Glu	Lys	Thr	Ser	Glu	Gly	Phe	Asp	Lys
					580			585							590
Met	Tyr	Tyr	Asp	Tyr	Phe	Pro	Asp	Ala	Ala	Lys	Met	Ile	Pro	Lys	Cys

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595	600	605
Ser Thr Gln Leu Lys Ala Val Thr Ala His Phe Gln Thr His Thr Thr		
610	615	620
Pro Ile Leu Leu Ser Asn Asn Phe Ile Glu Pro Leu Glu Ile Thr Lys		
625	630	635
Glu Ile Tyr Asp Leu Asn Asn Pro Glu Lys Glu Pro Lys Lys Phe Gln		
645	650	655
Thr Ala Tyr Ala Lys Lys Thr Gly Asp Gln Lys Gly Tyr Arg Glu Ala		
660	665	670
Leu Cys Lys Trp Ile Asp Phe Thr Arg Asp Phe Leu Ser Lys Tyr Thr		
675	680	685
Lys Thr Thr Ser Ile Asp Leu Ser Ser Leu Arg Pro Ser Ser Gln Tyr		
690	695	700
Lys Asp Leu Gly Glu Tyr Tyr Ala Glu Leu Asn Pro Leu Leu Tyr His		
705	710	715
Ile Ser Phe Gln Arg Ile Ala Glu Lys Glu Ile Met Asp Ala Val Glu		
725	730	735
Thr Gly Lys Leu Tyr Leu Phe Gln Ile Tyr Asn Lys Asp Phe Ala Lys		
740	745	750
Gly His His Gly Lys Pro Asn Leu His Thr Leu Tyr Trp Thr Gly Leu		
755	760	765
Phe Ser Pro Glu Asn Leu Ala Lys Thr Ser Ile Lys Leu Asn Gly Gln		
770	775	780
Ala Glu Leu Phe Tyr Arg Pro Lys Ser Arg Met Lys Arg Met Ala His		
785	790	795
Arg Leu Gly Glu Lys Met Leu Asn Lys Lys Leu Lys Asp Gln Lys Thr		
805	810	815
Pro Ile Pro Asp Thr Leu Tyr Gln Glu Leu Tyr Asp Tyr Val Asn His		
820	825	830
Arg Leu Ser His Asp Leu Ser Asp Glu Ala Arg Ala Leu Leu Pro Asn		
835	840	845
Val Ile Thr Lys Glu Val Ser His Glu Ile Ile Lys Asp Arg Arg Phe		
850	855	860
Thr Ser Asp Lys Phe Phe His Val Pro Ile Thr Leu Asn Tyr Gln		
865	870	875
Ala Ala Asn Ser Pro Ser Lys Phe Asn Gln Arg Val Asn Ala Tyr Leu		
885	890	895
Lys Glu His Pro Glu Thr Pro Ile Ile Gly Ile Asp Arg Gly Glu Arg		
900	905	910
Asn Leu Ile Tyr Ile Thr Val Ile Asp Ser Thr Gly Lys Ile Leu Glu		
915	920	925
Gln Arg Ser Leu Asn Thr Ile Gln Gln Phe Asp Tyr Gln Lys Lys Leu		
930	935	940
Asp Asn Arg Glu Lys Glu Arg Val Ala Ala Arg Gln Ala Trp Ser Val		
945	950	955
Val Gly Thr Ile Lys Asp Leu Lys Gln Gly Tyr Leu Ser Gln Val Ile		
965	970	975
His Glu Ile Val Asp Leu Met Ile His Tyr Gln Ala Val Val Val Leu		
980	985	990
Glu Asn Leu Asn Phe Gly Phe Lys Ser Lys Arg Thr Gly Ile Ala Glu		
995	1000	1005

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Lys Ala Val Tyr Gln Gln Phe Glu Lys Met Leu Ile Asp Lys Leu
 1010           1015           1020

Asn Cys Leu Val Leu Lys Asp Tyr Pro Ala Glu Lys Val Gly Gly
 1025           1030           1035

Val Leu Asn Pro Tyr Gln Leu Thr Asp Gln Phe Thr Ser Phe Ala
 1040           1045           1050

Lys Met Gly Thr Gln Ser Gly Phe Leu Phe Tyr Val Pro Ala Pro
 1055           1060           1065

Tyr Thr Ser Lys Ile Asp Pro Leu Thr Gly Phe Val Asp Pro Phe
 1070           1075           1080

Val Trp Lys Thr Ile Lys Asn His Glu Ser Arg Lys His Phe Leu
 1085           1090           1095

Glu Gly Phe Asp Phe Leu His Tyr Asp Val Lys Thr Gly Asp Phe
 1100           1105           1110

Ile Leu His Phe Lys Met Asn Arg Asn Leu Ser Phe Gln Arg Gly
 1115           1120           1125

Leu Pro Gly Phe Met Pro Ala Trp Asp Ile Val Phe Glu Lys Asn
 1130           1135           1140

Glu Thr Gln Phe Asp Ala Lys Gly Thr Pro Phe Ile Ala Gly Lys
 1145           1150           1155

Arg Ile Val Pro Val Ile Glu Asn His Arg Phe Thr Gly Arg Tyr
 1160           1165           1170

Arg Asp Leu Tyr Pro Ala Asn Glu Leu Ile Ala Leu Leu Glu Glu
 1175           1180           1185

Lys Gly Ile Val Phe Arg Asp Gly Ser Asn Ile Leu Pro Lys Leu
 1190           1195           1200

Leu Glu Asn Asp Asp Ser His Ala Ile Asp Thr Met Val Ala Leu
 1205           1210           1215

Ile Arg Ser Val Leu Gln Met Arg Asn Ser Asn Ala Ala Thr Gly
 1220           1225           1230

Glu Asp Tyr Ile Asn Ser Pro Val Arg Asp Leu Asn Gly Val Cys
 1235           1240           1245

Phe Asp Ser Arg Phe Gln Asn Pro Glu Trp Pro Met Asp Ala Asp
 1250           1255           1260

Ala Asn Gly Ala Tyr His Ile Ala Leu Lys Gly Gln Leu Leu Leu
 1265           1270           1275

Asn His Leu Lys Glu Ser Lys Asp Leu Lys Leu Gln Asn Gly Ile
 1280           1285           1290

Ser Asn Gln Asp Trp Leu Ala Tyr Ile Gln Glu Leu Arg Asn
 1295           1300           1305

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<400> SEQUENCE: 1152

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<400> SEQUENCE: 1153

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<400> SEQUENCE: 1154

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cuggu 65

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Molecule: Synthetic oligonucleotide"

<400> SEQUENCE: 1156

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<220> FEATURE:	
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
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<212> TYPE: DNA	
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic oligonucleotide"	
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<221> NAME/KEY: source	
<223> OTHER INFORMATION: /note="Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide"	
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Molecule: Synthetic oligonucleotide"

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<400> SEQUENCE: 1163
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Molecule: Synthetic oligonucleotide"

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<210> SEQ ID NO 1166
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<212> TYPE: DNA
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<400> SEQUENCE: 1167
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<210> SEQ ID NO 1168
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<212> TYPE: DNA
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<210> SEQ ID NO 1170
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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Molecule: Synthetic oligonucleotide"

<400> SEQUENCE: 1170

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<210> SEQ ID NO 1171

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<212> TYPE: DNA

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<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Combined DNA/RNA
Molecule: Synthetic oligonucleotide"

<400> SEQUENCE: 1171

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<210> SEQ ID NO 1172

<211> LENGTH: 66

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Combined DNA/RNA
Molecule: Synthetic oligonucleotide"

<400> SEQUENCE: 1172

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caccug 66

<210> SEQ ID NO 1173

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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1173

tgatgtgaga tttccacct g 21

<210> SEQ ID NO 1174

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<221> NAME/KEY: source

<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 1174

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aaagcacgta acgatcacta caaagaactg aaaccgatta tcgaccgcat ctataaaacc	180
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aaaaaaaaaccc gtgatcagaa aggttatcgt gaagcgctgt gtaaatggat tgatttcacc	2040
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catgcagcac cgcctaaaaa gaaacgtaaa gtt	3993

1. A method of inducing antibody-dependent cell-mediated cytotoxicity (ADCC) of a cancer cell, the method comprising contacting the cancer cell with a modified natural killer (NK) cell and an antibody, or an antigen-binding portion thereof, wherein the modified NK cell exhibits a loss of function of transforming growth factor beta receptor 2 (TGF β R2) and cytokine inducible SH2 containing protein (CISH), thereby inducing ADCC of the cancer cell.

2. The method of claim 1, wherein the contacting is in a subject.

3. A method of treating cancer in a subject, the method comprising administering to a subject a modified natural killer (NK) cell and an antibody, or an antigen-binding portion thereof, wherein the modified NK cell exhibits a loss of function of transforming growth factor beta receptor 2 (TGF β R2) and cytokine inducible SH2 containing protein (CISH), wherein the administering induces ADCC of a cancer cell in the subject, thereby treating the cancer in the subject.

4. The method of claim 3, wherein the administering (a) increases ADCC by at least about 20%, at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 2-fold, at least about 5-fold or at least about 10-fold as compared to ADCC of a cancer cell using an unmodified NK cell and the antibody; (b) decreases tumor volume in the subject by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% by about 10 days or about 20 days after administering, and optionally wherein the administering decreases tumor volume in the subject for at least about 10 days, at least about 20 days, at least about 30 days, or at least about 40 days after the administering; and/or (c) increases the survival time of the subject.

5-8. (canceled)

9. The method of claim 1, wherein the contacting is in vitro.

10. The method of claim 9, wherein the modified NK cell comprises (a) an increase in level of TNF α by at least about two fold as compared to a control level expression of TNF α , optionally wherein the control level of TNF α is a level of TNF α produced by an unmodified NK cell under the same conditions; (b) an increase in level of IFN γ by at least about two fold as compared to a control level expression of IFN γ , optionally wherein the control level of IFN γ is a level of IFN γ produced by an unmodified NK cell under the same conditions; (c) an increase in level of a cytolytic granule by at least about two fold as compared to a control level expression of the cytolytic granule, optionally wherein the cytolytic granule is selected from the group consisting of GZMB, GZMA and GZMH, optionally wherein the control level of cytolytic granule is a level of cytolytic granule produced by an unmodified NK cell under the same conditions; (d) an increase in production rate of a cytolytic granule by at least about two fold as compared to a control production rate of the cytolytic granule, wherein the cytolytic granule is selected from the group consisting of GZMB, GZMA and GZMH, optionally wherein the control production rate of cytolytic granule is a production rate of cytolytic granule by an unmodified NK cell under the same conditions; (e) an increase in level of CD107a by at least about two fold as compared to a control level expression of CD107a, optionally wherein the control level of CD107a is a level of CD107a in an unmodified NK cell under the same

conditions: (f) a decrease in normalized total integrated red object intensity in a tumor spheroid assay by at least about 20% as compared to a control level of normalized total integrated red object intensity, wherein the control level of normalized total integrated red object intensity is a level of normalized total integrated red object intensity produced using an unmodified NK cell under the same conditions; (g) an increase in cytotoxicity activity under a nutrient-depriving condition by at least about 20% as compared to a control level of cytotoxicity activity, optionally wherein the control level of cytotoxicity activity is a cytotoxicity level of an unmodified NK cell under the same conditions; and/or (h) an increase in spare respiratory capacity by at least 20% as compared to a control level of spare respiratory capacity, optionally wherein the control level of spare respiratory capacity is a level of spare respiratory capacity of an unmodified NK cell under the same conditions.

11-25. (canceled)

26. The method of claim 3, wherein the antibody, or antigen-binding portion thereof, binds an antigen on the cancer cell.

27. The method of claim 26, wherein the antigen on the cancer cell is epidermal growth factor receptor (EGFR), HER2, CD20, PD-L1, PD-1 (PEMBRO and NIVO), CTLA-4 (IPI), CD73, or TIGIT.

28. The method of claim 27, wherein the antibody is cetuximab,

rituximab, or trastuzumab, or an antigen-binding portion thereof.

29. The method of claim 3, wherein the modified NK cell is administered concurrently with the antibody, or the antigen-binding portion thereof.

30. The method of claim 3, wherein the antibody, or antigen-binding portion thereof, is administered prior to the modified NK cell, or wherein the modified NK cell is administered prior to the antibody, or the antigen-binding portion thereof.

31. The method of claim 3, wherein the cancer cell is a head and neck cancer cell, breast cancer cell, colorectal cancer cell, gastric cancer cell, renal cell carcinoma (RCC) cell, non-small cell lung cancer (NSCLC) cell, solid tumor cell, bladder cancer cell, hepatocellular carcinoma cell, prostate cancer cell, ovarian/uterine cancer cell, pancreatic cancer cell, mesothelioma cell, melanoma cell, glioblastoma cell, cervical cancer cell, oral cavity cancer cell, cancer of the pharynx, thyroid cancer cell, gallbladder cancer cell, soft tissue sarcoma, or a hematological cancer cell.

32. The method of claim 1, wherein the antibody, or antigen-binding portion thereof, binds an antigen on the cancer cell.

33. The method of claim 32, wherein the antigen on the cancer cell is epidermal growth factor receptor (EGFR), HER2, CD20, PD-L1, PD-1 (PEMBRO and NIVO), CTLA-4 (IPI), CD73, or TIGIT.

34. The method of claim 33, wherein the antibody is cetuximab, rituximab,

or trastuzumab, or an antigen-binding portion thereof.

35. The method of claim 1, wherein the cancer cell is a head and neck cancer cell, breast cancer cell, colorectal cancer cell, gastric cancer cell, renal cell carcinoma (RCC) cell, non-small cell lung cancer (NSCLC) cell, solid tumor cell, bladder cancer cell, hepatocellular carcinoma cell, prostate cancer cell, ovarian/uterine cancer cell, pancreatic cancer cell, mesothelioma cell, melanoma cell, glioblastoma

cell, cervical cancer cell, oral cavity cancer cell, cancer of the pharynx, thyroid cancer cell, gallbladder cancer cell, soft tissue sarcoma, or a hematological cancer cell.

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