METHODS FOR ENHANCING ANTIBODY-INDUCED CELL LYSIS AND TREATING CANCER

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ABSTRACT

The invention relates to methods and products for treating cancer. In particular the invention relates to combinations of nucleic acids and antibodies for the treatment and prevention of cancer. The invention also relates to diagnostic methods for screening cancer cells.

4 Claims, 6 Drawing Sheets
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Fig. 2
Fig. 4
Fig. 6
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METHODS FOR ENHANCING
ANTIBODY-INDUCED CELL LYSIS AND
TREATING CANCER

PRIORITY

This application claims the benefit of U.S. Provisional Application No. 60/213,346, filed Jun. 22, 2000.

FIELD OF THE INVENTION

The invention relates to the treatment and prevention of cancer using immunostimulatory nucleic acids and antibodies.

BACKGROUND OF THE INVENTION

Cancer is the second leading cause of death, resulting in one out of every four deaths in the United States. In 1997, the estimated total number of new diagnoses for lung, breast, prostate, colorectal and ovarian cancer was approximately two million. Due to the ever increasing aging population in the United States, it is reasonable to expect that rates of cancer incidence will continue to grow.

Cancer is a disease which involves the uncontrolled growth (i.e., division) of cells. Some of the known mechanisms which contribute to the uncontrolled proliferation of cancer cells include growth factor independence, failure to detect genomic mutation, and inappropriate cell signaling. The ability of cancer cells to ignore normal growth controls may result in an increased rate of proliferation. Although the causes of cancer have not been firmly established, there are some factors known to contribute, or at least predispose a subject, to cancer. Such factors include particular genetic mutations (e.g., BRCA gene mutation for breast cancer, APC for colon cancer), exposure to suspected cancer-causing agents, or carcinogens (e.g., asbestos, UV radiation) and familial disposition for particular cancers such as breast cancer.

Cancer is currently treated using a variety of modalities including surgery, radiation therapy and chemotherapy. The choice of treatment modality will depend upon the type, location and dissemination of the cancer. For example, surgery and radiation therapy may be more appropriate in the case of solid well-defined tumor masses and less practical in the case of non-solid tumor cancers such as leukemia and lymphoma. One of the advantages of surgery and radiation therapy is the ability to control to some extent the impact of the therapy, and thus to limit the toxicity to normal tissues in the body. However, surgery and radiation therapy are often followed by chemotherapy to guard against any remaining or radio-resistant cancer cells. Chemotherapy is also the most appropriate treatment for disseminated cancers such as leukemia and lymphoma as well as metastases.

More recently, the use of CpG containing nucleic acids has been proposed for the treatment and prevention of cancer. We have found that unmethylated CG-dinucleotides within certain sequence contexts (CpG DNA) are recognized by the vertebrate immune system as foreign DNA (bacterial or viral). CpG DNA activates a coordinated set of immune responses that include innate immunity (macrophages, dendritic cells, and natural killer cells), humoral immunity, and cellular immunity. Krieg A M et al., Pharmacol Ther 84:113-20 (1999); Krieg A M et al., Curr Top Microbiol Immunol 247:1-21 (2000); Wagner H, Adv Immunol 73:329-68 (1999).


SUMMARY OF THE INVENTION

The invention relates in some aspects to methods for treating and preventing cancer using immunostimulatory nucleic acids and antibodies. Thus in one aspect the invention is a method for treating or preventing cancer. The method involves administering to a subject having or at risk of developing cancer an effective amount to upregulate CD20 expression of a nucleic acid, and an anti-CD20 antibody. The cancer, in some embodiments, is B-cell lymphoma associated with low levels of CD20 expression. The B-cell lymphoma in other embodiments is B-cell chronic lymphocytic leukemia (B-CLL) or a marginal zone lymphoma. In some embodiments the CD20 antibody is C2B8 or Rituximab.

The invention in other aspects relates to a method for diagnosing lymphoma by isolating a B cell from a subject and identifying a change in cell surface markers when the B cell is contacted with an immunostimulatory nucleic acid, wherein the cell surface marker induced on the B cell is indicative of the type of lymphoma. In some embodiments the subject has a type of lymphoma. In some embodiments the subject is suspected of having a type of lymphoma. The method may optionally include a method for treating cancer by administering to the subject an immunostimulatory nucleic acid and an antibody specific for the cell surface antigens induced on the B cell in order to treat the cancer.

In another aspect the invention is a method for treating or preventing cancer by administering to a subject having or at risk of developing cancer an effective amount to induce expression of a surface antigen on a cancer cell surface, of a nucleic acid, and administering to the subject an antibody selected from the group consisting of an anti-CD22 antibody and an anti-CD19 antibody.

According to another aspect of the invention, a method for treating lymphoma is provided. The method includes the steps of isolating a B cell from a subject having lymphoma, identifying a surface antigen which is not expressed or which is expressed on the surface of the B cell in an amount lower than that of a control B cell, administering to the subject an antibody specific for the identified surface antigen and an immunostimulatory nucleic acid in order to treat the lymphoma, wherein the nucleic acid is administered in an effective amount to upregulate expression of the surface antigen on the lymphoma cell surface.

A method for treating a lymphoma resistant to antibody therapy is provided according to another aspect of the invention. The method includes administering to a subject having a lymphoma resistant to therapy with an antibody specific for a surface antigen, an antibody specific for the surface antigen to which the lymphoma is resistant and a nucleic acid in order to treat the lymphoma, wherein the nucleic acid is administered in an effective amount to upregulate expression of the surface antigen on the lymphoma cell surface.

The surface antigen may be any type of surface antigen which is capable of being expressed on the surface of a cancer cell and which is induced by stimulation with immunostimulatory nucleic acids. In some embodiments the surface antigen is CD20, CD40, CD22, or CD19. In other embodiments the lymphoma is B-CLL or marginal zone lymphoma. In
some embodiments the antibody is an anti-CD20 antibody. In some embodiments the anti-CD20 antibody is C2B8. In another embodiment the anti-CD20 antibody is Rituximab.

In some preferred embodiments the antibody is a human IgG1 antibody. In some preferred embodiments the antibody is a murine IgG2a antibody.

In some embodiments the methods also include administering an anti-cancer therapy to the subject.

The invention also includes a method for treating cancer in a human by administering to a human an immunostimulatory nucleic acid and an antibody of IgG1 isotype (an IgG1 isotype antibody as used herein refers to a human or humanized IgG1 unless otherwise specified), which binds to a cell surface antigen of a cancer cell and wherein the nucleic acid and the antibody are administered in an effective amount for killing the cancer cell.

Optionally the nucleic acid and the antibody are administered together. Alternatively the nucleic acid and the antibody may be administered separately.

In some embodiments the method includes the step of administering a cancer therapy. As used herein the term “a cancer therapy” is meant to include a single medication, a plurality of medications of a particular class and a plurality of medications of different classes, and includes but is not limited to chemotherapeutic agents, cancer vaccines, biological response modifiers, and hormone therapies.

A chemotherapeutic agent may be selected from the group consisting of methotrexate, vincristine, adriamycin, cisplatin, non-sugar containing chlorothiazolinhydrasoureas, 5-fluorouracil, mitomycin C, bleomycin, doxorubicin, dacarbazine, taxol, frajayl, Megalamine GLA, valrubicin, carmustine and poliferposan, MM1270, BAY 12-9566, RAS famesyl transferase inhibitor, famesyl transferase inhibitor, MMF, MTX1L231514, LY2646181 (lonetoxol), Glomilase, CI-994, TNK-470, Hyacint/Topotecan, PKC412, Valspodar/PS833, Noveltrane/Mitoxantrone, Metureset/Stranim, Butinast, E7070, BCI-4556, CS-68, 9-AC, AG3340, AG3433, Incel/VX-710, VX-853, ZD1001, ISEL61, ODN 698, TA 2516/Marmist, BB2516/Marmist, CDP 485, D2163, PD183805, DX951f, Lemonal DP 2200, FK 317, Picibanil/OK-432, AD 32/Valrubin, Metustrom/stromium derivative, Temodal/Temozolomide, Evacet/leptomosol doxorubicin, Yewtaxan/Paclitaxel, Taxol/Paclitaxel, Xelodal/Carboplatin, Pauplor/Docetaxel, Cyclopa/porc plactaxel, Oral Taxoid, SPU-077/Cisplatin, HMR 1275/Flavopiridol, CP-358 (774)/EGFR, CP-609 (754)/RAS oncogene inhibitor, BMS-12175/oral platinum, UFT (Tegafur/Uracil), Eragamilis/Levamisole, Eniluracil/77685/5FU enhancer, Camptor/Levamisole, Camptosar/Topotecan, Tumodex/Ralithrexed, Leustatin/Cadribine, Pafox/Paclitaxel, Doxil/leptomosol doxorubicin, Caelyx/leptomosol doxorubicin, Fludara/Fludarabine, Pharmarubicin/Epirubicin, DepoCyt, ZD1839, LU 79553/Bis-Naplatamid, LU 103793/Dolastain, Caelyx/leptomosol doxorubicin, Genzar/Gemcitabine, ZD 0473/Anonorn, YM 116, Iodine seeds, CDK4 and CDK2 inhibitors, PARP inhibitors, D4809/Docisamide, Iles/Mesnix/Ipamose, Yumon/Tenoseide, Paraplatin/Carboplatin, Plantinol/Cisplatin, Vepeside/Etoposide, ZD 9331, Taxotere/Doxetaxel, prodrug of gynanarabino side, Taxane Analog, nitrosoureas, alkylating agents such as Melphalan, Cyclophosphamide, Aminoglutethimide, Asparaginase, Busulfan, Carboplatin, Chlorambucil, Cytra bare HCl, Daunorubicin HCl, Eastramustine phosphate sodium, Etoposide (VP 16-213), Flurixuridine, Fluorouracil (5-FU), Flutamide, Hydroxyurea (hydroxy carbamide), Iosamide, Interferon Alfa-2a, Interferon Alfa-2b, Leuprolide acetate (LHRH-releasing factor analog), Lomustine (CCNU), Methotrexatine HCl (nitrogen mustard), Mercaptopurine, Methylchloretamine (m-DDD), Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl, Streptozocin, Tamoxifen citrate, Thioguanine, Thiopeta, Vinblastine sulfate, Amsacrine (m-AMS), Azacamidine, Erythropoetin, Hexanamthylmelamine (HMM), Interleukin 2, Mitoguazone (methyl-GAG; methyl glyoxal bis-guanlylyl- drazo; MGB-9), Pentostatin (2'-deoxycoformycin), Semustine (methyl-CCNU), Teniposide (VM-26) and Vindesine sulfate.

In some preferred embodiments the chemotherapeutic agent may be selected from the group consisting of methotrexate, vincristine, adriamycin, cisplatin, mitomycin C, bleomycin, doxorubicin, dacarbazine, taxol, valrubicin, Novantrone/Mitoxantrone, Evacet/leptomosol doxorubicin, Yewtaxan/Paclitaxel, Taxol/Paclitaxel, SPU-077/Cisplatin, HMR 1275/Flavopiridol, BMS-12175/oral platinum, Leustatin/Cadribine, Pafox/Paclitaxel, Doxil/leptomosol doxorubicin, Caelyx/leptomosol doxorubicin, Fludara/Fludarabine, Pharmarubicin/Epirubicin, DepoCyt, Caelyx/leptomosol doxorubicin, Genzar/Gemcitabine, Iles/Mesnix/Ipos amide, Yumon/Tenoseide, Paraplatin/Carboplatin, Plantinol/Cisplatin, Vepeside/Etoposide, Taxotere/Doxetaxel, prodrug of gynanarabino side, nitrosoureas, alkylating agents such as melphalan and cyclophosphamide, Asparaginase, Busulfan, Carboplatin, Chlorambucil, Cyto rine HCl, Daunorubicin HCl, Etoposide (VP16-213), Hydroxyurea (hydroxy carbamide), Iosamide, Interferon Alfa-2a, Interferon Alfa-2b, Lomustine (CCNU), Methotrexatine HCl (nitrogen mustard), Mercaptopurine, Mitoxantrone HCl, Procarbazine HCl, Thioguanine, Thiopeta, Vinblastine sulfate, Azacamidine, Interleukin 2, Pentostatin (2'-deoxycoformycin), Teniposide (VM-26), GM-CSF, and Vindesine sulfate.

A cancer vaccine may be selected from the group consisting of EGF, Anti-idiotypic cancer vaccines, Sp57 antigen, GMK melanoma vaccine, MGV ganglioside conjugate vaccine, Her2/neu, Ovarex, M-Vax, O-Vax, L-Vax, STn-KHL therope, BLP25 (MUC-1), liposomal idiotypic vaccine, Melicine, peptide antigen vaccines, toxinn/antigen vaccines, MVA-based vaccine, PACIS, BCG vaccine, TA-HPV, TA-CIN, DISC-virus and Immucys/ThermCys. Biological response modifiers include interferon, and lymphokines such as IL-2, and thymic hormone-thyroid replacement therapy includes tamoxifen alone or in combination with progesterone. In a further embodiment, the cancer therapy is interferon-alpha (e.g., INTRON® A, Schering).

The cancer may be selected from the group consisting of basal cell carcinoma, bladder cancer, bone cancer, brain and central nervous system (CNS) cancer, breast cancer, cervical cancer, colon and rectum cancer, connective tissue cancer, esophageal cancer, eye cancer, kidney cancer, larynx cancer, leukemia, liver cancer, lung cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, melanoma, myeloma, oral cavity cancer (e.g., lip, tongue, mouth, and pharynx), ovarian cancer, pancreatic cancer, prostate cancer, rhabdomyosarcoma, skin cancer, stomach cancer, testicular cancer, and uterine cancer. In preferred embodiments, the cancer to be treated may be selected from the group consisting of bone cancer, brain and CNS cancer, connective tissue cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer (e.g., lip, tongue, mouth, and pharynx), skin cancer, and testicular cancer.

In another aspect the invention encompasses a kit. The kit includes a package including at least two containers, the first container housing an immunostimulatory nucleic acid, the second container housing an antibody specific for a cell surface antigen, and instructions for screening a cell to determine
whether the immunostimulatory nucleic acid upregulates expression of the cell surface antigen. In one embodiment the antibody is selected from the group consisting of an anti-CD20 antibody, an anti-CD19 antibody, and an anti-CD22 antibody.

The nucleic acids useful according to the invention are immunostimulatory nucleic acids and in some embodiments are immunostimulatory CpG nucleic acids having an unmethylated CpG motif, immunostimulatory T-rich nucleic acids, immunostimulatory poly-G nucleic acids, bacterial DNA, yeast DNA, or eukaryotic DNA.

In some embodiments the nucleic acid does not hybridize with genomic DNA or RNA under stringent conditions. In other embodiments the nucleic acid does hybridize with genomic DNA or RNA under stringent conditions.

The nucleic acid may have natural linkages or may include at least one modified backbone internucleotide linkage. In some embodiments the modified backbone is a phosphate backbone modification. In other embodiments the modified backbone is a peptide modified oligonucleotide backbone. The nucleic acid may also include native bases or modified bases. The nucleotide backbone may be chimeric, or the nucleotide backbone is entirely modified.

The immunostimulatory nucleic acid can have any length greater than 6 nucleotides, but in some embodiments is between 8 and 100 nucleotide residues in length. In other embodiments the nucleic acid comprises at least 20 nucleotides, at least 24 nucleotides, at least 27, nucleotides, or at least 30 nucleotides. The nucleic acid may be single-stranded or double-stranded. In some embodiments the nucleic acid is isolated and in other embodiments the nucleic acid may be a synthetic nucleic acid.

The CpG nucleic acid in one embodiment contains at least one unmethylated CpG dinucleotide having a sequence including at least the following formula: 5'X1GX2X3' wherein G is unmethylated, where X1, X2, X3, and X4 are nucleotides. In one embodiment the 5'X1GX2X3X4' sequence of the CpG nucleic acid is a non-palindromic sequence, and in other embodiments it is a palindromic sequence.

In some embodiments X1, X2, are nucleotides selected from the group consisting of: GpG, GpA, ApA, ApT, ApG, CpT, CpA, GpG, TpA, TpT, and TpG; and X1, X2, X3, and X4 are nucleotides selected from the group consisting of: TpT, Cpt, ApT, TpG, GpG, Cpc, Tpc, ApA, and ApG. In other embodiments X1, X2, and X3, or both are purines and X4, or X4, or both are pyrimidines or X1, X2, are GpA and X3, or X4, or both are purines. In one embodiment X1, X2, are A and X3, is a pyrimidine.


In some embodiments the T-rich immunostimulatory nucleic acid is a poly-T nucleic acid comprising 5'TTTT3'. In yet other embodiments the poly-T nucleic acid comprises 5'X1X2X3X4' wherein X1, X2, X3, and X4 are nucleotides. In some embodiments X1, X2, is TT and/or X3, X4, is TT. In other embodiments X1, X2, is selected from the group consisting of: TA, TG, TC, AT, AA, AG, AC, CT, CC, CA, CG, GT, GG, GA, and GC; and/or X3, X4, is selected from the group consisting of: TA, TG, TC, AT, AA, AG, AC, CT, CC, CA, CG, GT, GG, GA, and GC.

The T-rich immunostimulatory nucleic acid may have only a single poly-T motif or it may have a plurality of poly-T nucleic acid motifs. In some embodiments the T-rich immunostimulatory nucleic acid comprises at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 T nucleotides. In other embodiments it comprises at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 CpG motifs. In some embodiments the plurality of CpG motifs and poly-T motifs are interpersed.

In yet other embodiments at least one of the plurality of poly-T motifs comprises at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, or at least 9 contiguous T nucleotide residues. In other embodiments the plurality of poly-T motifs is at least 3 motifs and wherein at least 3 motifs each comprises at least 3 contiguous T nucleotide residues or the plurality of poly-T motifs is at least 4 motifs and wherein at least 4 motifs each comprises at least 3 contiguous T nucleotide residues.

The T-rich immunostimulatory nucleic acid may include one or more CpG motifs. In other embodiments the T-rich immunostimulatory nucleic acid is free of one or more CpG dinucleotides.

In other embodiments the T-rich immunostimulatory nucleic acid has poly A, poly-G, and/or poly C motifs. In other embodiments the T-rich immunostimulatory nucleic acid is free of two poly G sequences of at least 3 contiguous G nucleotide residues. Preferably the T-rich immunostimulatory nucleic acid is free of two poly A sequences of at least 3 contiguous A nucleotide residues. In other embodiments the T-rich immunostimulatory nucleic acid comprises a nucleotide composition of greater than 25% C or greater than 25% A. In yet other embodiments the T-rich immunostimulatory nucleic acid is free of poly-C sequences, poly-G sequences or poly-A sequences.

In some embodiments the T-rich immunostimulatory nucleic acid may be free of poly-T motifs, but rather, comprises a nucleotide composition of greater than 25% T. In other embodiments the T-rich immunostimulatory nucleic acid may have poly-T motifs and also comprises a nucleotide composition of greater than 25% T. In some embodiments the T-rich immunostimulatory nucleic acid comprises a nucleotide composition of greater than 25% T, greater than 30% T, greater than 40% T, greater than 50% T, greater than 60% T, greater than 80% T, or greater than 90% T nucleotide residues.

In some embodiments the poly-G nucleic acid comprises: 5'X1X2GGGX3X4' wherein X1, X2, X3, and X4 are nucleotides. In embodiments at least one of X1, X2, or both of X3, X4, are G. In other embodiments the poly-G nucleic acid comprises the following formula: 5'GGNXGGG3' wherein N represents between 0 and 20 nucleotides. In yet other embodiments the poly-G nucleic acid comprises the following formula: 5'GGNGGGG3' (SEQ ID NO:849) wherein N represents between 0 and 20 nucleotides.

The poly-G immunostimulatory nucleic acid may include one or more CpG motifs or T-rich motifs. In other embodiments the poly-G nucleic acid is free of one or more CpG dinucleotides or poly-T motifs.

Each of the limitations of the invention can encompass various embodiments of the invention. It is, therefore, anticipated that each of the limitations of the invention involving any one element or combinations of elements can be included in each aspect of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts data from flow cytometry which demonstrates the induction of a morphologic change in marginal
zone lymphoma cells upon CpG oligonucleotide stimulation. Malignant B cells from a patient with marginal zone lymphoma were stimulated with no oligonucleotide (A and D), control oligonucleotide (ODN 2017, SEQ ID NO: 168, B and E) or CpG oligonucleotide (ODN 2006, SEQ ID NO: 729, C and F) and analyzed by flow cytometry. A, B, and C illustrate forward scatter (FSC; x-axis) vs. side scatter (SSC; y-axis), D, E and F illustrate CD19 expression (x-axis) against FSC (y-axis).

FIG. 2 depicts data from flow cytometry which demonstrates the change in expression of surface antigens on marginal zone lymphoma cells upon CpG oligodeoxynucleotide (ODN) treatment. Flow cytometric analysis of surface antigen expression on malignant B cells from a patient with marginal zone lymphoma was performed using either CpG or non-CpG oligonucleotide. Thin curves indicate incubation with medium alone, dotted curves indicate incubation with control oligonucleotide, and bold curves indicate incubation with CpG oligonucleotide.

FIG. 3 is a set of bar graphs depicting changes in expression of surface antigens on primary cells representing different B-cell malignancies and cells of a benign follicular hyperplasia upon treatment with, from left to right in each panel: negative control, no oligonucleotide, control oligonucleotide (ODN 2017, SEQ ID NO: 168), or CpG oligonucleotide (ODN 2006, SEQ ID NO: 729). Each panel represents one experiment.

FIG. 4 is a set of graphs depicting the observation that the effect of CpG oligonucleotide on CD20 (top) and CD40 (bottom) is dependent on the baseline level of expression of CD20 and CD40. Cells from lymph node biopsies, peripheral blood or pleural fluid from patients with different B-cell malignancies were incubated with or without CpG oligonucleotide, and expression of CD20 and CD40 was measured by flow cytometry.

FIG. 5 depicts data from flow cytometry which demonstrates the effect of CpG oligonucleotide-induced proliferation of malignant and normal B cells. Peripheral blood mononuclear cells from patients with B-CLL (left) or marginal zone lymphoma with circulating malignant cells (right), were incubated with CpG oligonucleotide (bottom) or medium alone (top) and evaluated by two-color flow cytometry. CFSE fluorescence (x-axis) and expression of CD5 (B-CLL) or CD19 (marginal zone lymphoma) (y-axis) were evaluated.

FIG. 6 is a graph depicting the survival of mice injected on Day 0 with tumor cells in response to CpG stimulation in combination with murine IgG2a and murine IgG1 anti-tumor antibodies. Treatments are shown as filled squares, untreated controls; filled circles, murine IgG1; filled triangles, murine IgG1 plus CpG; filled diamonds, murine IgG2a; and open squares, murine IgG2a plus CpG.

DETAILED DESCRIPTION

Present cancer treatments are often ineffective as well as being associated with a high degree of patient morbidity. The invention provides methods and products for the more effective treatment of cancer using a combination of immunostimulatory nucleic acids, antibodies, and optionally cancer therapies.

The invention is based, in part, on the surprising discovery that administration to a subject of immunostimulatory nucleic acids induces the expression of cell surface antigens including CD20, CD19, and CD22 on the surface of a cancer cell and that the induction of these antigens leads to enhanced antibody-dependent cellular cytotoxicity (ADCC). It was previously believed that CpG oligonucleotides enhanced ADCC by influencing the effector cell (e.g., by activating natural killer (NK) cells). Now it has been discovered according to the invention that immunostimulatory nucleic acids actually cause the induction of specific antigens CD20, CD19, and CD22, each of which can be targeted by specific antibody therapies. The discovery that immunostimulatory nucleic acids are capable of upregulating expression of certain target antigens on the surface of cancer cells, supports the development of therapies using immunostimulatory nucleic acids in combination with specific antibodies which interact with these cell surface antigens. Thus, in one aspect, the invention provides a method for treating or preventing cancer which involves the administration to a subject of a combination of an immunostimulatory nucleic acid and an antibody which specifically interacts with CD20, CD19, and CD22 in an effective amount to prevent or treat the cancer.

Additionally, it was discovered that the increased expression of these and other cell surface antigens varies widely depending upon the histological state of the tumor cell studied. The effect of immunostimulatory nucleic acids on different types of primary malignant B cells and reactive follicular hyperplasia was extensively examined. All B-cell lymphoma cells tested increased in size and granularity, upregulated activation markers (CD80, CD86, CD40, CD54, CD69), and upregulated antigen presentation molecules (class I major histocompatibility complex (MHC I), class II major histocompatibility complex (MHC II)) in response to immunostimulatory nucleic acids. A control poly-C oligodeoxynucleotide (ODN) showed only minor effects. The extent of phenotypic change induced by immunostimulatory nucleic acids differed from sample to sample. Immunostimulatory nucleic acids, but not control nucleic acids, increased the expression of co-stimulatory molecules (e.g., CD40, CD80, CD86, CD54) on malignant B cells without altering the phenotype of B cells derived from reactive follicular hyperplasia. Immunostimulatory nucleic acids also increased expression of both class I and class II MHC in most samples. CD20 expression was increased in response to immunostimulatory nucleic acids, most notably in B-CLL and marginal zone lymphoma.

Furthermore, an inverse correlation was found between baseline expression of specific cell surface antigens and their expression after exposure to immunostimulatory nucleic acids. Thus the most significant increase in expression of these molecules was found in those samples that had the lowest (or no) baseline levels. These data indicate that immunostimulatory nucleic acids may reverse low expression of co-stimulatory molecules on malignant B cells that correspond to a low level of activation, while their effects on cells that are already in an activated state are less profound.

Thus, the invention relates to methods for identifying an appropriate therapy for a lymphoma patient, and for treating the patient using that therapy. The method can be accomplished by isolating a B cell from a lymphoma patient and comparing the surface antigens expressed on the malignant B cell with those expressed on normal B cells. The antigens which are expressed in low levels or not at all on the malignant B cell can be identified. The subject can then be treated using a combination of an immunostimulating nucleic acid and an antibody which specifically recognizes the antigen(s) which are expressed in low levels or not at all on the malignant B cell.

The invention is also useful for treating cancers which are resistant to monoclonal antibody therapy. It has been discovered according to the invention, that immunostimulatory nucleic acids can reverse the resistance of tumor cells and render tumor cells which were previously non-responsive or
only weakly responsive, sensitive to therapy. In particular it has been discovered that immunostimulatory nucleic acids can cause a phenotypic change to a resistant tumor cell that renders it sensitive to monoclonal antibody therapy. For instance, the monoclonal anti-CD20 antibody Rituximab has been shown to be effective clinically in several trials and has recently been approved for the therapy of follicular B cell lymphoma. Maloney D G, *Semin Oncol* 26:74-8 (1999); Foran J M et al., *J Clin Oncol* 18:317-24 (2000); Witzig T E et al., *J Clin Oncol* 17:3793-805 (1999); Davis T A et al., *J Clin Oncol* 17:1851-7 (1999); Wiseman G A et al., *Clin Cancer Res* 5:3281s-3286s (1999); Grillo-Lopez A J et al, *Semin Oncol* 26:66-73 (1999). There are reports that with lymphomas a small minority of tumors that re-emerge following Rituximab therapy can lack CD20 expression. Davis T A et al., *Clin Cancer Res* 5:611-5 (1999); Kinoshita T et al., *J Clin Oncol* 16:3916 (1998). The immunostimulatory nucleic acids of the invention are useful for treating this set of resistant tumors. Additionally, Rituximab has not been useful for the treatment of all types of B-cell malignancies. Expression of CD20 is relatively low on B-CLL cells, which provides an explanation for why Rituximab is less effective for CLL than for some other B-cell malignancies. Grimaldi L et al., *J Clin Pathol* 51:364-9 (1998). The immunostimulatory nucleic acids of the invention are also useful for treating these tumors.

The humanized monoclonal antibody ID101 recognizes an HLA-DR variant antigen. Link B K et al., *Blood* 81:3343-9 (1993). This antibody is currently being tested in a phase I clinical trial in patients with lymphoma. One limitation to the use of this antibody is that the target antigen is only expressed by approximately 50% of B-cell lymphomas. Interestingly, its expression was upregulated by immunostimulatory nucleic acids in all lymphoma samples tested. It was discovered according to the invention that immunostimulatory nucleic acids may enhance the efficacy of therapy with these and other antibodies by increasing expression of target antigen. Thus in another aspect the invention includes methods for treating lymphoma by administering to a subject an immunostimulatory nucleic acid and antibodies specific for HLA-DR. One useful antibody is the humanized monoclonal antibody ID101. It is particularly useful for treating resistant tumors.

The invention also relates to the discovery of a specific subclass, or isotype, of antibody which when combined with immunostimulatory nucleic acids produces a synergistic immune response. Another subclass, or isotype, does not even provide an additive response when combined with immunostimulatory nucleic acids. It was discovered according to the invention that the combination of immunostimulatory nucleic acids and human antibodies of the IgG1 isotype results in an increased (synergistic) survival rate. When immunostimulatory nucleic acids are combined with human antibodies of the IgG2 isotype, no increase in survival rate is observed over the use of the IgG2 antibody alone. The IgG2 isotype (which correlates with the murine IgG1 isotype) is believed to be recognized by the Fc receptor designated CD16 that is expressed largely by NK cells. Immunostimulatory nucleic acids are known to activate NK cells, and thus, it is surprising that immunostimulatory nucleic acids do not enhance the therapeutic effect of human IgG2 or murine IgG1 antibodies. Since NK cells are believed to be involved in ADCC and are activated by immunostimulatory nucleic acids, it was surprising that antibodies of the human IgG2 (or murine IgG1) isotype do not produce a synergistic or even additive response when administered with immunostimulatory nucleic acids.

A cancer cell is a cell that divides and reproduces abnormally due to a loss of normal growth control. Cancer cells almost always arise from at least one genetic mutation. In some instances, it is possible to distinguish cancer cells from their normal counterparts based on profiles of expressed genes and proteins, as well as to the level of their expression. Genes commonly affected in cancer cells include oncogenes, such as ras, neu/HER2/erbB, myb, myc and abl, as well as tumor suppressor genes such as p53, Rb, DCC, RET and WT. Cancer-related mutations in some of these genes leads to a decrease in their expression or a complete deletion. In others, mutations cause an increase in expression or the expression of an activated variant of the normal counterpart.

The term “tumor” is usually equated with neoplasm, which literally means “new growth” and is used interchangeably with “cancer.” A “neoplastic disorder” is any disorder associated with cell proliferation, specifically with a neoplasm. A “neoplasm” is an abnormal mass of tissue that persists and proliferates after withdrawal of the carcinogenic factor that initiated its appearance. There are two types of neoplasms, benign and malignant. Nearly all benign tumors are encapsulated and are noninvasive; in contrast, malignant tumors are almost never encapsulated but invade adjacent tissue by infiltrative destructive growth. This infiltrative growth can be followed by tumor cells implanting at sites discontinuous with the original tumor. The method of the invention can be used to treat neoplastic disorders in humans, including but not limited to: sarcoma, carcinoma, fibroma, glioma, leukemia, lymphoma, melanoma, myeloma, neuroblastoma, retinoblastoma, and rhabdomyosarcoma, as well as each of the other tumors described herein.

“Cancer” as used herein refers to an uncontrolled growth of cells which interferes with the normal functioning of the bodily organs and systems. Cancers which migrate from their original location and seed vital organs can eventually lead to the death of the subject through the functional deterioration of the affected organs. Hemopoietic cancers, such as leukemia, are able to out-compete the normal hemopoietic compartments in a subject, thereby leading to hemopoietic failure (in the form of anemia, thrombocytopenia and neutropenia), ultimately causing death.

A metastasis is a region of cancer cells, distinct from the primary tumor location, resulting from the dissemination of cancer cells from the primary tumor to other parts of the body. At the time of diagnosis of the primary tumor mass, the subject may be monitored for the presence of metastases. Metastases are most often detected through the sole or combined use of magnetic resonance imaging (MRI) scans, computed tomography (CT) scans, blood and platelet counts, liver function studies, chest X-rays and bone scans in addition to the monitoring of specific symptoms.

Cancers include, but are not limited to, basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and CNS cancer; breast cancer; cervical cancer; chorocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer; intra-epithelial neoplasm; kidney cancer; larynx cancer; leukemia; liver cancer; lung cancer (e.g., small cell and non-small cell); lymphoma including Hodgkin’s and non-Hodgkin’s lymphoma; melanoma; myeloma; neuroblastoma; oral cavity cancer (e.g., lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; renal cancer; cancer of the respiratory system; sarcoma; skin cancer; stom-
ach cancer; testicular cancer; thyroid cancer; uterine cancer; cancer of the urinary system, as well as other carcinomas and sarcomas.

The immunostimulatory nucleic acids and antibodies are useful for treating or preventing cancer in a subject. A “subject” unless otherwise specified shall mean a human or vertebrate mammal including but not limited to a dog, cat, horse, cow, pig, sheep, goat, or primate, e.g., monkey. Thus the invention can be used to treat cancer and tumors in human and nonhuman subjects. Cancer is one of the leading causes of death in companion animals (i.e., cats and dogs). Cancer usually strikes older animals which, in the case of house pets, have become integrated into the family. Forty-five percent of dogs older than 10 years of age are likely to succumb to the disease. The most common treatment options include surgery, chemotherapy and radiation therapy. Other treatment modalities which have been used with some success are laser therapy, cryotherapy, hyperthermia and immunotherapy. The choice of treatment depends on the type of cancer and degree of dissemination. Unless the malignant growth is confined to a discrete area in the body, it is difficult to remove only malignant tissue without affecting normal cells.

Malignant disorders commonly diagnosed in dogs and cats include but are not limited to lymphosarcoma, osteosarcoma, mammary tumors, mastocytoma, brain tumor, melanoma, adenosquamous carcinoma, carcinoid lung tumor, bronchial gland tumor, bronchial adenocarcinoma, fibroma, myxochondroma, pulmonary sarcoma, neurosarcoma, osteoma, papilloma, retinoblastoma, Ewing’s sarcoma, Wilms’ tumor, Burkitt’s lymphoma, microglioma, neuroblastoma, osteoclastoma, oral neoplasia, fibrosarcoma, osteosarcoma and rhabdomyosarcoma. Other neoplasias in dogs include genital squamous cell carcinoma, transmissible venereal tumor, testicular tumor, seminoma, Sertoli cell tumor, hemangioendothelioma, hystiocytoma, chloroma (granulocytic sarcoma), coro
cellular papilloma, corneal squamous cell carcinoma, hemangiosarcoma, pleural mesothelioma, basal cell tumor, thymoma, stomach tumor, adenoid gland carcinoma, oral papillomatosis, hemangioendothelioma and cystadenoma. Additional malignancies diagnosed in cats include follicular lymphoma, intestinal lymphosarcoma, fibrosarcoma and pulmonary squamous cell carcinoma. The ferret, an ever more popular house pet, is known to develop insulinoma, lymphoma, sarcoma, neurona, pancreatic islet cell tumor, gastric MALT lymphoma and gastric adenocarcinoma.

Neoplasias affecting agricultural livestock include leukemia, hemangioendothelioma and bovine ocular neoplasia (in cattle); preputial fibrosarcoma, ulcerative squamous cell carcinoma, preputial carcinoma, connective tissue neoplasia and mastocytoma (in horses); hepatocellular carcinoma (in swine); lymphoma and pulmonary adenomatosis (in sheep); pulmonary sarcoma, lymphoma, Ros sarcoma, reticulon
dothelioma, fibrosarcoma, nephroblastoma, B-cell lymphoma and lymphoid leukemia (in avian species); retinoblastoma, hepatic neoplasia, lymphosarcoma (lymphoblastic lymphoma), plasmacytoid leukemia and swimbladder sarcoma (in fish), caseous lymphadenitis (CLA): chronic, infectious, contagious disease of sheep and goats caused by the bacterium Corynebacterium pseudotuberculosis, and contagious lung tumor of sheep caused by jagsielle.

In one aspect, a method for treating cancer is provided which involves administering the compositions of the invention to a subject having cancer. A “subject having cancer” is a subject that has been diagnosed with a cancer. In some embodiments, the subject has a cancer type characterized by a solid mass tumor. The solid tumor mass, if present, may be a primary tumor mass. A primary tumor mass refers to a growth of cancer cells in a tissue resulting from the transformation of a normal cell of that tissue. In most cases, the primary tumor mass is identified by the presence of a cyst, which can be found through visual inspection or palpation methods, or by irregularity in shape, texture or weight of the tissue.

However, some primary tumors are not palpable and can be detected only through medical imaging techniques such as X-rays (e.g., mammography), or by needle aspirations. The use of these latter techniques is more common in early detection. Molecular and phenotypic analysis of cancer cells within a tissue will usually confirm if the cancer is endogenous to the tissue or if the lesion is due to metastasis from another site.

With respect to the prophylactic treatment methods, the invention is aimed at administering the compositions of the invention to a subject at risk of developing cancer. A subject at risk of developing a cancer is one who has a high probability of developing cancer. These subjects include, for instance, subjects having a genetic abnormality, the presence of which has been demonstrated to have a correlative relation to a higher likelihood of developing a cancer. Subjects exposed to cancer-causing agents such as tobacco, asbestos, or other chemical toxins are also subjects at risk of developing cancers used herein. When a subject at risk of developing a cancer is treated with an immunostimulatory nucleic acid, an antibody and optionally a cancer therapy, on a regular basis, such as monthly, the cancer growth will be prevented from initiating. This aspect of the invention is particularly advantageous when the subjects employed in certain trades which are exposed to cancer-causing agents on an ongoing basis. For example, many airborne, or inhaled, carcinogens such as tobacco smoke and asbestos have been associated with lung cancer.

A carcinogen is an agent capable of initiating development of malignant cancers. Exposure to carcinogens generally increases the risk of neoplasms in subjects, usually by affecting DNA directly. Carcinogens may take one of several forms such as chemical, electromagnetic radiation, or may be an inert solid body.

Substances for which there is sufficient evidence to establish a causal relationship in cancer in humans are referred to as confirmed human carcinogens. Included in this category are the following substances: Afatoxins, Alcoholic beverages, Aluminium production, 4-aminohippurin, Arsenic and arsenic compounds, Asbestos, Manufacture of alumimine, Azathioprine, Benzene, Benzidine, Beryllium and beryllium compounds, Benel quid with tobacco, Bis(chloromethyl)ether and chloromethyl methyl ether (technical grade), Boot and shoe manufacture and repair (occupational exposure), 1,4 Butanediol dimethanesulphonate (Myleran), Cadmium and cadmium compounds, Chlorambucil, Chloraphazine, 1-(2-Chloromethyl)-3-(4-methylcyclohexyl)-1 nitrosourea, Chloromethyl methyl ether (technical), Chromium compounds (hexavalent), Coal gasification, Coal tar pitches, Coal tar, Coke production, Cyclophosphamide, Cyclosporin, Eriodine, Ethylene oxide, Furniture and cabinet making. Underground haematite mining with exposure to radon, Iron and steel founding, Isopropyl alcohol manufacture (strong acid process), Manufacture of magnesia, Melphalan, 8-Methoxyxypyrrole (Methoxsalene) plus ultraviolet radiation, Mineral oils-untreated and mildly-treated oils, MOPP and other combined chemotherapy for cancer, Mustard gas (sulphur mustard), 2-Naphthylamine, Nickel and nickel compounds (essentially sulphate and sulphide), Nonsteroidal estrogens (not necessarily all in group) includes diethylstilbestrol, Estrogen replacement therapy, and Combined oral contraceptives and sequen-
Substances for which there is a lesser degree of evidence in humans but sufficient evidence in animal studies, or degrees of evidence considered unequivocal of mutagenicity in mammalian cells, are referred to as possible human carcinogens. This category of substances includes: Acrylamide, Acrylonitrile, Adriamycin, Anabolic steroids, Azacitidine, Benzonatene, Benzidine-based dyes (technical grade), Direct Black 38, Direct Blue 6, Direct Brown 95, Benzopyrene, 3-Butadiene, Captisol, Bischlorohydroxyethyl nitrosourea (BCNU), 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), Chloramphenicol, 1-(Para-chloro-orthotoluidine) and its strong acid salts, Chlorozotocin, Cisplatin, Cresotes, Dibenzo-thenacene, Diesel engine exhaust, Diethyl sulfide, Dimethyl carbamoyl chloride, Dimethyl sulfoxide, Epichlorohydrin, Ethylene dibromide, N-ethyl-N-nitrosourea, Formaldehyde, Glass manufacturing industry (occupational exposure), Art glass (glass containers and pressed ware), Hairdresser or barber (occupational exposure, probably dyes), Insecticide use (occupational), IQ (2-Amino-3-methylimidazo[4,5-f]-quinoline), Mate drinking (hot), 5-Methoxyxypyrrole, 4-4'-Methylenbis(2-chloroaniline) (MOCA), N-Methyl-N-nitro-N-nitrosoguanidine (MNNG), N-Methyl-N-nitrosourea, Nitrogen mustard, N-Nitrosodiethylamine, N-Nitrosodimethylamine, Petroleum refining (occupational exposure), Phenacetin, Polychlorinated biphenyls, Procarbazine hydrochloride, Silica (crystalline), Styrene-7,8-oxide, Tris[(-azadieny]-phosphine sulfide (Thiotepa), Tris(2,3-dibromopropyl) phosphate, Ultraviolet radiation: A, B and C including sunlamps and sunbeds, and Vinyl bromide.

Substances for which there is sufficient evidence in animal tests are referred to as possible human carcinogens. This category of substances includes: A-Cl (2-Amino-3-H1-pyridol[2,3-b]indole), Acetaldehyde, Acetamide, AF-2[2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide, para-Aminozobenzene, ortho-Aminozobenzene, 2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole, Amirole, ortho-Anisidine, Antimony trioxide, Arazine, Atapulgite, Azaserine, Benzol[4]fluoranthene, Benzol[5]fluoranthene, Benzol[6]fluoranthene, Benzo[a]pyrene, Bitumens (extracts of steam-refined and air-refined bitumens), Bleomycins, Bracken ferns, Bromodichloromethane, Butyldiarylsilane (BDA), 4-Butyltoluene, Caffeic acid, Carbon black extract, Carbon tetrachloride, Carrageenan (degraded), Ceramic fibres, Chloramphenicol, Chlordecone, Chloroacetic acid, Chlorinated paraffins or average carbon chain length C12 and average degree of chlorination approx 60%, alpha-Chlorinated toluenes (not necessarily all in group), Benzotrichloride, para-Chloroaniline, Chlorofom, Chlorophenols, Pentachlorophenol, 2,4,6-Trichlorophenol, Chlorophenoxycarbides (not necessarily all in group), 4-Chloro-ortho-phenylenediamine, CI Acid Red 114, CI Basic Red 9, CI Direct Blue 15, CI Ultramarine Blue 2, Cobalt and cobalt compounds, Coffee (bladder), para-Cresidine, Cyclic, Daesebranae, Dantron (1,8-dihydroxyanthraquinone), Daunomycin, DDT, NF-Dicetylbutyrate, 4,4'-Diaminodiphenyl ether, 2,4-Diaminothiophene, Dibenzo[a,h]acridine, Dibenzo[a,j]acridine, 7H-Dibenzo[c,e]carbazole, Dibenz[a,e]pyrene, Dibenz[a,h]pyrene, Dibenzo[a,l]pyrene, Dibenzo[a,j]pyrene, 1,2-Dibromo-3-chloropropane, para-Dichlorobenzene, 3,3'-Dichlorobenzene, 3,3'-Dichloro-4,4'-diaminodiphenyl ether, 1,2-Dichloroethane, Dichloromethane, 1,3-Dichloropropene (technical grade), Dichlorvos, Dipropoxybutane, Diesel fuel (marine), Di(2-ethylhexyl)phthalate, 1,2-Diethylhydrazine, Diglycyclyl resorcinol ether, Dihydrosulfolane, Dipropyl sulfate, 3,3'-Dimethoxybenzidine, para-Dimethylaminoazobenzene, trans-(2-([(dimethylamino)methyl]iminio)-[5-2-(5-nitro-2-furyl)vinyl]-1,3,4-oxidiazole, 2,6-Dimethylaniline (2,6-Xyldiene), 3,3'-Dimethyldibenzene (ortho-toluidine), Dimethylformamide, 1,1-Dimethylhydrazine, 1,2-Dimethylhydrazine, 1,6-Dinitropyrene, 1,8-Dinitropyrene, 1,4-Dioxane, Disperse Blue, Ethyl acrylate, Ethylene thiourea, Ethyl Nmethanesulphonate, 2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole, Fuel oils (residual, heavy), Fusarium moniliforme (toxins derived from), Fumonisin B1; Fumonisin B2; Fusarin C, Gasoline, Gasoline engine exhausts, Glasswool, Glu-P-2-(2-Amino-3-methyl-5-(5-nitro-2-furyl)thiazole), Glu-P-2-(Aminopyridine)-[1,2,3,5,2-5,2'-dijamidazoles], Glycidaldehyde, Griseofulvin, HC Blue No 1, Heptochlor, Hexachlorobenzene, Hexachlorocyclohexanes Technical grades alpha isomer gamma isomer (lindane), Hexamethylylphosphoramide, Hydrazine, Indeno[1,2,3-cd]pyrene, Iron dextran complex, Isoprene, Lasicarpine, Lead and lead compounds (inorganic), Magneta (containing CI Basic Red 9), Man-made mineral fibres (see glasswool, rockwool, slagwool, and ceramic fibres), Mea-c-C (2-Amino-3-methyl-4-H-pyridol[2,3-b]indole), MelQx (2-Amino-3,4-dimethylimidazo[4,5-f]-quinoline), MelQx (2-Amino-3,4-dimethylimidazo[4,5-f]-quinoxaline), Methylmercury compounds (methylmercuric chloride), Melphalan, 2-Methylaziridine, Methylazoxymethanol and its acetate, 5-Methylchrysene, 4,4'-Methylenbis(2-methylaniline), Methylmethanesulphonate, 2-Methyl-1-nitroantraquinone (uncertain purity), N-Methyl-N-nitrosourea, Methyliisouracil, Metolodiazole, Mirex, Nitrobenzene, Monocrotaline, 5-(Morpholinomethyl)-3-[(5-nitrofurfiurilidene) amino]-2-oxazolidinone, Nafenopin, Nirdazolone, 5-Nitroacenaphthene, 6-Nitrochrysene, Nitrofen (technical grade), 2-Nitrofluorenone-[5-(5-nitrofurfiurilidene)amino]-2-imidazolidinone, N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide, Nitrogen mustard, N-Oxide, Nitroloptracitic acid and its salts, 2-Nitropropanol-Nitropyrene, 4-Nitropyrene, N-Nitrosodi-n-butylamine, N-Nitrosodethanalamine, N-Nitrosodi-n-propylamine, 3-(N-Nitrosomethylaminopropionitride, 4-(N-Nitrosomethylenimino)-1-(3-pyridyl)-1-butanone (NNK), N-Nitrosomethylethylamine, N-Nitrosomethylvinylamine, N-Nitrosomorpholine, N-Nitrosomonicotinene, N-Nitrosopiperidine, N-Nitrosopyrrolidene, N-Nitrososarcosine, Ochratoxin A, Oil Orange, Panfurin S (containing dihydroxymethylfurfuril), Phenylglycidyl ether. Phenytoin in PHL (2-Amino-1-methyl-5-nitroimidazo[4,5-H]pyridine: Pickled vegetables, traditional Asian, Polybrominated biphenyls, Poneceu MXXPoneceu 3R, Potassium bromate, 1,3-Propane sultone, Propylene oxide, Progestins. Medroxyprogesterone acetate, -Propiolic tone, Propylthiouracil, Rockwool, Saccharin, Safrole, Slagwool, Sodium ortho-phenphenylenedine, Sterigmatocystin, Streptococcin, Styrene, Sulfaflinate, 2,3,7,8-Tetrachlorodibenzo-paradoxin (TCDD), Tetrachloroethylene, Textile manufacturing (occupational exposure), Thioacetamide, 4,4'-Thiodianthrene, Thiourea, Toluene, disocyanatesortho-Toluidine, Toxaphene (polychlorinated campheines), Trichloromethane (trimustine hydrochloride), Trp-P-1 (3-Amino-1,4-dimethyl-5-H-pyridol[4,3-b]indole), Trp-P-2 (3-Amino-1,4-dimethyl-5-H-pyridol[4,3-b]indole), Trypan blue, Uracil mustards, Urethane, 4-Vinylpy-
clohexene, 4-Vinylclohexene diepoxyide, Welding fumes, Wood industries and Carpentry and joinery.

Subjects at risk of developing cancer also include those who have a genetic predisposition to cancer. In many cases, genetic predisposition to cancer can be identified by studying the occurrence of cancer in family members. Examples of genetic predisposition to common forms of cancer include, but are not limited to, mutation of BRCA1 and BRCA2 in familial breast cancer, mutation of APC in familial colon cancer (familial polyposis coli), mutation of MSH2 and MLH1 in hereditary nonpolyposis colon cancer (HNPCC), mutation of p53 in Li-Fraumeni syndrome, mutation of RB1 in retinoblastoma, mutation of RET in multiple endocrine neoplasia type 2 (MEN2), mutation of VHL in renal cancer and mutation of WT1 in Wilms' tumor. Other cancers for which a familial predisposition has been identified include ovarian, prostate, melanoma and lung cancer.

It has been estimated that almost half of all currently diagnosed cancers will be treated with some form of cancer medication. However, many forms of cancer, including melanoma, colorectal, prostate, endometrial, cervical and bladder cancer, do not respond well to treatment with cancer medications. In fact, only about 5-10 percent of cancers can be cured using cancer medications alone. These include some forms of leukemias and lymphomas, testicular cancer, chorioncarcinoma, Wilms' tumor, Ewing's sarcoma, neuroblastoma, small-cell lung cancer and ovarian cancer. Treatment of still other cancers, including breast cancer, requires a combination therapy of surgery or radiotherapy in conjunction with a cancer medication.

The immunostimulatory nucleic acids are administered in combination with antibodies which specifically bind to cancer cell surface antigens. These antibodies include but are not limited to anti-CD20 antibodies, anti-CD40 antibodies, anti-CD19 antibodies, anti-CD22 antibodies, anti-HLA-DR antibodies, anti-CD80 antibodies, anti-CD86 antibodies, anti-CD54 antibodies, and anti-CD69 antibodies. These antibodies are available from commercial sources or may be synthesized de novo.

Commercially available anti-CD20 antibodies include but are not limited to those presented in Table 1 below.

<table>
<thead>
<tr>
<th>Commercially Available Anti-CD20 Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product/Supplier</strong></td>
</tr>
<tr>
<td>Mouse anti-Human CD20, Purified, 100 µg</td>
</tr>
<tr>
<td>CD20, B-Cell Bab Mouse: anti-Human</td>
</tr>
<tr>
<td>Clone: L26 Isotype: IgG2a, Kappa: Concentrated</td>
</tr>
<tr>
<td>Biorenda Corporation</td>
</tr>
<tr>
<td>CD20, B-Cell BAB Mouse: anti-Human</td>
</tr>
<tr>
<td>Clone: L26 Isotype: IgG2a, Kappa: Dehydrated</td>
</tr>
<tr>
<td>Biorenda Corporation</td>
</tr>
<tr>
<td>Mouse anti-Human CD20</td>
</tr>
<tr>
<td>BioSource International</td>
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<tr>
<td>Mouse anti-Human CD20</td>
</tr>
<tr>
<td>Mouse anti-Human CD20</td>
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<tr>
<td>BioSource International</td>
</tr>
<tr>
<td>Mouse anti-Human CD20</td>
</tr>
<tr>
<td>BioSource International</td>
</tr>
<tr>
<td>Product/Supplier</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Mouse Monoclonal Anti-CD20 Ab-1 (B-Cell Marker) IgG2a Antibody, Clone: B9E9, Workshop V; 10 μg</td>
</tr>
<tr>
<td>Mouse Monoclonal Anti-CD20 Ab-1 (B-Cell Marker) IgG2a Antibody, Clone: B9E9, Workshop V; 20 μg</td>
</tr>
<tr>
<td>Mouse Monoclonal Anti-CD20 Ab-1 (B-Cell Marker) IgG2a Antibody, Clone: B9E9, Workshop V; 100 μg</td>
</tr>
<tr>
<td>Mouse Monoclonal Anti-CD20 Ab-1 (B-Cell Marker) IgG2a Antibody, Clone: B9E9, Workshop V; 200 μg</td>
</tr>
<tr>
<td>Antibodies are well known to those of ordinary skill in the science of immunology. As used herein, the term “antibody” means not only intact antibody molecules but also fragments of antibody molecules retaining specific binding ability. Such fragments are also well known in the art and are regularly employed both in vitro and in vivo. In particular, as used herein, the term “antibody” means not only intact immunoglobulin molecules but also the well-known active fragments F(a)β, Fab, F(ab)γ, and Fab fragments which lack the Fc</td>
</tr>
</tbody>
</table>
fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding of an intact antibody. Wahl R.L. et al., J Nucl Med 24:316-25 (1983). Antibody fragments which are particularly useful according to the methods of the invention are those which are bispecific and constructed to enhance FeR binding, e.g., include an Fe portion. These include, but are not limited to Medarex antibodies (MDX-210, 220, 22, 447, and 260). Other non-Fc containing fragments which interact with the antigens induced on the cell surface are also useful. These are particularly useful in combination with immunotoxins and/or radioactivity. The fragments can be delivered separately from the immunotoxins or radioactivity or conjugated thereto (e.g., radiolabeled antibodies or antibody fragments).

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity-determining regions (CDRs), which directly interact with the epitope of the antigen, and framework regions (FRs), which maintain the tertiary structure of the paratope (see, in general, Clark, 1986; Roitt, 1991). In both the heavy chain Fd fragment and the light chain of IgG immunoglobulins, there are four framework regions (FR1 through FR4) separated respectively by three complementarity-determining regions (CDR1 through CDR3). The CDRs, and in particular the CDR3 region, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of conspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly manifested in the development and use of “humanized” antibodies in which non-human CDRs are covalently joined to human FR and/or Fe/βFe regions to produce a functional antibody. Thus, for example, PCT International Publication Number WO 92/04381 teaches the production and use of humanized murine RSV antibodies, in which at least a portion of the murine FR regions have been replaced by FR regions of human origin. Such antibodies, including fragments of intact antibodies with antigen-binding ability, are often referred to as “chimeric” antibodies. A “humanized monoclonal antibody” as used herein is a human monoclonal antibody or functionally active fragment thereof having human constant regions and a binding CDR3 region from a mammal of a species other than a human. Humanized monoclonal antibodies may be made by any method known in the art. Humanized monoclonal antibodies, for example, may be constructed by replacing the non-CDR regions of a non-human mammalian antibody with similar regions of human antibodies while retaining the epitopic specificity of the original antibody. For example, non-human CDRs and optionally some of the framework regions may be covalently joined to human FR and/or Fe/βFe regions to produce a functional antibody. There are entities in the United States which will synthesize humanized antibodies from specific murine antibody regions commercially, such as Protein Design Labs (Mountain View Calif.).

European Patent Application 0239400, the entire contents of which is hereby incorporated by reference, provides an exemplary teaching of the production and use of humanized monoclonal antibodies in which at least the CDR portion of a murine (or other non-human mammal) antibody is included in the humanized antibody. Briefly, the following methods are useful for constructing a humanized CDR monoclonal antibody including at least a portion of a mouse CDR. A first replicable expression vector including a suitable promoter operably linked to a DNA sequence encoding at least a variable domain of an Ig heavy or light chain and the variable domain comprising framework regions from a human antibody and a CDR region of a murine antibody is prepared. Optionally a second replicable expression vector is prepared which includes a suitable promoter operably linked to a DNA sequence encoding at least the variable domain of a complement human Ig light or heavy chain respectively. A cell line is then transformed with the vectors. Preferably the cell line is an immortalized mammalian cell line of lymphoid origin, such as a myeloma, hybridoma, trionia, or quadroma cell line, or is a normal lymphoid cell which has been immortalized by transformation with a virus. The transformed cell line is then cultured under conditions known to those of skill in the art to produce the humanized antibody.

As set forth in European Patent Application 0239400 several techniques are well known in the art for creating the particular antibody domains to be inserted into the replicable vector. (Preferred vectors and recombinant techniques are discussed in greater detail below.) For example, the DNA sequence encoding the domain may be prepared by oligonucleotide synthesis. Alternatively a synthetic gene lacking the CDR regions in which four framework regions are fused together with suitable restriction sites at the junctions, such that double-stranded synthetic or restricted subcloned CDR cassettes with sticky ends could be ligated at the junctions of the framework regions. Another method involves the preparation of the DNA sequence encoding the variable CDR containing domain by oligonucleotide site-directed mutagenesis. Each of these methods is well known in the art. Therefore, those skilled in the art may construct humanized antibodies containing a murine CDR region without destroying the specificity of the antibody for its epitope.

Human monoclonal antibodies may be made by any of the methods known in the art, such as those disclosed in U.S. Pat. No. 5,567,610, issued to Borrebbe et al., U.S. Pat. No. 5,565,354, issued to Ostberg, U.S. Pat. No. 5,571,893, issued to Baker et al., Kozbor D et al., J Immunol 133:3001-5 (1984), Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987), and Boerner P et al., J Immunol 147:86-95 (1991). In addition to the conventional methods for preparing human monoclonal antibodies, such antibodies may also be prepared by immunizing transgenic animals that are capable of producing human antibodies (e.g., Jakobovits A et al., Proc Natl Acad Sci USA 90:2551-5 (1993); Jakobovits A et al., Nature 362:255-8 (1993); Bruggemann et al., Year in Immunology 7:33 (1993); and U.S. Pat. No. 5,569,825 issued to Lonberg). Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W. R. (1986) The Experimental Foundations of Modern Immunology: Wiley & Sons, Inc., New York; Roitt, I. (1991) Essential Immunology, 7th Ed., Blackwell Scientific Publications, Oxford). The βFe and Fe regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the βFe region has been enzymatically cleaved, or which has been produced without the βFe region, designated an F(ab')2 fragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fe region has been enzymatically cleaved, or which has been produced without the Fe region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Proceeding further, Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificitity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.
Other antibodies useful according to the invention are antibodies of the IgG1 isotype. As mentioned above, anti-IgG1 isotype antibody as used herein refers to a human or humanized anti-IgG1 unless otherwise specified. IgG1 isotype antibodies are well known in the art and include at least the antibodies listed in Table 2 below.

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<tr>
<th>Marketer</th>
<th>Brand Name (Generic Name)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>CytoGen Corp.</td>
<td>Ireactin, anti-Her2 hMAb</td>
<td>Breast/ovarian</td>
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<tr>
<td>Centocor/Glaxo/Ajinomoto</td>
<td>Panoex® (17-1A) (murine monoclonal antibody)</td>
<td>Bone metastases</td>
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<td>Centocor/Ajinomoto</td>
<td>Panoex® (17-1A) (chimeric murine monoclonal antibody)</td>
<td>Adjuvant therapy for colorectal (Dukes-C)</td>
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<td>IDEC</td>
<td>IDEC-Y2B8 (murine, anti-CD20 MAb labeled with Yttrium-90)</td>
<td>Pancreatic, lung, breast, ovary</td>
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<td>ImClone Systems</td>
<td>BEC2 (anti-idiotypic MAb, mimics the GD3 epitope) (with BCG)</td>
<td>non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>ImClone Systems</td>
<td>C225 (chimeric monoclonal antibody to epidermal growth factor receptor (EGF))</td>
<td>Renal cell</td>
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<tr>
<td>Techniclon International/Alpha Therapeutics</td>
<td>Oncoly (Lyn-1 monoclonal antibody linked to 131 I)</td>
<td>Small cell lung</td>
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<tr>
<td>Protein Design Labs</td>
<td>SMART M195 Ab, humanized 131I LYM-1 (Oncoly)</td>
<td>Acute myeloid leukemia</td>
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<tr>
<td>Arcgene Pharmaceuticals, Inc.</td>
<td>ATRAGEN®</td>
<td>non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>IntClone Systems</td>
<td>C225 (chimeric anti-EGF receptor monoclonal antibody) + cisplatin or radiation</td>
<td>Head &amp; neck, non-small cell lung cancer</td>
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<td>Altarex, Canada</td>
<td>Ovaex (B34.13, anti-idiotypic CA125, mouse MAb)</td>
<td>Ovarian</td>
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<tr>
<td>Coulter Pharma (Clinical results have been positive, but the drug has been associated with significant bone marrow toxicity)</td>
<td>Bexar (anti-CD20 MAb labeled with 131I)</td>
<td>non-Hodgkin’s lymphoma</td>
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<tr>
<td>IDEC Pharmaceuticals Corp./Gensetech LeukoSite/lex Oncology</td>
<td>Rituxan® (MAb against CD20) par-B Ab in combo, with chemotherapy</td>
<td>Kaposi’s sarcoma, B cell lymphoma, Chronic lymphocytic leukemia (CLL)</td>
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<td>LDP-03, hMAb to the leukocyte antigen CAMPATH</td>
<td>Cancer, Breast, ovarian</td>
</tr>
<tr>
<td>Medarex/Novartis</td>
<td>iot 16 (anti CD6, murine MAb) CTCL MDX-210 (humanized anti-HER-2 bispecific antibody)</td>
<td>Prostate, non-small cell lung, pancreatic, breast, Acute myelogenous leukemia (AML)</td>
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<td>Medarex</td>
<td>MDX-210 (humanized anti-HER-2 bispecific antibody)</td>
<td>Renal and colon</td>
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<td>Medarex</td>
<td>MDX-11 (complement activating receptor (CAR) monoclonal antibody)</td>
<td>Ex vivo bone marrow purging in acute myelogenous leukemia (AML), Acute myeloid leukemia</td>
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<td>OV103 (Ytrium-90 labelled antibody)</td>
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<td>Ares Pharmaceuticals, Inc. Glaxo Wellcome plc</td>
<td>ATRAGEN®</td>
<td>non-Hodgkin’s lymphoma, non-small cell lung, prostate (adjuvant)</td>
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<tr>
<td>Genentech</td>
<td>Anti-VEGF, RhMAB (inhibits angiogenesis)</td>
<td>Lung, breast, prostate, colorectal</td>
</tr>
<tr>
<td>Protein Design Labs</td>
<td>Zenapax (SMART Anti-Tac (IL-2 receptor) Ab, humanized)</td>
<td>Leukemia, lymphoma</td>
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<tr>
<td>Protein Design Labs</td>
<td>SMART M195 Ab, humanized</td>
<td>Acute promyelocytic leukemia</td>
</tr>
<tr>
<td>ImClone Systems</td>
<td>C225 (chimeric anti-EGF receptor monoclonal antibody) + taxol</td>
<td>Breast</td>
</tr>
<tr>
<td>ImClone Systems (licensed from RPR)</td>
<td>C225 (chimeric anti-EGF receptor monoclonal antibody) + doxorubicin</td>
<td>Prostate</td>
</tr>
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</table>
TABLE 2-continued

<table>
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<tr>
<th>Manufacturer</th>
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<td>C225 (chimeric anti-EGF monoclonal antibody) + adriamycin</td>
<td>Prostate</td>
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<tr>
<td>InfClone Systems</td>
<td>BEC2 (anti-idiotypic Mab, mimics the GD3 epitope)</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Medarex</td>
<td>MDX-210 (humanized anti-HER-2 bispecific antibody)</td>
<td>Cancer</td>
</tr>
<tr>
<td>Medarex</td>
<td>MDX-210 (bispecific for tumors that express TAG-72)</td>
<td>Lung, colon, prostate, ovarian, endometrial, pancreatic and gastric</td>
</tr>
<tr>
<td>Medarex</td>
<td>MDX-447 (humanized anti-EGF receptor bispecific antibody)</td>
<td>EGF receptor cancers (head &amp; neck, prostate, lung, bladder, cervical, ovarian) Comb. Therapy with G-CSF for various cancers, cap. breast</td>
</tr>
<tr>
<td>Medarex</td>
<td>MDX-210 (humanized anti-HER-2 bispecific antibody)</td>
<td>Prostate</td>
</tr>
<tr>
<td>IDEC</td>
<td>MELIMMUNE-2 (murine monoclonal antibody therapeutic vaccine)</td>
<td>Melanoma</td>
</tr>
<tr>
<td>IDEC</td>
<td>MELIMMUNE-1 (murine monoclonal antibody therapeutic vaccine)</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Immunomedics, Inc.</td>
<td>CEACIDE® (E-131)</td>
<td>Colorectal and other non-Hodgkin's B-cell lymphoma</td>
</tr>
<tr>
<td>NeoRx</td>
<td>PreTarget® radioactive antibodies</td>
<td>Cancer</td>
</tr>
<tr>
<td>Novapharm Biotech, Inc.</td>
<td>NovoMab-G2 (pancreatic cancer specific Ab)</td>
<td>Brain</td>
</tr>
<tr>
<td>Technicione Corporation / Cambridge Antibody Technology</td>
<td>TNT (chimeric MAb to histone antigens)</td>
<td>Brain</td>
</tr>
<tr>
<td>International/Cambridge Antibody Technology</td>
<td>TNT (chimeric MAb to histone antigens)</td>
<td>Brain</td>
</tr>
<tr>
<td>Novapharm Biotech, Inc.</td>
<td>Giomab-H (Monoclonals - Humanized Ab)</td>
<td>Brain, melanomas, neuroblastomas</td>
</tr>
<tr>
<td>Genetics Institute/AHP</td>
<td>GNT-250 Mab</td>
<td>Colorectal</td>
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<tr>
<td>Merck KgaA</td>
<td>EMD-72000 (chimeric-EGF antagonist)</td>
<td>Cancer</td>
</tr>
<tr>
<td>Immunomedics</td>
<td>Lymphotox (humanized IL-2 antibody)</td>
<td>Non-Hodgkin's B-cell lymphoma</td>
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<td>Immunex/AHP</td>
<td>CMA 676 (monoclonal antibody conjugate)</td>
<td>Acute myelogenous leukemia</td>
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<td>Novapharm Biotech, Inc.</td>
<td>Monopharm-C</td>
<td>Colon, lung, pancreatic</td>
</tr>
<tr>
<td>Novapharm Biotech, Inc.</td>
<td>4B5 anti-idiotypic Ab</td>
<td>Melanoma, small-cell lung</td>
</tr>
<tr>
<td>Center of Molecular Immunology</td>
<td>ior efgv3 (anti EGF-R humanized Ab)</td>
<td>Radioimmunotherapy</td>
</tr>
<tr>
<td>Center of Molecular Immunology</td>
<td>ior 65 (murine MAb colorectal)</td>
<td>Colorectal</td>
</tr>
<tr>
<td>Creative BioMolecules/Chiron</td>
<td>BAUS (biosynthetic antibody binding site)</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>InfClone Systems/Clagai</td>
<td>Protein</td>
<td>Tumor-associated angiogenesis</td>
</tr>
<tr>
<td>ImmunoGen, Inc.</td>
<td>FLK-2 (monoclonal antibody to fetal liver kinase-2 (FLK-2))</td>
<td>Small-cell lung</td>
</tr>
<tr>
<td>Medarex, Inc.</td>
<td>Humanized MAb/small drug conjugate</td>
<td>Melanoma, glioma, neuroblastoma</td>
</tr>
<tr>
<td>Medarex, Inc.</td>
<td>MDX-260 bispecific, targets GD-2</td>
<td>Cancer</td>
</tr>
<tr>
<td>Precyion Biopharma, Inc.</td>
<td>ANA Ab</td>
<td>B-cell lymphoma</td>
</tr>
<tr>
<td>Protein Design Labs</td>
<td>SMART 1D10 Ab</td>
<td>Breast, lung, colon</td>
</tr>
<tr>
<td>Protein Design Labs/Novartis</td>
<td>SMART ABL 364 Ab</td>
<td>Colorectal</td>
</tr>
<tr>
<td>Immunomedics, Inc.</td>
<td>ImmunKIT®-CEA</td>
<td></td>
</tr>
</tbody>
</table>

In some embodiments the nucleic acid and antibody are administered in combination with a cancer therapy. As used herein, a “cancer therapy” refers to an agent which prevents growth of a cancer cell by decreasing or slowing the rate of growth, by inhibiting growth altogether, or by killing or inducing apoptosis of the cancer cell. Thus, as used herein, “treating cancer” includes preventing the development of a cancer, reducing the symptoms of cancer, and/or inhibiting the growth of an established cancer. In other aspects, the cancer therapy is administered to a subject at risk of developing a cancer for the purpose of reducing the risk of developing the cancer. Various types of medicaments for the treatment of cancer are described herein. For the purpose of this specification, cancer therapies are classified as chemothapeutic agents, cancer vaccines, hormone therapy, biological response modifiers, surgical procedures, and radiotherapy aimed at treating cancer. Additionally, the methods of the invention are intended to embrace the use of more than one cancer therapy along with the immunostimulatory nucleic acids and antibody. As an example, where appropriate, the immunostimulatory nucleic acids may be administered with a both a chemothapeutic agent and a radiotherapy.

Cancer therapies function in a variety of ways. Some cancer therapies work by targeting physiological mechanisms that are specific to tumor cells. Examples include the targeting of specific genes and their gene products (i.e., proteins
primarily) which are mutated in cancers. Such genes include but are not limited to oncogenes (e.g., Ras, Her2, bel-2), tumor suppressor genes (e.g., EGFR, p53, Rb), and cell cycle targets (e.g., CDK4, p21, telomerase). Cancer therapies can alternately target signal transduction pathways and molecular mechanisms which are altered in cancer cells.

Other cancer therapies target cells other than cancer cells. For example, some medications prime the immune system to attack tumor cells (i.e., cancer vaccines). Still other medications, called angiogenesis inhibitors, function by attacking the blood supply of solid tumors. Since the most malignant cancers are able to metastasize (i.e., exit the primary tumor site and seed a distal tissue, thereby forming a secondary tumor), medications that impede this metastasis are also useful in the treatment of cancer. Angiogenic mediators include basic FGF, VEGF, angiopeptins, angiotatin, endostatin, TNF-α, TNF-470, thrombospondin-1, platelet factor 4, CAI, and certain members of the integrin family of proteins. One category of this type of medication is a metalloproteinase inhibitor, which inhibits the enzymes used by the cancer cells to exit the primary tumor site and extravasate into another tissue.

As used herein, chemotherapeutic agents encompass both chemical and biological agents. These agents function to inhibit a cellular activity which the cancer cell is dependent upon for continued survival. Categories of chemotherapeutic agents include alkylating/alkoid agents, antimetabolites, hormones or hormone analogs, and miscellaneous antineoplastic drugs. Most if not all of these agents are directly toxic to cancer cells and do not require immune stimulation. Chemotherapeutic agents which are currently in development or in use in a clinical setting are shown in Table 3 below.

TABLE 3

<table>
<thead>
<tr>
<th>Marketer</th>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>TNP 470/AGM 1470</td>
<td>Fraguylne</td>
<td>Anti-Angiogenesis in Cancer</td>
</tr>
<tr>
<td>Takeda</td>
<td>TNP 470/AGM 1470</td>
<td>Fraguylne</td>
<td>Anti-Angiogenesis in Cancer</td>
</tr>
<tr>
<td>Scotia</td>
<td>Meglamine GLA</td>
<td>Meglamine GLA</td>
<td>Bladder Cancer</td>
</tr>
<tr>
<td>Medeva</td>
<td>Valstar</td>
<td>Valnubin</td>
<td>Bladder Cancer - Refractory in situ carcinomas</td>
</tr>
<tr>
<td>Rhone Poulenc</td>
<td>Glialde Wafer</td>
<td>Camustaine +</td>
<td>Bladder Cancer - Papillary Cancer</td>
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<tr>
<td>Warner Lambert</td>
<td>Undisclosed Cancer</td>
<td>Undisclosed</td>
<td>Brain Tumor</td>
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<td>Bristol-Myers</td>
<td>RAS Farnesy Transfer</td>
<td>RAS Farnesy</td>
<td>Cancer</td>
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<td>Squibb</td>
<td>Inhibitor</td>
<td>Farnesy</td>
<td>Cancer</td>
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<td>Novartis</td>
<td>MMD 170</td>
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<td>Merck</td>
<td>Farnesy Transfer</td>
<td>Farnesy</td>
<td>Cancer (Solid tumors - pancreas, colon, lung, breast)</td>
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<td>MMP</td>
<td>Cancer, angiogenesis</td>
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<td>Tyrosine Kinase</td>
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<td>PSC 833</td>
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<td>Celltech</td>
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<td>Aggrecanase Inhibitor</td>
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<td>Chiroscience</td>
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TABLE 3-continued

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<td>Taxotere</td>
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<td>Bristol-Myers Squibb</td>
<td>Taxane Analog</td>
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<td>Taxol follow up</td>
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Another useful anti-cancer therapy is Interferon-α (e.g., INTRON® A, Schering).

The compounds useful according to the invention are nucleic acids. The nucleic acids may be double-stranded or single-stranded. Generally, double-stranded molecules may be more stable in vivo, while single-stranded molecules may have increased activity. The terms “nucleic acid” and “oligonucleotide” refer to multiple nucleotides (i.e., molecules comprising a sugar (e.g., ribose or deoxyribose) linked to a phosphate group and to an exchangeable organic base, which is either a substituted pyrimidine (e.g., cytosine (C), thymine (T) or uracil (U)) or a substituted purine (e.g., adenine (A) or guanine (G)) or a modified base. As used herein, the terms refer to oligoribonucleotides as well as oligodeoxyribonucleotides. The terms shall also include polynucleotides (i.e., a polynucleotide minus the phosphate) and any other organic base-containing polymer. The terms “nucleic acid” and “oligonucleotide” also encompass nucleic acids or oligonucleotides with a covalently modified base and/or sugar. For example, they include nucleic acids having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3’ position and other than a phosphate group at the 5’ position. Thus modified nucleic acids may include a 2’-O-alkylated ribose group. In addition, modified nucleic acids may include sugars such as arabinose instead of ribose. Thus the nucleic acids may be heterogeneous in backbone composition thereby containing any possible combination of polymer units linked together such as peptide-nucleic acids (which have amino acid backbone with nucleic acid bases). In some embodiments the nucleic acids are homogeneous in backbone composition.

Nucleic acids also can include base analogs such as C-5 propyne modified bases, Wagner R W et al., Nature Biotechnol 14:840-4 (1996). Purines and pyrimidines include but are not limited to adenine, cytosine, guanine, thymine, 5-methylcytosine, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, and other naturally and non-naturally occurring nucleobases, substituted and unsubstituted aromatic moieties.

The nucleic acid is a linked polymer of bases or nucleotides. As used herein with respect to linked units of a nucleic acid, “linked” or “linkage” means two entities are bound to one another by any physicochemical means. Any linkage known to those of ordinary skill in the art, covalent or non-covalent, is embraced. Such linkages are well known to those of ordinary skill in the art. Natural linkages, which are those ordinarily found in nature connecting the individual units of a nucleic acid, are most common. The individual units of a nucleic acid may be linked, however, by synthetic or modified linkages.

Whenever a nucleic acid is represented by a sequence of letters it will be understood that the nucleotides are in 5’→3’ order from left to right and that “A” denotes adenosine, “C” denotes cytosine, “G” denotes guanosine, “T” denotes thymidine, and “U” denotes uracil unless otherwise noted.

Nucleic acid molecules useful according to the invention can be obtained from natural nucleic acid sources (e.g., genomic nuclear or mitochondrial DNA or cDNA), or are synthetic (e.g., produced by oligonucleotide synthesis). Nucleic acids isolated from existing nucleic acid sources are referred to herein as native, natural, or isolated nucleic acids. The nucleic acids useful according to the invention may be isolated from any source, including eukaryotic sources, prokaryotic sources, nuclear DNA, mitochondrial DNA, etc. Thus, the term nucleic acid encompasses both synthetic and isolated nucleic acids. The term “isolated” as used herein refers to a nucleic acid which is substantially free of other nucleic acids, proteins, lipids, carbohydrates or other materials with which it is naturally associated. The nucleic acids can be produced on a large scale in plasmids, (see Sambrook T et al., “Molecular Cloning: A Laboratory Manual”, Cold Spring Harbor Laboratory Press, New York, 1989) and separated into smaller pieces or administered whole. After being administered to a subject the plasmid can be degraded into oligonucleotides. One skilled in the art can purify viral, bacterial,
eukaryotic, etc., nucleic acids using standard techniques, such as those employing restriction enzymes, exonucleases or endonucleases.

For use in the instant invention, the nucleic acids can be synthesized de novo using any of a number of procedures well known in the art. For example, the b-cyanoethyl phosphoramidite method (Beaucage S L et al., Tetrahedron Lett 22:1859, 1981); nucleoside H-phosphonate method (Garegg et al., Tetrahedron Lett 27:4051-4, 1986; Froehler et al., Nucl Acid Res 14:5399-407, 1986; Garegg et al., Tetrahedron Lett 27:4055-8, 1986; Gaffney et al., Tetrahedron Lett 29:2619-22, 1988). These chemistries can be performed by a variety of automated oligonucleotide synthesizers available in the market.

In some embodiments, the nucleic acids useful according to the invention are immunostimulatory nucleic acids. An immunostimulatory nucleic acid is any nucleic acid, as described above, which is capable of modulating an immune response. A nucleic acid which modulates an immune response is one which produces any form of immune stimulation, including, but not limited to, induction of cytokines, B-cell activation, T-cell activation, monocyte activation. Immunostimulatory nucleic acids include, but are not limited to, CpG nucleic acids, methylated CpG nucleic acids, T-rich nucleic acids, poly-G nucleic acids, and nucleic acids having phosphate modified backbones, such as phosphorothioate backbones.

A “CpG nucleic acid” or a “CpG immunostimulatory nucleic acid” as used herein is a nucleic acid containing at least one unmethylated CpG dinucleotide (cytosine-guanine dinucleotide sequence, i.e., “CpG DNA” or DNA containing a 5’-cytosine followed by 3’-guanosine and linked by a phosphate bond) and activates a component of the immune system. The entire CpG nucleic acid can be unmethylated or portions may be unmethylated but at least the C of the 5’-CG 3’ must be unmethylated.

In one embodiment the invention provides a CpG nucleic acid represented by at least the formula:

\[ 5’ N’X_1 CGX_2 N_1 3’ \]

wherein \( X_1 \) and \( X_2 \) are nucleotides and \( N \) is any nucleotide and \( N_1 \) and \( N_2 \) are nucleic acid sequences composed of from about 0.25 to 0.5 \( N \)’s each. In some embodiments \( X_1 \) is adenine, guanine, or thymine and \( X_2 \) is cytosine, adenine or thymine.

In other embodiments \( X_1 \) is cytosine and/or \( X_2 \) is guanine.

In other embodiments the CpG nucleic acid is represented by at least the formula:

\[ 5’ N_1 X_1 CGX_2 N_1 3’ \]

wherein \( X_1 \), \( X_2 \), and \( X_3 \) are nucleotides. In some embodiments, \( X_1 \) and \( X_2 \) are nucleotides selected from the group consisting of: GpT, GpG, GpA, ApA, ApT, ApG, CpT, CpA, CpG, TpA, TpT, and TpG; and \( X_1 \) and \( X_2 \) are nucleotides selected from the group consisting of: TpT, TpA, TpG, ApG, CpG, TpC, ApC, CpC, TpA, ApA, and CpA; \( N \) is any nucleotide and \( N_1 \) and \( N_2 \) are nucleic acid sequences composed of from about 0.25 to 0.5 \( N \)’s each. In some embodiments, \( X_1 \) or \( X_2 \) or both are purines or \( X_1 \) or \( X_3 \) or both are pyrimidines or \( X_2 \) are GpA and \( X_3 \) or both are pyrimidines.

In some embodiments \( N_1 \) and \( N_2 \) of the nucleic acid do not contain a CCGG or CCGG quadrammer or more than one CCG or CGG trimer. The effect of a CCGG or CCGG quadrammer more than one CCG or CGG trimer depends in part on the status of the nucleic acid backbone. For instance, if the nucleic acid has a phosphodiester backbone or a chimeric backbone the inclusion of these sequences in the nucleic acid will only have minimal if any affect on the biological activity of the nucleic acid. If the backbone is completely phosphorothioate or significantly phosphorothioate then the inclusion of these sequences may have more influence on the biological activity or the kinetics of the biological activity, but compounds containing these sequences are still useful. In another embodiment the CpG nucleic acid has the sequence 5’TGNX,TX,CGX,X4 3’ (SEQ ID NO:850).

A “T-rich nucleic acid” or “T-rich immunostimulatory nucleic acid” is a nucleic acid which includes at least one poly-T sequence and/or which has a nucleotide composition of greater than 25% T nucleotide residues and which activates a component of the immune system. A nucleic acid having a poly-T sequence includes at least four Ts in a row, such as 5’TITTT 3’. Preferably the T-rich nucleic acid includes more than one poly-T sequence. In preferred embodiments the T-rich nucleic acid may have 2, 3, 4, etc., poly-T sequences, such as oligonucleotide #2183 (5’ TGGTTGTTTGCAGTATTTG 3’, SEQ ID NO: 841). Other T-rich nucleic acids have a nucleotide composition of greater than 25% T nucleotide residues, but do not necessarily include a poly-T sequence. In these T-rich nucleic acids the T nucleotide residues may be separated from one another by other types of nucleotide residues, i.e., G, C, and A. In some embodiments the T-rich nucleic acids have a nucleotide composition of greater than 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 95% T nucleotide residues and every integer % in between. Preferably the T-rich nucleic acids have at least one poly-T sequence and a nucleotide composition of greater than 25% T nucleotide residues.

In one embodiment the T-rich nucleic acid is represented by at least the formula:

\[ 5’ N_1 X_1 TTTTXX_3 3’ \]

wherein \( X_1 \), \( X_2 \), \( X_3 \), and \( X_4 \) are nucleotides. In one embodiment \( X_1 \) is T and \( X_2 \) is T. In another embodiment \( X_1 \) or \( X_2 \) or both are purines or both are pyrimidines.

In some embodiments it is preferred that the T-rich nucleic acid does not contain poly-C (CCCC), poly-A (AAAA), poly-G (GGGG), CpG motifs, or multiple Gs. In other embodiments the T-rich nucleic acid includes these motifs. Thus in some embodiments of the invention the T-rich nucleic acids include CpG dinucleotides and in other embodiments the T-rich nucleic acids are free of CpG dinucleotides. The CpG dinucleotides may be methylated or unmethylated.


Poly G nucleic acids preferably are nucleic acids having the following formulas:

\[ 5’ N_1 X_1 GGGX_3 3’ \]
wherein X₁, X₂, X₃, and X₄ are nucleotides. In preferred embodiments at least one of X₁ and X₄ are A. In other embodiments both of X₁ and X₄ are G. In yet other embodiments the preferred formula is 5’GGGNGGGG 3’, or 5’GGGNGGNGGGG 3’ (SEQ ID NO:849) wherein N represents between 0 and 20 nucleotides. In other embodiments the poly-G nucleic acid is free of unmethylated CG dinucleotides, such as, for example, the nucleic acids listed in Table 4 below as SEQ ID NOs: 12-14, 23, 56, 100, 155, 162, 227, 237, 246, 400, 407, 429, 430, 432, 435, 438, 439, 446, 450, 451, 480, 487, 493, 522, 661, 662, 671-673, 807, 808, 821, 823, and 834. In other embodiments the poly-G nucleic acid includes at least one unmethylated CG dinucleotide, such as, for example, the nucleic acids listed in Table 4 below as SEQ ID NOs: 6, 7, 22, 26, 28-30, 87, 115, 141, 177, 191, 209, 254, 258, 267, 303, 317, 329, 335, 344, 345, 359, 414, 417, 418, 423-426, 428, 431, 433, 434, 436, 437, 440, 442-445, 447-449, 458, 460, 463, 467-469, 474, 515, 516, 594, 638-640, 663, 664, 727, 752, 776, 795, 799, 817, 818, 831, and 832.

Nucleic acids having modified backbones, such as phosphorothioate backbones, also fall within the class of immunostimulatory nucleic acids. U.S. Pat. Nos. 5,723,335 and 5,663,153 issued to Hutcherson, et al. and related PCT publication WO95/26204 describe immunostimulation using phosphoroethioate oligonucleotide analogues. These patents describe the ability of the phosphorothioate backbone to stimulate an immune response in a non-sequence specific manner.

The immunostimulatory nucleic acids may be of any size but in some embodiments are in the range of between 6 and 100 or in some embodiments between 8 and 35 nucleotides in size. Immunostimulatory nucleic acids can be produced on a large scale in plasmids. These may be administered in plasmid form or alternatively they can be degradable into oligonucleotides.

“Palindromic sequence” shall mean an inverted repeat (i.e., a sequence such as ABCDE|EDCBA in which A and A’ are bases capable of forming the usual Watson-Crick base pairs and which includes at least 6 nucleotides in the palindrome. In vivo, such sequences may form double-stranded structures. In one embodiment the nucleic acid contains a palindromic sequence. In some embodiments when the nucleic acid is a CpG nucleic acid, a palindromic sequence used in this context refers to a palindrome in which the CpG is part of the palindrome and, optionally, is the center of the palindrome. In another embodiment the nucleic acid is free of a palindrome.

A nucleic acid that is free of a palindrome does not have any regions of 6 nucleotides or greater in length which are palindromic. A nucleic acid that is free of a palindrome can include a region of less than 6 nucleotides which are palindromic.

A “stabilized nucleic acid molecule” shall mean a nucleic acid molecule that is relatively resistant to in vivo degradation (e.g., via an exonuclease or endonuclease). Stabilization can be a function of length or secondary structure. Nucleic acids that are tens to hundreds of kbs long are relatively resistant to in vivo degradation. For shorter nucleic acids, secondary structure can stabilize and increase their effect. For example, if the 3’ end of an oligonucleotide has self-complementarity to an upstream region, so that it can fold back and form a sort of stem loop structure, then the oligonucleotide becomes stabilized and therefore exhibits more activity.

Some stabilized oligonucleotides of the instant invention have a modified backbone. It has been demonstrated that modification of the oligonucleotide backbone provides enhanced activity of the nucleic acids when administered in vivo. Nucleic acids, including at least two phosphorothioate linkages at the 5’ end of the oligonucleotide and multiple phosphorothioate linkages at the 3’ end, preferably 5, may provide maximal activity and protect the oligonucleotide from degradation by intracellular exo- and endo-nucleases.

Other modified oligonucleotides include phosphodiester modified oligonucleotide, combinations of phosphodiester and phosphorothioate oligonucleotide, methylphosphonate, methylphosphorothioate, phosphorothioate, and combinations thereof. Each of these combinations and their particular effects on immune cells is discussed in more detail in PCT Published Patent Application WO98/18810 claiming priority to U.S. Ser. Nos. 08/738,652 (now issued as U.S. Pat. No. 6,207,646 B1) and Ser. No. 08/960,774 (now issued as U.S. Pat. No. 6,239,116 B1), filed on Oct. 30, 1996 and Oct. 30, 1997 respectively, the entire contents of which is hereby incorporated by reference. It is believed that these modified oligonucleotides may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding, and/or altered intracellular localization. Both phosphorothioate and phosphodiester nucleic acids are active in immune cells.

Other stabilized oligonucleotides include: nonionic DNA analogs, such as alkyl- and aryl-phosphates (in which the charged phosphate oxygen is replaced by an alkyl or aryl group), phosphodiester and arylphosphoritiesters, in which the charged oxygen moiety is alkylated. Oligonucleotides which contain diol, such as tetraethyleneglycol or hexethyl-eneeglycol, at either or both termini have also been shown to be substantially resistant to nuclease degradation.

For use in vivo, nucleic acids are preferably relatively resistant to degradation (e.g., via endonucleases and exonucleases). Secondary structures, such as stem loops, can stabilize nucleic acids against degradation. Alternatively, nucleic acid stabilization can be accomplished via phosphate backbone modifications. One type of stabilized nucleic acid has at least a partial phosphorothioate modified backbone. Phosphorothioates may be synthesized using automated techniques employing either phosphoramidate or H-phosphonate chemistries. Aryl- and alkyl-phosphonates can be made, e.g., as described in U.S. Pat. No. 4,469,863; and arylphosphoriesters (in which the charged oxygen moiety is alkylated as described in U.S. Pat. No. 5,023,243 and European Patent No. 922,574) can be prepared by automated solid phase synthesis using commercially available reagents. Methods for making other DNA backbone modifications and substitutions have been described. Ulmann E et al., Chem Rev. 90:544-84 (1990); Goodchild J, Bioconjugate Chem 1:165-87 (1990).

The immunostimulatory nucleic acids having backbone modifications useful according to the invention in some embodiments are S- or R-chiral immunostimulatory nucleic acids. An “S chiral immunostimulatory nucleic acid” as used herein is an immunostimulatory nucleic acid wherein at least two nucleotides have a backbone modification forming a chiral center and wherein a plurality of the chiral centers have S chirality. An “R chiral immunostimulatory nucleic acid” as used herein is an immunostimulatory nucleic acid wherein at least two nucleotides have a backbone modification forming a chiral center and wherein a plurality of the chiral centers have R chirality. The backbone modification may be any type of modification that forms a chiral center. The modifications include but are not limited to phosphorothioate, methylphosphonate, methylphosphorothioate, phosphorothioate, 2’-O-Me and combinations thereof. In other embodiments they are non-chiral. A non-chiral nucleic acid is any nucleic acid which does not have at least two chiral centers.

The chiral immunostimulatory nucleic acids must have at least two nucleotides within the nucleic acid that have a
backbone modification. All or less than all of the nucleotides in the nucleic acid, however, may have a modified backbone. Of the nucleotides having a modified backbone (referred to as chiral centers), a plurality have a single chirality, S or R. A “plurality” as used herein refers to an amount greater than or equal to 75%. Thus, less than all of the chiral centers may have S or R chirality as long as a plurality of the chiral centers have S or R chirality. In some embodiments at least 75%, 80%, 85%, 90%, 95%, or 100% of the chiral centers have S or R chirality. In other embodiments at least 75%, 80%, 85%, 90%, 95%, or 100% of the nucleotides have backbone modifications.


Other sources of nucleic acids useful according to the invention include standard viral and bacterial vectors, many of which are commercially available. In its broadest sense, a “vector” is any nucleic acid material which is ordinarily used to deliver and facilitate the transfer of nucleic acids to cells. The vector as used herein may be an empty vector or a vector carrying a gene which can be expressed. In the case when the vector is carrying a gene the vector generally transports the gene to the target cells with reduced degradation relative to the extent of degradation that would result in the absence of the vector. In this case the vector optionally includes gene expression sequences to enhance expression of the gene in target cells such as immune cells, but it is not required that the gene be expressed in the cell.

In general, vectors include, but are not limited to, plasmids, phagemids, viruses, other vehicles derived from viral or bacterial sources. Viral vectors are one type of vector and include, but are not limited to, nucleic acid sequences from the following viruses: retrovirus, such as Moloney murine leukemia virus, Harvey murine sarcoma virus, murine mammary tumor virus, and Rous sarcoma virus; adenovirus, adeno-associated virus; SV40-type viruses; polyoma viruses; Epstein-Barr viruses; papilloma viruses; herpes virus; vaccinia virus; polio virus; and RNA virus such as a retrovirus. One can readily employ other vectors not named but known to the art. Some viral vectors are based on non-cytopathic eukaryotic viruses in which non-essential genes have been replaced with a nucleic acid to be delivered. Non-cytopathic viruses include retroviruses, the life cycle of which involves reverse transcription of genomic viral RNA into DNA.


Other vectors include plasmid vectors. Plasmid vectors have been extensively described in the art and are well-known to those of skill in the art. See e.g., Sambrook et al., “Molecular Cloning: A Laboratory Manual,” Second Edition, Cold Spring Harbor Laboratory Press, 1989. In the last few years, plasmid vectors have been found to be particularly advantageous for delivering genes to cells in vivo because of their inability to replicate within and integrate into a host genome. Some plasmids, however, having a promoter compatible with the host cell, can express a peptide from a gene operatively encoded within the plasmid. Some commonly used plasmids include pBR322, pUC18, pUC19, pC/NA3.1, pSV40, and pBlueScript. Other plasmids are well-known to those of ordinary skill in the art. Additionally, plasmids may be custom designed using restriction enzymes and ligation reactions to remove and add specific fragments of DNA.

It has recently been discovered that plasmids (empty or gene-carrying) can be delivered to the immune system by use of bacteria. Modified forms of bacteria such as Salmonella can be transfected with the plasmid and used as delivery vehicles. The bacterial delivery vehicles can be administered to a host subject orally or by other administration means. The bacteria deliver the plasmid to immune cells, e.g., dendritic cells, probably by passing through the gut barrier. High levels of immune protection have been established using this methodology. Such methods of delivery are useful for the aspects of the invention utilizing systemic delivery of nucleic acid.

As used herein, administration of an immunostimulatory nucleic acid is intended to embrace the administration of one or more immunostimulatory nucleic acids which may or may not differ in terms of their profile, sequence, backbone modifications and biological effect. As an example, CpG nucleic acids and T-rich nucleic acids may be administered to a single subject along with an antibody and optionally a cancer therapy. In another example, a plurality of CpG nucleic acids which differ in nucleotide sequence may also be administered to a subject.

Some of the nucleic acids useful according to the invention and described herein are presented in Table 4 below.

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In Table 4 with respect to sequences the letter symbols aside from a, c, t, and g are defined as follows: "b" indicates a biotin moiety attached to that end of the oligonucleotide when it is single and is listed on the 5' or 3' end of oligonucleotide; "d" represents a, g, or t; "i" represents fluorescein isothiocyanate (FITC) moiety attached to the 5' or 3' end of oligonucleotide; "h" represents a, c, or t; "i" represents inosine; "n" represents any nucleotide; "z" represents 5-methylcytosine.

Also in Table 4 with respect to backbones the notations are defined as follows: "o" represents phosphodiester; "os" represents phosphorothioate and phosphodiester chimeric with phosphodiester on 5' end; "os2" represents phosphorothioate and phosphodiester chimeric with phosphodiester on 5' end; "p-ethoxy" represents p-ethoxy backbone (see, e.g., U.S. Pat. No. 6,015,886); "po" represents phosphodiester; "s" represents phosphorothioate; "s2" represents phosphorothioate; "s2o" represents phosphorothioate and phosphodiester chimeric with phosphodiester on 5' end; and "ss" represents chimeric phosphorothioate/phosphodiester with phosphorothioate at the 5' and 3' ends.

The nucleic acids are delivered in effective amounts. The term "effective amount" of an immunostimulatory nucleic acid refers to the amount necessary or sufficient to realize a desired biologic effect. For example, an effective amount of an immunostimulatory nucleic acid could be that amount necessary to cause activation of the immune system. According to some aspects of the invention, an effective amount is that amount of an immunostimulatory nucleic acid and that amount of an antibody, which when combined or co-administered, results in the prevention or the treatment of the cancer. In some embodiments a synergistic effect is observed. A synergistic amount is that amount which produces an anti-cancer response that is greater than the sum of the individual effects of either the immunostimulatory nucleic acid and the antibody alone. For example, a synergistic combination of an immunostimulatory nucleic acid and an antibody provides a biological effect which is greater than the combined biological effect which could have been achieved using each of the components (i.e., the nucleic acid and the antibody) separately. The biological effect may be the amelioration and or absolute elimination of symptoms resulting from the cancer. In another embodiment, the biological effect is the complete abrogation of the cancer, as evidenced for example, by the absence of a tumor or a biopsy or blood smear which is free of cancer cells.

The effective amount of immunostimulatory nucleic acid necessary to treat a cancer or in the reduction of the risk of developing a cancer may vary depending upon the sequence of the immunostimulatory nucleic acid, the backbone constituents of the nucleic acid, and the mode of delivery of the nucleic acid.

The effective amount for any particular application can also vary depending on such factors as the cancer being treated, the particular immunostimulatory nucleic acid being administered (e.g., the nature, number or location of immunostimulatory motifs in the nucleic acid), the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular immunostimulatory nucleic acid and antibody combination without necessitating undue experimentation. Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is entirely effective to treat the particular subject.

Therapeutic doses of cancer therapies are well known in the field of medicine for the treatment of cancer. These dosages have been extensively described in references such as Remington's Pharmaceutical Sciences, 18th ed., 1990; as well as many other medical references relied upon by the medical profession as guidance for the treatment of cancer. Therapeutic dosages of immunostimulatory nucleic acids have also been described in the art and methods for identifying therapeutic dosages in subjects are described in more detail herein.

Subject doses of the compounds described herein typically range from about 0.1 µg to mg per administration, which depending on the application could be given daily, weekly, or monthly and any other amount of time therebetween. More typically mucosal or local doses range from about 10 µg to 5 mg per administration, and most typically from about 100 µg to 1 mg, with 2-4 administrations being spaced hours, days or weeks apart. More typically, immune stimulant doses range from 1 µg to 10 mg per administration, and most typically 10 µg to 1 mg. with daily or weekly administrations. Subject doses of the compounds described herein for parenteral deliv-
ery, wherein the compounds are delivered without another therapeutic agent are typically 5 to 10,000 times higher than the effective mucosal dose or for immune stimulant applications, and more typically 10 to 1,000 times higher, and most typically 20 to 100 times higher. More typically parenteral doses for these purposes range from about 10 μg to 5 mg per administration, and most typically from about 100 μg to 1 mg, with 2-4 administrations being spaced hours, days or weeks apart. In some embodiments, however, parenteral doses for these purposes may be used in a range of 5 to 10,000 times higher than the typical doses described above.

For any compound described herein the therapeutically effective amount can be initially determined from animal models, e.g., the animal models described herein. A therapeutically effective dose can also be determined from human data for CpG nucleic acids which have been tested in humans (human clinical trials have been initiated and the results publicly disseminated) and for compounds which are known to exhibit similar pharmacological activities. Higher doses may be required for parenteral administration, as described above. The applied dose can be adjusted based on the relative bioavailability and potency of the administered compound. Adjusting the dose to achieve maximal efficacy based on the methods described above and other methods as are well-known in the art is well within the capabilities of the ord-

arily skilled artisan.

The formulations of the invention are administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

For use in therapy, an effective amount of the nucleic acid can be administered to a subject by any mode that delivers the nucleic acid to a subject. “Administering” the pharmaceutical composition of the present invention may be accomplished by any means known to the skilled artisan. Some routes of administration include but are not limited to oral, intranasal, intratracheal, inhalation, ocular, vaginal, rectal, parenteral (e.g., intramuscular, intradermal, intravenous or subcutaneous injection) and direct injection.

For oral administration, the compounds (i.e., nucleic acids and antibodies) can be delivered alone without any pharmaceutical carriers or formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. The term “pharmaceutically acceptable carrier” means one or more compatible solid or liquid filler, diluents or encapsulating substances which are suitable for administration to a human or other vertebrate animal. The term “carrier” denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the compounds of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained as solid excipient, optionally grading a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum trag-
canth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alg-}

in acid or a salt thereof such as sodium alginate. Optionally, the oral formulations may also be formulated in saline or buffers for neutralizing intestinal acid conditions.

Dragee cores may be provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, tala, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or tita-

nium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to character-

ize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft cap-

sules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Microspheres formulated for oral administration may also be used. Such microspheres have been well defined in the art. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention may be conveniently deliv-
ered in the form of an aerosol spray, from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichloro-
rufuroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be deter-
mained by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds, when it is desirable to deliver them system-
ically, may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as sus-

pending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-
soluble form. Additionally, suspensions of the active com-

pounds may be prepared as appropriate oily injection suspens-
sions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the vis-

cosity of the suspension, such as sodium carboxymethyl cel-
lulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.
Alternatively, the active compounds may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. The compounds may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be formulated with suitable polymeric or hydrophilic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for inhalation, microencapsulated, encocchelated, coated onto microscopic gold particles, contained in liposomes, nebulized aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions may also include granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protected release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems. For a brief review of present methods for drug delivery, see Langer R. Science 249:1527-33 (1990), which is incorporated herein by reference.

The nucleic acids and/or antibodies may be administered per se (neat) or in the form of a pharmaceutically acceptable salt. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulphonic, tartaric, citric, methane sulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzene sulphonic. Also, such salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

Suitable buffering agents include: acetic acid and a salt (1-2% w/v); citric acid and a salt (1-3% w/v); borax and a salt (0.5-2.5% w/v); and phosphoric acid and a salt (0.8-2% w/v). Suitable preservatives include benzalkonium chloride (0.003-0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v) and thimerosal (0.004-0.02% w/v).

The nucleic acids or other therapeutics useful in the invention may be delivered in mixtures with additional antibodies. A mixture may consist of several antibodies in addition to the nucleic acid.

A variety of administration routes are available. The particular mode selected will depend, of course, upon the particular nucleic acids or antibodies selected, the particular condition being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of an immune response without causing clinically unacceptable adverse effects. Preferred modes of administration are discussed above.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the compounds into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product. Liquid dose units are vials or ampoules. Solid dose units are tablets, capsules and suppositories.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the compounds, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as polylactide-glycolide, copoloyxolates, polyacetates, polyesters, polyethers, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Pat. No. 5,075,109. Delivery systems also include non-polymer systems that are: lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono- di- and tri-glycerides; hydrogel release systems; sylastic systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to:

(a) erosional systems in which an agent of the invention is contained in a form within a matrix—such as those described in U.S. Pat. Nos. 4,452,775, 4,675,189, and 5,736,152, and
(b) diffusion systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Pat. Nos. 3,854,480, 5,133,974 and 5,407,686. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

The nucleic acid may be directly administered to the subject or may be administered in conjunction with a pharmaceutically acceptable carrier or a delivery vehicle. The nucleic acid and optionally other therapeutic agents may be administered alone (e.g., in saline or buffer) or using any delivery vehicles known in the art. One type of delivery vehicle is referred to herein as a nucleic acid delivery complex. A "nucleic acid delivery complex" shall mean a nucleic acid molecule associated with (e.g., ionically or covalently bound to; or encapsulated within) a targeting means (e.g., a molecule that results in higher affinity binding to target cell (e.g., dendritic cell surfaces and/or increased cellular uptake by target cells). Examples of nucleic acid delivery complexes include nucleic acids associated with: a sterol (e.g., cholesterol), a lipid (e.g., a cationic lipid, virosome or liposome), or a target cell specific binding agent (e.g., a ligand recognized by target cell specific receptor). Preferred complexes may be sufficiently stable in vivo to reduce significant uncoupling prior to internalization by the target cell. However, the complex may be cleavable under appropriate conditions within the cell so that the nucleic acid may be released in a functional form.

The nucleic acids may be delivered by non-invasive methods as described above. Non-invasive delivery of compounds is desirable for treatment of children, elderly, animals, and even adults and also to avoid the risk of needle-stick injury.

Delivery vehicles for delivering compounds to mucosal surfaces have been described and include but are not limited to: Coatees (Gould-Fogerite et al., 1994, 1996); Emulsomes
(Vancott et al., 1998, Lowell et al., 1997); ISCOMs (Mowat et al., 1993, Carlson et al., 1991, Hu et al., 1998, Morein et al., 1999); Liposomes (Childers et al., 1999, Michalek et al., 1989, 1992, de Haan 1995a, 1995b); Live bacterial vectors (e.g., Salmonella, Escherichia coli; Bacillus Calmette-Guerin, Shigella Lactobacillus) (Hone et al., 1996, Pouwels et al., 1998, Chatfield et al., 1993, Stover et al., 1991, Nugent et al., 1998); Live viral vectors (e.g., Vaccinia, adenovirus, Herpes Simplex) (Galliaich et al., 1993, 1995, Moss et al., 1996, Nugent et al., 1998, Flexner et al., 1988, Morrow et al., 1999); Microspheres (Gupta et al., 1998, Jones et al., 1996, Maloy et al., 1994, Moore et al., 1995, O’Hagan et al., 1994, Eldridge et al., 1989); nucleic acid vaccines (Fynn et al., 1993, Kuklin et al., 1997, Sasaki et al., 1998, Okada et al., 1997, Ishii et al., 1997); Polymers (e.g., carboxymethylcellulose, chitosan) (Hamajima et al., 1998, Jabbal-Gill et al., 1998); Polymer rings (Wyatt et al., 1998); Proteosomes (Vancott et al., 1998, Lowell et al., 1988, 1996, 1997); Sodium Fluoride (Hashi et al., 1998); Transgenic plants (Tacket et al., 1998, Mason et al., 1998, Haq et al., 1995); Virosomes (Gluck et al., 1992, Mengardi et al., 1995, Cryz et al., 1998); Virus-like particles (Jiang et al., 1999, Leibl et al., 1998).

The invention also includes kits. The kits generally include a package with a plurality of containers housing active ingredients and instructions for carrying out the methods of the invention. The active ingredients include but are not limited to immuno-stimulatory nucleic acids, antibodies such as antibodies specific for a cell surface antigen, and anti-cancer therapies.

The following examples are provided to illustrate specific instances of the practice of the present invention and are not to be construed as limiting the present invention to these examples. As will be apparent to one of ordinary skill in the art, the present invention will find application in a variety of compositions and methods.

**EXAMPLES**

Introduction:

Extensive cross-talk exists between healthy B cells and T cells. There is evidence that malignant B cells also communicate with T cells. However, malignant cells appear to differ from their normal counterparts in a number of ways, including a decreased tendency to undergo apoptosis in response to normal signals, altered expression of a variety of surface markers, and altered ability to function as effective antigen presenting cells. Lagneaux L et al., *Blood* 91:2387-96 (1998); Gordon J et al., *Leukemia* 7 Suppl:25-9 (1993); Gordon J et al., *Adv Exp Med Biol* 406:139-44 (1996); Chaperot L et al., *Exp Hematol* 27:479-88 (1999). Immunotherapeutic approaches have recently become part of our therapy of some subtypes of B-cell malignancy. Improved immunotherapy of B-cell malignancy will need to be designed based on the growing understanding of the cellular immunology of this disease. Schultze J L et al., *J Mol Med* 77:322-32 (1999).


**Materials and Methods:**

Cell culture: Fresh lymph node samples were obtained from the operating suite and were minced with a scalpel under aseptic conditions. The resulting suspension was passed sequentially through a sterilized sieve-tissue grinder containing a nylon mesh screen, a 150 μm mesh screen and a 60 μm mesh screen. Alternatively, mononuclear cells were obtained from peripheral blood or pleural fluid as described. Hartmann G et al., *J Pharmacol Exp Ther* 285:920-8 (1998). Red blood cells were removed by resuspending the cells in 5 ml ACK lysis buffer according to standard procedures. Cells were frozen slowly and stored in liquid nitrogen. For analysis, cells were thawed and resuspended in 10% (v/v) heat-inactivated (56° C, 1 h) FCS (HyClone, Logan, UT), 1.5 mM L-glutamine (all from Gibco BRL, Grand Island, NY) and incubated on a 96-well-plate (1x10^5 cells/ml) in the presence of ODN as indicated below. Not all assays were performed for all samples because of the limited number of cells available for some samples.

**Oligonucleotides**

Nucleic-resistant phosphorothioate-modified oligodeoxynucleotide (ODN) were purchased from Optron Technologies (Alameda, Calif.) and Hybridon Speciality Products (Milford, Mass.). Sequences were as follows: Cpg ODN 2006: 5'-TCTGCTTTTGTCTGGTGTCTCT-3' (SEQ ID NO: 729), and control ODN 2017: 5'-CCCCCCCCCCCCCCCCCCCCCCCCC-3' (SEQ ID NO: 168). ODN was diluted in TE (10 mM Tris-HCl, 1 mM EDTA, pH 8) using pyrogen-free reagents. ODN was added at a final concentration of 5 μg/ml.

Flow cytometry: Cells were washed and resuspended in ice-cold PBS or Annexin V binding buffer (10 mM HEPES/NaOH, 140 mM NaCl, 2.5 mM CaCl2, pH 7.4). Murine or human serum was added (final concentration 1%) to block non-specific binding of antibodies. Surface antigen staining was performed as described. Hartmann G et al., *J Pharmacol Exp Ther* 285:920-8 (1998). In brief, 1x10^5 cells per sample were stained with Cychrome-labeled anti-CD19 and FITC- or PE-labeled antibodies as indicated for 20 min on ice. They were then washed and analyzed by flow cytometry. Monoclonal antibodies to CD40 (5C3), CD69 (FN50), CD80 (L107.4), CD86 (IT2.2), CD54 (HA58), MHC I (G46-2.6) and MHC II (TU39) as well as isotype controls (IgG1, MOPC-21 and IgG2a, G155-178) were purchased from PharMingen, San Diego, Calif. FITC-labeled polyclonal antihuman Ig was purchased from Southern Biotech, Birmingham, Ala. 1D10, a monoclonal humanized antibody directed against a variant of HLA-DR was produced in our laboratory as described earlier. Link B K et al., *Blood* 81:3343-9 (1993). C2B8, a monoclonal humanized anti-CD20 antibody, was purchased from IDEC Pharmaceuticals, San Diego, Calif. 1D10 and C2B8 were labeled with FITC according to standard protocols. The analysis gate was set on viable cells identified according to FSC/SSC characteristics and Annexin V staining (>97% viable cells within analysis gate). Spectral
CFSE staining: CFSE 5- and 6-carboxyfluorescein diacetate succinimidyl ester, Molecular Probes, USA, is a fluorescein-derived intracellular fluorescent label which is divided equally between daughter cells upon cell division. Staining of cells with CFSE allows both quantification and immunophenotyping of proliferating cells in a mixed cell suspension. Interference between oligonucleotide degradation products and thymidine uptake (standard proliferation assay) is avoided by using this method. The technique has described in detail previously. Lyons A B et al., J Immunol Methods 171:131-7 (1994). Briefly, cells were washed twice in PBS, resuspended in PBS (1x10^6 cells/ml) containing CFSE at a final concentration of 1 μM, and incubated at 37°C for 10 minutes. Cells were washed three times with PBS.

TUNEL assay: A two-color DNA strand break labeling assay, based on a modification of the assay described by Li et al. (Li X et al., Exp Cell Res 222:28-37 (1996)) was used to assess B-cell proliferation in response to CpG ODN. This assay involved terminal deoxytransferase-mediated dUTP nick end labeling (TUNEL) before and after induction of DNA strand breaks in BrdU-labeled cells. Briefly, cells were cultured for 3 days with and without ODN. They were then incubated for 16 hours in 10 μM BrdU and placed onto slides by cytospin. Cells were then in 1% paraformaldehyde in PBS for 15 minutes followed by 20 minutes in 70% ethanol. DNA cleavage indicative of apoptosis was detected by labeling the 3'-DNA end of nicked strands with FITC-dUTP (Boehringer-Mannheim). The use of deoxydU-dUTP prevented further elongation of the 3'-ends in subsequent steps. Slides were then placed face-down on a 2 mm support at both ends on a UV transilluminator and exposed for 5 minutes. The new DNA strand breaks induced by photolysis at sites of BrdU incorporation (i.e., proliferating cells) were detected by a second TUNEL labeling using tetramethylrhodamine dUTP (TMR-dUTP, Boehringer-Mannheim). Both TUNEL staining steps included incubating slides in 50 μl of TdT mix (34 μl distilled water, 10 μl of 5xTdT buffer, 5 μl of 25 mM cobalt chloride, 12.5 units terminal transferase and 0.5 nmol fluorochrome-conjugated-dUTP) (Boehringer-Mannheim) under a coverslip for one hour at 37°C in a humidified chamber. The slides were then washed in 5 quick changes of distilled water followed by 3 changes of 2xSSC containing 30% formamide for 5 minutes each at room temperature. After the second TUNEL labeling step, cells were counterstained for CD19, and also stained with Wright solution for blood cell differentiation and mounted in Vectorshiel media containing DAPI counterstain (Vector Laboratories, Burlingame, Calif.). The morphology and staining of cells were assessed using both visible light and fluorescence microscopy. Apoptotic cells were identified by green fluorescence (FITC label), and proliferating cells by red fluorescence (TMR label). The percentage of apoptotic and proliferating cells was determined by counting at least 200 cells per sample by three observers blinded to whether cells were treated with ODN. Mean and standard error were determined for each sample based on these three readings.

Our prior studies demonstrated that activation of naive human B cells by CpG ODN results in increased cell size (FSC) and granularity (SSC). Hartmann G et al., J Immunol 164:944-53 (2000). We therefore first determined whether such changes also occur in malignant B cells. Primary malignant B cells were obtained from lymph node biopsies, peripheral blood, or pleural fluid of patients with various types of B-cell malignancy. In addition, cells from the lymph node of a patient with benign reactive follicular hyperplasia were studied. Nine samples in total were evaluated (see Table 5). Cells were incubated for 4 hours in media containing CpG ODN 2006 (5 μg/ml) or control ODN 2017. FSC and SSC were examined with gating on CD19+ viable cells (FIG. 1). Varying degrees of change in FSC and SSC were noted in response to CpG ODN 2006 when compared to control ODN 2017 or medium alone. Comparable changes were not found in the cells from the patient with benign reactive follicular hyperplasia.

FIG. 1 depicts the morphologic changes of marginal zone lymphoma cells upon CpG ODN stimulation. Malignant B cells from a patient with marginal zone lymphoma were stimulated with 5 μg/ml of no ODN (A and D), control ODN (B and E) or CpG ODN (C and F) for 4 hours and analyzed by flow cytometry. A, B, and C illustrate FSC (x-axis) vs. SSC (y-axis). D, E, and F illustrate CD19 expression (x-axis) against FSC (y-axis), allowing for separation of B cells from other leukocyte subpopulations. Upon stimulation with CpG ODN, B cells shifted up and to the right, indicating an increase in granularity and size. No changes could be detected without stimulation or on stimulation with the non-CpG ODN.

Expression of CD20, CD40, CD69, CD80, CD86, surface Ig, CD54, MHC I, MHC II, and an HLA-DR variant antigen (mAb 1D10) were examined in viable CD19+ cells after incubation of cells with CpG ODN for 48 hours. Each of these markers was upregulated to varying extents in response to the CpG ODN 2006 compared to the control ODN 2017 (FIG. 2, FIG. 3).

FIG. 2 depicts the expression of surface antigens on marginal zone lymphoma cells upon CpG ODN treatment. Flow cytometric analysis of surface antigen expression on malignant B cells from a patient with marginal zone lymphoma was performed 72 hours after stimulation with 5 μg/ml of either CpG ODN or non-CpG ODN. Upon stimulation with CpG ODN, median fluorescence intensity for all markers tested shifted to the right, indicating an increase in surface expression. Thin curves indicate incubation with medium alone, dotted curves incubation with control ODN, and bold curves incubation with CpG ODN.

FIG. 3 depicts the expression of surface antigens on primary cells representing different B-cell malignancies and cells of a benign follicular hyperplasia upon CpG ODN treatment. Cells from lymph node biopsies, peripheral blood or pleural fluid from patients with different B-cell malignancies were incubated for 72 hours with either media alone, control ODN or CpG ODN. Each panel represents one experiment. CD20 was expressed to varying degrees in all samples tested. As is well known, baseline CD20 expression was lower in the B-CLL samples when compared to the B-cell malignancies of other histologies. CpG-ODN 2006 but not the control ODN 2017 increased CD20 expression in both
B-CLLs and both marginal zone lymphomas. No or only little upregulation was seen in the other lymphoma samples. Non-malignant CD19+ cells derived from the reactive follicular hyperplasia decreased CD20 expression in response to CpG (FIG. 3). This data demonstrated a reverse correlation between the baseline expression of CD20 and CD40, and expression of these markers after incubation with CpG-ODN; thus the lower the baseline level of CD20 and CD40, the higher was the responsiveness to CpG-ODN (r: ~0.6; ~0.4) (FIG. 4). This correlation was less clear for the other markers. CD19+ cells derived from the reactive follicular hyperplasia showed high baseline expression of activation markers which was not further upregulated by CpG.

FIG. 4 shows the CpG-ODN effect on CD20 and CD40 is dependent on the baseline level of expression. Cells from lymph node biopsies, peripheral blood or pleural fluid from patients with different B-cell malignancies (see Table 5) were incubated with or without CpG-ODN for 72 hours. Expression of CD20 and CD40 was measured by flow cytometry. Baseline expression of CD20 and CD40 with medium alone was compared to the expression of CD20 and CD40 in the presence of CpG-ODN. The coefficients of correlation are indicated.

### TABLE 5

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### Example 2

**Immunostimulatory Nucleic Acids Induce Proliferation and Apoptosis of Malignant B Cells**

CpG induces a strong proliferative response of primary human B cells. Hartmann G et al., J Immunol 164:944-53 (2000). Two techniques were used to assess whether CpG-ODN is capable of inducing proliferation of B-CLL cells. For select samples, cells were stained with CFSE and incubated for four days. Proliferation of cells is indicated by a loss of CFSE stain with every cell division. In B-CLL, CD5 can be used to identify malignant B among CD19+ cells. Proliferation of malignant B cells (CD5+ and CD19+) was lower than proliferation of normal B cells (CD5- and CD19+) (FIG. 5). For the marginal zone lymphoma, CpG-ODN 2006 induced proliferation of the CD19+ cell population (FIG. 5).

FIG. 5 shows a comparison of CpG-ODN induced proliferation of malignant and normal B cells. Peripheral blood mononuclear cells from two patients, one with B-CLL and one with marginal zone lymphoma with circulating malignant cells, were incubated for 72 hours with CpG-ODN or medium alone and evaluated by two-color flow cytometry.

### Example 3

**CpG ODN Enhance the Therapeutic Effect of Murine IgG2a (Which Relates to Human IgG1) but not Murine IgG1 (Which Relates to Human IgG2) Anti-tumor Antibody**

CpG ODN when combined with antibody of murine subtype IgG2a dramatically promotes survival in mice having tumors. Mice were injected i.p. with 5000 T3C cells on day 0. They were then given 100 μg anti-idiotypic monoclonal antibody as either IgG1 (MSA10) or IgG2a (MS11G6) on days 5, 7, and 10. In this model, the target antigen is the idiotype expressed by the lymphoma cells. Therefore, the anti-tumor antibodies are also "anti-idiotypic." These antibodies (MSA10 and MS11G6) are simultaneously both anti-tumor antibodies and anti-idiotype antibodies. Twenty micrograms of CpG ODN 1826 (5′ TCCATGACGTTCTCGAGTTT 3′; SEQ ID NO: 560) was given at the same time. Results are shown in FIG. 6. Untreated controls had a median survival time (MST) of 17 days after inoculation with tumor. Mice treated with murine IgG1 antibody plus CpG ODN had sur-
vival that was similar to those treated with murine IgG1 antibody alone (MST 28 days and 27 days, respectively). In contrast, mice treated with murine IgG2a plus Cpg ODN had survival that was significantly improved when compared to mice treated with murine IgG2a alone (MST 45 days and 37 days, respectively).

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention.

All references, patents and patent publications that are recited in this application are incorporated in their entirety herein by reference.

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aagctgagc cttccat 17

<210> SEQ ID NO 17
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 17
aagctgagc cttccagtc 20

<210> SEQ ID NO 18
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 18
aagctt 6

<210> SEQ ID NO 19
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 19
aagctttc 8

<210> SEQ ID NO 20
<211> LENGTH: 7
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone
SEQUENCE: 20
aacgttg

SEQ ID NO 21
LENGTH: 8
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
SEQUENCE: 21
aacgttgag

SEQ ID NO 22
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
SEQUENCE: 22
aacgttgagg gcag

SEQ ID NO 23
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
SEQUENCE: 23
aacgagggc agtcctaggg a

SEQ ID NO 24
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
SEQUENCE: 24
aatagtcgc atacaaaaac

SEQ ID NO 25
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
SEQUENCE: 25
aatagtcgc atacaaaaac
aatagtgcc atcccccccc

<210> SEQ ID NO 26
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 26

aatagtgcc atccccggac

<210> SEQ ID NO 27
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 27

aatagtgcc atccccggac

<210> SEQ ID NO 28
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 28

aatagtgcc atgccgggc

<210> SEQ ID NO 29
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 29

aatttactgt cgggtctct tgggtccttg ctgggtcgc tttat

<210> SEQ ID NO 30
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 30

accaaccag gaacgggaaac

<210> SEQ ID NO 31
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) . . . (0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 31
aciasgtt

SEQ ID NO 32
LENGTH: 10
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) . . . (0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 32
aciasggtga

SEQ ID NO 33
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 33
accacactga gagcaacgca

SEQ ID NO 34
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 34
accacactga ggocatcogg

SEQ ID NO 35
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) . . . (0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 35
accatggaac aactgttccc cctc

SEQ ID NO 36
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) . . . (0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 36
accatggaac aactgttccc cctc
<210> SEQ ID NO 37
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc.feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 37
accatggagc aacctgtttccc cctc

<210> SEQ ID NO 38
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 38
accatggagc aacctgtttccc cctc

<210> SEQ ID NO 39
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc.feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 39
accatggagc aacctgtttccc cctc

<210> SEQ ID NO 40
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc.feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 40
accatggagc aacctgtttccc cctc

<210> SEQ ID NO 41
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc.feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 41
accatggagc aacctgtttccc cctc

<210> SEQ ID NO 42
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 42

acccatgacg ttctgtttccc cctc 24

<210> SEQ ID NO 43
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 43

accatcaat agctctgtgac 20

<210> SEQ ID NO 44
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 44

accgctgcta attatagaa aaccc 25

<210> SEQ ID NO 45
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 45

acccatgga ttctaggcc 20

<210> SEQ ID NO 46
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 46

acctattaa gttgtgcaaa tgtgacgtcc tttagcatgc gsaag 45

<210> SEQ ID NO 47
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 47

acgctggacc ttccat 16
<210> SEQ ID NO 48
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 48
acgtggtcc cccccccccc

<210> SEQ ID NO 49
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 49
acgtgt

<210> SEQ ID NO 50
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 50
actagcgttt agtgta

<210> SEQ ID NO 51
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 51
actagcgttt agtgta

<210> SEQ ID NO 52
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 52
actgagcgttt agctgta

<210> SEQ ID NO 53
<211> LENGTH: 25
acctotcata gtccttgg tccag

agacgcga

gacagacac gaacgaccc

agactcatgg gaaatcccc cattga

agatagcaca tgcgtgaccc

agatagcaca tcggctgaccc
agatgttct cagataaagc ggaa

<210> SEQ ID NO 59
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 59
agcaccgac gtgagagg

agcaccgtag cttctctta

<210> SEQ ID NO 60
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 60
agcaccgtag cttctctta

agcagctttta gacgcttttag gtt

<210> SEQ ID NO 61
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 61
agcagctttta gacgcttttag gtt

agcatcagga acgacatgga

<210> SEQ ID NO 62
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 62
agcatcagga acgacatgga

agcatcagga cagacatgga

<210> SEQ ID NO 63
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 63
agcatcagga cagacatgga

agcatcagga cogacatgga

<210> SEQ ID NO 64
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
agcgctga 8

agctcaagctcagc 15

agctccatgctgtcactg 19

aggtatc 8

aggtacagccagactacga 20
<223> OTHER INFORMATION: 1
<221> NAME/KEY: modified_base
<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: 1
<221> NAME/KEY: modified_base
<222> LOCATION: (14)...(14)
<223> OTHER INFORMATION: 1

<400> SEQUENCE: 69
agncgccgga agacattcacc

<210> SEQ ID NO: 70
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 70
agtgaccttc cagcgtttc

<210> SEQ ID NO: 71
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 71
agtgcgattc ggcgatg

<210> SEQ ID NO: 72
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 72
agtgcgattg cagatcg

<210> SEQ ID NO: 73
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 73
agtgct

<210> SEQ ID NO: 74
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 74

agtgc

<210> SEQ ID NO 75
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 75

agttgcacat

<210> SEQ ID NO 76
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 76

ataaagcggactgccagcagtct

<210> SEQ ID NO 77
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 77

ataacgtt

<210> SEQ ID NO 78
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 78

atastactccagcagacagct

<210> SEQ ID NO 79
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 79

atastacgcactcagcaagcc
ataatccag ttaaaccgaag

ataatccag ttcgaagcaag

ataatccag ttccccccc

ataatccag ttcaagcaag

ataatccag gttaaagaaa g

ataagcaaaa atttcccocccc cggagcc
<210> SEQ ID NO 85
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 85
atatatatatatatatatat  18

<210> SEQ ID NO 86
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 86
atatatatc aasacattas c  24

<210> SEQ ID NO 87
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 87
atcggacag tcatggaagc  21

<210> SEQ ID NO 88
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 88
atcgcacctc gtcgltcttc  20

<210> SEQ ID NO 89
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (18) ...(18)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 89
atcgcacctc gtcgttnmct  20
SEQ ID NO 90
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) (0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 90
atcgactcga ggtttctc

SEQ ID NO 91
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) (0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 91
atcgactcctc ggcgtttctc

SEQ ID NO 92
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) (0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 92
atcgactcctc ggcggtttctc

SEQ ID NO 93
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) (0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 93
atcgactcctc ggtgtttctc

SEQ ID NO 94
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (14) (14)
OTHER INFORMATION: m5c

SEQUENCE: 94
atcgactcctc ggcgtttctc
<210> SEQ ID NO 95
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 95

atcgaacttc tcgagcggtc tc

<210> SEQ ID NO 96
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 96

atcgaacttc agcgttctc

<210> SEQ ID NO 97
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 97

atcgaatcg acgttctc

<210> SEQ ID NO 98
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 98

atcgatgt

<210> SEQ ID NO 99
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 99

atcgagagac tgtgcgcgccg

<210> SEQ ID NO 100
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
LOCATION: (0)...

OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 100

atcgtgtag gccaagtcat g

SEQ ID NO: 101
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 101

tgaaccttc ctagcgttgc

SEQ ID NO: 102
LENGTH: 17
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 102

atgcatgtc gagctttcgc

SEQ ID NO: 103
LENGTH: 8
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 103

atgcatgt

SEQ ID NO: 104
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 104

atgcctgca acgtt

SEQ ID NO: 105
LENGTH: 23
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 105

atgcctgca acgtt
atgctaaagg aagtcacatt gca

<210> SEQ ID NO 106
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 106

atggaagtc cagccttccc

<210> SEQ ID NO 107
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 107

atggaagtc cagccttccc

<210> SEQ ID NO 108
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 108

atggaagtc cagccttccc

<210> SEQ ID NO 109
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 109

atggaagtc cagccttccc

<210> SEQ ID NO 110
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 110

atggaagtc gcgcttccc
<210> SEQ ID NO 111
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 111

atgaccttc cagggtcttc

20

<210> SEQ ID NO 112
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 112

atgcctccgg tctgtgactc

20

<210> SEQ ID NO 113
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 113

atgtttacta gacaaatc cccgagagt ttt

33

<210> SEQ ID NO 114
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 114

atgttcttt ottaaatc cccgagagt ttt

33

<210> SEQ ID NO 115
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 115

atccgagcgg gcgggggaga g

21

<210> SEQ ID NO 116
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: m5c

SEQUENCE: 116

atatcgctac tgtcgtgttc

<210> SEQ ID NO 117
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: m5c
<221> NAME/KEY: modified_base
<222> LOCATION: (14)...(14)
<223> OTHER INFORMATION: m5c

SEQUENCE: 117

atatcgctac gagnngtttc

<210> SEQ ID NO 118
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: biotinylated at 5' end

SEQUENCE: 119

atatcgctac cagcggttc

<210> SEQ ID NO 119
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: biotinylated 5' end

SEQUENCE: 119

gagacgcgtc cagcactgat

<210> SEQ ID NO 120
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

NAME/KEY: misc_feature
LOCATION: (0)...(0)

OTHER INFORMATION: phosphodiester backbone
NAME/KEY: misc_feature
LOCATION: (1)...(1)

OTHER INFORMATION: biotinylated 5' end

SEQUENCE: 120

gagaacgctc gaccttcgat

SEQ ID NO 121
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)

OTHER INFORMATION: phosphodiester backbone
NAME/KEY: misc_feature
LOCATION: (1)...(1)

OTHER INFORMATION: biotinylated 5' end
NAME/KEY: modified_base
LOCATION: (6)...(6)

OTHER INFORMATION: m5c

SEQUENCE: 121

gagaangctc cagcactgat

SEQ ID NO 122
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)

OTHER INFORMATION: phosphodiester backbone
NAME/KEY: misc_feature
LOCATION: (1)...(1)

OTHER INFORMATION: biotinylated 5' end
NAME/KEY: modified_base
LOCATION: (6)...(6)

OTHER INFORMATION: m5c

SEQUENCE: 122

gagaangctc gaccttcgat

SEQ ID NO 123
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)

OTHER INFORMATION: phosphodiester backbone
NAME/KEY: misc_feature
LOCATION: (1)...(1)

OTHER INFORMATION: biotinylated at 5' end

SEQUENCE: 123

gagcaagctg gaccttcgat

SEQ ID NO 124
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
<210> SEQ ID NO 125
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: biotinylated at 5' end

<400> SEQUENCE: 124

gcaagntg gaccttocat

<410> SEQ ID NO 126
<411> LENGTH: 8
<412> TYPE: DNA
<413> ORGANISM: Artificial Sequence
<420> FEATURE:
<423> OTHER INFORMATION: Synthetic oligonucleotide
<421> NAME/KEY: misc_feature
<422> LOCATION: (0)...(0)
<423> OTHER INFORMATION: phosphodiester backbone
<421> NAME/KEY: misc_feature
<422> LOCATION: (1)...(1)
<423> OTHER INFORMATION: biotinylated at 5' end

<400> SEQUENCE: 125

gctagacggt agcgtga

<410> SEQ ID NO 127
<411> LENGTH: 20
<412> TYPE: DNA
<413> ORGANISM: Artificial Sequence
<420> FEATURE:
<423> OTHER INFORMATION: Synthetic oligonucleotide
<421> NAME/KEY: misc_feature
<422> LOCATION: (0)...(0)
<423> OTHER INFORMATION: phosphodiester backbone
<421> NAME/KEY: misc_feature
<422> LOCATION: (1)...(1)
<423> OTHER INFORMATION: biotinylated at 5' end

<400> SEQUENCE: 127

tccagcgt tctgatgct

<410> SEQ ID NO 128
<411> LENGTH: 20
<412> TYPE: DNA
<413> ORGANISM: Artificial Sequence
<420> FEATURE:
<423> OTHER INFORMATION: Synthetic oligonucleotide
<421> NAME/KEY: misc_feature
<422> LOCATION: (0)...(0)
<423> OTHER INFORMATION: phosphodiester backbone
<421> NAME/KEY: misc_feature
<222> LOCATION: (1)...
<223> OTHER INFORMATION: biotinylated at 5' end

<400> SEQUENCE: 128

tca tgtgact tcgtgact

<210> SEQ ID NO 129
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphodiester on 5' end
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...
<223> OTHER INFORMATION: biotinylated at 5' end

<400> SEQUENCE: 129

tca tgtgact gcgtgtcgtg atgcttcca

<210> SEQ ID NO 130
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphodiester on 5' end
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...
<223> OTHER INFORMATION: biotinylated at 5' end

<400> SEQUENCE: 130

tca tgtgact tctagggctcg atgcttcca

<210> SEQ ID NO 131
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphodiester on 5' end
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...
<223> OTHER INFORMATION: biotinylated at 5' end

<400> SEQUENCE: 131

tcgt gttttttt gcgtttttt tgttttttt

<210> SEQ ID NO 132
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphodiester on 5' end
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...
<223> OTHER INFORMATION: biotinylated at 5' end
<400> SEQUENCE: 132

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tttttccatg tggctctga tgcttttt
```

<210> SEQ ID NO 133
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . (0)
<223> OTHER INFORMATION: chimeric phosphoroxythioate/phosphodiester backbone with phosphodiester on 5' end
<221> NAME/KEY: misc_feature
<222> LOCATION: (1) . . (1)
<223> OTHER INFORMATION: biotinylated at 5' end

<400> SEQUENCE: 133

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tttttcgtcg ttcccccccc ccccc
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<210> SEQ ID NO 134
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 134

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caacgtt
```

<210> SEQ ID NO 135
<211> LENGTH: 7
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 135

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caacgtt
```

<210> SEQ ID NO 136
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . (0)
<223> OTHER INFORMATION: phosphoroxythioate backbone

<400> SEQUENCE: 136

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caagagatgc taacaatgca
```

<210> SEQ ID NO 137
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 137

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caatcaatct gaggagaacc
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<210> SEQ ID NO 138
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 138

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caatcaatct gaggagaacc
```

<210> SEQ ID NO 139
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 139

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caatcaatct gaggagaacc
```
<210> SEQ ID NO 138
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 139

cacaccttg tcaatgtcag

<210> SEQ ID NO 139
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 139

cacaccttgg tcaatgtca cgt

<210> SEQ ID NO 140
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 140

cacggtggcc ttctca

<210> SEQ ID NO 141
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 141

cacggttggag ggcga

<210> SEQ ID NO 142
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 142

cactgcctcc cgctcga

<210> SEQ ID NO 143
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 143

cagacoacaga agccgatatg acg

SEQ ID NO 144
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 144

cagatgtgctaatgtctcg

SEQ ID NO 145
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 145

cataacatatgataatattac tctctcg

SEQ ID NO 146
LENGTH: 31
TYPE: DNA
ORGANISM: Artificial sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 146

cataggtct cgagctcgga aagtccoccta c

SEQ ID NO 147
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 147

catgagctca tctggaggaag cgg

SEQ ID NO 148
LENGTH: 16
TYPE: DNA
ORGANISM: Artificial sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 148
cattttcaac attttccaa
  18

<210> SEQ ID NO 149
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 149
cattttcagg ggggcccggc
  20

<210> SEQ ID NO 150
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 150
ccaaatatcg gtgtcaagc ac
  22

<210> SEQ ID NO 151
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 151
ccaacgttt
  8

<210> SEQ ID NO 152
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 152
ccagtcgac cttcaggcga
  20

<210> SEQ ID NO 153
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 153
ccagcttgac ctcctagc
  17

<210> SEQ ID NO 154
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 154
ccactcact ctcgtgtccc acaag 25
<210> SEQ ID NO 155
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 155
ccagatgagc tcgaggtgct ctcg 24
<210> SEQ ID NO 156
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 156
ccaggttaeg aggaatgac ttgagc 26
<210> SEQ ID NO 157
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 157
ccaggtgtga tagagc 17
<210> SEQ ID NO 158
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 158
ccagtgctga tcaccgatc ctcgctcgcg aagtcg 35
<210> SEQ ID NO 159
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 159
ccatcgat 8
<210> SEQ ID NO 160
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 160

ccatgcat

<210> SEQ ID NO: 161
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 161

ccatgctaac ctctagc

<210> SEQ ID NO: 162
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 162

ccatgctogt ccctagct

<210> SEQ ID NO: 163
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 163

ccccaaaggg atgagaagtt

<210> SEQ ID NO: 164
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 164

ccccaaaggg atgagaagtt

<210> SEQ ID NO: 165
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 165

ccccccc

<210> SEQ ID NO 166
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 166

cccccccc

<210> SEQ ID NO 167
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 167

cccccccccc cc

<210> SEQ ID NO 168
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 168

cccccccccc cccccccccc

<210> SEQ ID NO 169
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 169

cccccccccc cccccccccc

<210> SEQ ID NO 170
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 170

cccccccc ccccccccc cccc

SEQ ID NO 171
LENGTH: 28
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 171

cccccccc ccccccccc ccccc

SEQ ID NO 172
LENGTH: 35
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 172

cccccccc ccccccccc ccccccccc cccc

SEQ ID NO 173
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 173

ccccctgacg ttttccccccc

SEQ ID NO 174
LENGTH: 26
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 174

ccccagagta ttctctotta acctgg

SEQ ID NO 175
LENGTH: 26
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 175

cocoaagagta ttctctgat cagcac
<210> SEQ ID NO 176
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 176
cggcttcct cagstgacct ctag

<210> SEQ ID NO 177
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 177
cggcttcct cagstgacct catggtttc tccaccasg

<210> SEQ ID NO 178
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 178
cggccggcc ggccggccgg

<210> SEQ ID NO 179
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_difference
<222> LOCATION: (0) . . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 179
cggcttcct ccccccccccc

<210> SEQ ID NO 180
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . . (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 180
cccaacagtct gtcgccccag ct

<210> SEQ ID NO 181
<211> LENGTH: 20
<212> TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 181

cctccaaatgc asagacocccc 20

SEQ ID NO 182
LENGTH: 19
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 182
cctctataca aacctgggac 19

SEQ ID NO 183
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 183
cctccatgt cggtcctgtgat 20

SEQ ID NO 184
LENGTH: 8
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 184
ccttccgt 8

SEQ ID NO 185
LENGTH: 8
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 185
cgaaacgtt 8

SEQ ID NO 186
LENGTH: 6
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 186
cgsa
<210> SEQ ID NO 187
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone
<400> SEQUENCE: 187
cgsagt
<210> SEQ ID NO 188
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<400> SEQUENCE: 188
cgactctcga ggttctc
<210> SEQ ID NO 189
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<400> SEQUENCE: 189
cgactgccga acaggatc ggtgactgc acctg
<210> SEQ ID NO 190
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<400> SEQUENCE: 190
cgcgctcggc ggcgttgg
<210> SEQ ID NO 191
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<400> SEQUENCE: 191
cgcctggggc tggcttgg
<210> SEQ ID NO 192
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 192

cgcgcgcgcgcgcgcgcgcgcgc
20

SEQ ID NO 193
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 193

cgcgcgcgcgcgcgcgcgcgcgc
20

SEQ ID NO 194
LENGTH: 6
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 194
cgcgta
6

SEQ ID NO 195
LENGTH: 10
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 195
cgctagaggt tagctg
18

SEQ ID NO 196
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 196
cgctggacct tocat
15

SEQ ID NO 197
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 197

cgctggacct tcagctgctgg

SEQ ID NO 198
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 198

cgctgacct catcaaa

SEQ ID NO 199
LENGTH: 16
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 199

cgccgcctct ccgctctttagtgg

SEQ ID NO 200
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 200

cggtctacg gcggtgcctg

SEQ ID NO 201
LENGTH: 14
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 201

cgtagctctt cctct

SEQ ID NO 202
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 202

cgtatcttctc cgtga

SEQ ID NO 203
LENGTH: 6
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 203
cgtacg

<210> SEQ ID NO 204
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<222> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 204
cgtcga

<210> SEQ ID NO 205
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<222> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 205
cgtcga

<210> SEQ ID NO 206
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<222> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 206
cgtcgt

<210> SEQ ID NO 207
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<222> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 207
cgtcgtcgt

<210> SEQ ID NO 208
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<222> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)(0)
<223> OTHER INFORMATION: phosphorothioate backbone
cgtcgtcgtc gtcgtcgtc t 21

<210> SEQ ID NO: 209
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 209

cgtctatcgg gctctgtgtg ctg 23

<210> SEQ ID NO: 210
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 210

cgttcg 6

<210> SEQ ID NO: 211
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 211

ctaacgtt 8

<210> SEQ ID NO: 212
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 212

ctaacttcttc taatttttttctaa 24

<210> SEQ ID NO: 213
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 213

ctagataaag ccgaaccgc aacagacaca gaagoccnga tagag 45

<210> SEQ ID NO: 214
LENGTH: 8
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
SEQUENCE: 214
ctagcgct

SEQ ID NO: 215
LENGTH: 26
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone
SEQUENCE: 215
ctagcgctg agctatataa gctagc

SEQ ID NO: 216
LENGTH: 25
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
SEQUENCE: 216
ctagcgctg agctatataa gctagc

SEQ ID NO: 217
LENGTH: 25
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
SEQUENCE: 217
ctagcgctg agctatataa tctag

SEQ ID NO: 218
LENGTH: 26
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone
SEQUENCE: 218
ctagcgctg agctatataa gctagc

SEQ ID NO: 219
LENGTH: 25
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 219

cattggtg gacgtcagcc gctag

25

<210> SEQ ID NO 220
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 220

cattggtg gacgtcagcc gctag

25

<210> SEQ ID NO 221
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 221

cattgcatt gacgtcagcc gctagc

26

<210> SEQ ID NO 222
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 222

cattggtgac gtcatcaagc tagt

24

<210> SEQ ID NO 223
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 223

cattgtgctag acgtcatcaagc gctag

25

<210> SEQ ID NO 224
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 224
ctatcggagg actggegcgc c 21

<210> SEQ ID NO 225
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 225

ctatcggagg actggegcgc cg 22

<210> SEQ ID NO 226
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 226

cctcaacgcg gaccttccat 20

<210> SEQ ID NO 227
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 227

cctatgggtcttccaccaag g 21

<210> SEQ ID NO 229
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 229

cctcgcttc asgaagggc g 21

<210> SEQ ID NO 229
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 229

cctgcccggg cccgtagagaa t 21

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

SEQUENCE: 230

tcttcaag tcacttaaag 20

SEQ ID NO 231
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ... (0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 231

tcttctgtag gccgtcttg 20

SEQ ID NO 232
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 232

tctttgcaac ctggaagcta 20

SEQ ID NO 233
LENGTH: 10
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ... (0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 233
tgacgtcat 10

SEQ ID NO 234
LENGTH: 8
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ... (0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 234
tgacgtg 8

SEQ ID NO 235
LENGTH: 10
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ... (0)
OTHER INFORMATION: chimeraic phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 235
tgatgtgca tctgcrga 18

OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends
<210> SEQ ID NO 236
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
  <223> OTHER INFORMATION: Synthetic oligonucleotide
  <221> NAME/KEY: misc_feature
  <222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 236
ctgattgctc tctgtgta

<210> SEQ ID NO 237
<211> LENGTH: 14
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
  <223> OTHER INFORMATION: Synthetic oligonucleotide
  <221> NAME/KEY: misc_feature
  <222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 237
c tgacgctg gga c

<210> SEQ ID NO 238
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
  <223> OTHER INFORMATION: Synthetic oligonucleotide
  <221> NAME/KEY: misc_feature
  <222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 239
c tgacgctgac aat t aactg tg

<210> SEQ ID NO 239
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
  <223> OTHER INFORMATION: Synthetic oligonucleotide
  <221> NAME/KEY: misc_feature
  <222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 239
c tgctgagac tgtgag

<210> SEQ ID NO 240
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
  <223> OTHER INFORMATION: Synthetic oligonucleotide
  <221> NAME/KEY: misc_feature
  <222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 240
c tgctgctgc tgc tgtgctgct gt g

<210> SEQ ID NO 241
<211> LENGTH: 16
<
ctgacccctc catggtc
16

ctgacccctc catggtgc
18

ctgtctcttc tggggtttttt cttgg
24

ctgtctcttc tggggtttttt cttgg
24

ctgtaagtgacctggagagag
20
ctgtatgaaa caaatttccc toccttgcccactg

ctgtcagggcctgacgtaa gg

tgtcactata tttttagaca

tgtgctcgcg

tgtgctcgcg
<210> SEQ ID NO 252
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 252

ctgtcgctcc ccccccccc

<210> SEQ ID NO 253
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 253

c tgtgcttttc tgtg

<210> SEQ ID NO 254
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 254

c tttggagggc ttcctggccgg

<210> SEQ ID NO 255
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 255

c tttggagga g aacccctg a g

<210> SEQ ID NO 256
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 256

c tttggagga g aacccctg a g c ttcctgg a ggca g ccgg

<210> SEQ ID NO 257
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: [0]...
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 257

ctttcggtg gcccccgtgg

<210> SEQ ID NO 259
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: [0]...
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: [2]...
<233> OTHER INFORMATION: m5c
<221> NAME/KEY: modified_base
<222> LOCATION: [6]...
<223> OTHER INFORMATION: m5c
<221> NAME/KEY: modified_base
<222> LOCATION: [10]...
<223> OTHER INFORMATION: m5c
<221> NAME/KEY: modified_base
<222> LOCATION: [15]...
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 258

cnggcn gcgcgcgcgg

<210> SEQ ID NO 259
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: [0]...
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: misc_feature
<222> LOCATION: [1]...
<223> OTHER INFORMATION: FITC labeled

<400> SEQUENCE: 259

acggttg

<210> SEQ ID NO 260
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: [0]...
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: misc_feature
<222> LOCATION: [1]...
<223> OTHER INFORMATION: FITC labeled

<400> SEQUENCE: 260

cggcaattcg cg

<210> SEQ ID NO 261
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<223> NAME/KEY: misc_feature
<222> LOCATION: (1)...(1)
<223> OTHER INFORMATION: FITC labeled

<400> SEQUENCE: 261

tcaacggt 8

<210> SEQ ID NO 262
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 262
gaaacggt 8

<210> SEQ ID NO 263
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 263

gaaactgtcgctagttttgc tttat 25

<210> SEQ ID NO 264
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 264
gaaccttcga tgctgtt 17

<210> SEQ ID NO 265
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 265
gaaccttcga tgcgtgcagcgc 20

<210> SEQ ID NO 266
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 266
gaacgctgga cctcccat 18

<210> SEQ ID NO 267
<211> LENGTH: 21

gaa
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 267

gagtttcacg tgaggggca t

<210> SEQ ID NO 268
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 268

gagttttctg gtaagctttc g

<210> SEQ ID NO 269
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 269

gaccttcacat

<210> SEQ ID NO 270
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 270

gaccttcacat gtcggctctcg at

<210> SEQ ID NO 271
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 271

gaccttcctat gtcggctctcg

<210> SEQ ID NO 272
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 272

gacgtcat

<210> SEQ ID NO 273
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 273

gactgacgtc agcgt

<210> SEQ ID NO 274
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 274

gagaacgatg gaccttccat

<210> SEQ ID NO 275
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 275

gagaacgcta gaccttccat

<210> SEQ ID NO 276
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 276

gagaacgctc caccttccat

<210> SEQ ID NO 277
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 277

gagaacgctc cagcactgat

<210> SEQ ID NO 278
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 279

```gagaagctc cagctttcgat```

SEQ ID NO 279
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphothioate backbone

SEQUENCE: 279

```gagaagctc cagctttcga t```

SEQ ID NO 280
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 280

```gagaagctc gacctttccat```

SEQ ID NO 281
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphothioate backbone
NAME/KEY: misc_feature
LOCATION: (20)...(20)
OTHER INFORMATION: biotinylated at 3' end

SEQUENCE: 281

```gagaagctc gaccttccgat```

SEQ ID NO 282
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 282

```gagaagctg gacctatccga t```

SEQ ID NO 283
LENGTH: 25
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 283

gagaacgtg gcctcatac tccat

<210> SEQ ID NO 284
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 284

gagaacgtg gcctcatacc at

<210> SEQ ID NO 285
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 285

gagaacgtg gccttcc

<210> SEQ ID NO 286
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 286

gagaacgtg gccttccatcac tcat

<210> SEQ ID NO 287
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 287

gagaacgtg gccttccatcactc

<210> SEQ ID NO 288
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 288

gagaacgtg gccttccatcactc gt

<210> SEQ ID NO 289
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 209

gagaacgtg gaccttcgat

20

<210> SEQ ID NO 290
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 290

gagaacgtg gaccttcgta

20

<210> SEQ ID NO 291
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 291

gagaacgtg gaccttcgcat

20

<210> SEQ ID NO 292
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 292

gagaacgtg gacgtcactc cat

23

<210> SEQ ID NO 293
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 293

gagaacgtg gacctccat

19

<210> SEQ ID NO 294
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
NAME/KEY: modified_base
LOCATION: (14)...(14)
OTHER INFORMATION: m5c

SEQUENCE: 294

gagaacgtgc gacnttcccat

SEQ ID NO 295
LENGTH: 17
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 295

gagaacgtgc gatcccat

SEQ ID NO 296
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 296

gagasatgctg gaccttcccat

SEQ ID NO 297
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
NAME/KEY: modified_base
LOCATION: (6)...(6)
OTHER INFORMATION: m5c

SEQUENCE: 297

gagasangctg gaccttcccat

SEQ ID NO 298
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 298

gagascgctc gaccttccgt

SEQ ID NO 299
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorochloate backbone
gagcaagctg gccttcctac 20

<210> SEQ ID NO 300
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)...(20)
<223> OTHER INFORMATION: biotinylated at 3' end

<400> SEQUENCE: 300

<210> SEQ ID NO 301
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 301

gaggaacgtc atggagagga acgctca gggagagtc atgga 45

<210> SEQ ID NO 302
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: I
<221> NAME/KEY: modified_base
<222> LOCATION: (11)...(11)
<223> OTHER INFORMATION: I
<221> NAME/KEY: modified_base
<222> LOCATION: (15)...(15)
<223> OTHER INFORMATION: I

<400> SEQUENCE: 302

gaggaagng nggagacgt 20

<210> SEQ ID NO 303
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 303

gagggagcca tttacgggc 20

<210> SEQ ID NO 304
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 304

gatccagatt ctgccaggtc actgtgactg gat

<210> SEQ ID NO 305
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 305

gatccagatt ctgctgagtc actgtgactg gat

<210> SEQ ID NO 306
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 306

gatccagtcg cagtaaactg gcagaatctg gat

<210> SEQ ID NO 307
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 307

gatccagtcg cagtaaactg gcagaatctg gat

<210> SEQ ID NO 308
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 308

gatcggctg actcatcaact agatc

<210> SEQ ID NO 309
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 309

```
gatcgctgat ctaatgctcg
```

SEQUENCE: 310

```
gatcgggaggt cggcgcgcgc g
```

SEQUENCE: 311

```
gatcctagtaga tgaatcgcgcgc gatatc
```

SEQUENCE: 312

```
gatcggacttcg gcgtcatct taggc
```

SEQUENCE: 313

```
gcagacgtt
```

SEQUENCE: 314

```
gcagtt
```

SEQ ID NO 310
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQ ID NO 311
LENGTH: 25
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQ ID NO 312
LENGTH: 25
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQ ID NO 313
LENGTH: 8
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQ ID NO 314
LENGTH: 10
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
NAME/KEY: misc_feature
LOCATION: (10)...(10)
OTHER INFORMATION: biotinylated at 3' end

SEQ ID NO 315
LENGTH: 8
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
NAME/KEY: misc_feature
LOCATION: (10)...(10)
gcaatattgc

<210> SEQ ID NO 315
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . . (0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: misc_feature
<222> LOCATION: (10) . . . (10)
<223> OTHER INFORMATION: FITC labeled

<400> SEQUENCE: 315

 gcaatattgc

<210> SEQ ID NO 316
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 316

gcacacgctc cgcagcgcga

<210> SEQ ID NO 317
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 317

gcagccctctt ttcacacctgg gacggga

<210> SEQ ID NO 318
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . . (0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 319

gcatagcgtt gagct

<210> SEQ ID NO 319
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) . . . (0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 319

gcatagcgtt gagct

<210> SEQ ID NO 320
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 320

gcatgacggtt gagct

15

<210> SEQ ID NO 321
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 321

gcatgacggtt gagct

15

<210> SEQ ID NO 322
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 322

gcatgacggtt gagctga

17

<210> SEQ ID NO 323
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 323

gcatgagtt gagctga

17

<210> SEQ ID NO 324
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 324

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<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 325

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gcatgtaggt gactg 15
gcatgtgtagt gactg 15

gcattccatt gcgggcaag aat 23

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 329

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FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 330

gcctgggtt gacgt

SEQ ID NO 331
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 331

gcattggag gacgt

SEQ ID NO 332
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 332

gccaccaaaa cttgtcgcag

SEQ ID NO 333
LENGTH: 17
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

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gcagatgtt agctgga

SEQ ID NO 334
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TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 334

gcctggagc asctgtccccc cctc

SEQ ID NO 335
LENGTH: 20
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ORGANISM: Artificial Sequence
FEATURE:
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gcgcgggcgc gcgcgcgcgcgc

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<400> SEQUENCE: 346

gcg cgctcg cgcg cgccc

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<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 347

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<400> SEQUENCE: 348

gcg cgctcg cgcg cgccc

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<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 349

gcg cgctgc ccggggcccc

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<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 350

gcg cgctgc ccggggcccc

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<223> OTHER INFORMATION: phosphorothioate backbone

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gcg ccgggg ggccg
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<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 352

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<400> SEQUENCE: 353

gctaaagtt agcgt

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<400> SEQUENCE: 354

gctaccctag gctga

15

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<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 355

gctaccctag ngtga

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OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 362

gctagacgtt agc

SEQ ID NO 363
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
- OTHER INFORMATION: Synthetic oligonucleotide
  NAME/KEY: misc_feature
  LOCATION: (0)...

OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 363

gctagacgtt agcgt

SEQ ID NO 364
LENGTH: 17
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
- OTHER INFORMATION: Synthetic oligonucleotide
  NAME/KEY: misc_feature
  LOCATION: (0)...

OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 364

gctagacgtt agctgta

SEQ ID NO 365
LENGTH: 17
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
- OTHER INFORMATION: Synthetic oligonucleotide
  NAME/KEY: misc_feature
  LOCATION: (0)...

OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 365

gctagacgtt agctgta

SEQ ID NO 366
LENGTH: 17
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
- OTHER INFORMATION: Synthetic oligonucleotide
  NAME/KEY: misc_feature
  LOCATION: (0)...

OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 366

gctagacgtt agctgta

SEQ ID NO 367
LENGTH: 17
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURES:
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OTHER INFORMATION: phosphodiester backbone
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gctagcggtt aggcatga  

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<400> SEQUENCE: 370

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<221> NAME/KEY: misc_feature
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<400> SEQUENCE: 371

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<400> SEQUENCE: 386

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<400> SEQUENCE: 391

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FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 399
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SEQ ID NO 400
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 400
gcttgaggg cctgtaagtg

SEQ ID NO 401
LENGTH: 8
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 401
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SEQ ID NO 402
LENGTH: 13
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 402
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SEQ ID NO 403
LENGTH: 25
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 403
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SEQ ID NO 404
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
SEQUENCE: 404

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SEQ ID NO 405
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 405

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SEQ ID NO 406
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 406

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SEQ ID NO 407
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 407

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SEQ ID NO 408
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 408

ggcatcoca cattgaaagt t

SEQ ID NO 409
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 409

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TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
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NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 410

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SEQ ID NO 411
LENGTH: 20
TYPE: DNA
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FEATURE:
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NAME/KEY: misc_feature
LOCATION: (0) ... (0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 411

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SEQ ID NO 412
LENGTH: 19
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ... (0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 412

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SEQ ID NO 413
LENGTH: 19
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ... (0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 413

ggt atg tgc tt ccc

SEQ ID NO 414
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ... (0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 414

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SEQ ID NO 415
LENGTH: 20
TYPE: DNA
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backbone with phosphorothioate at 5' and 3' ends

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ORGANISM: Artificial Sequence
FEATURE:
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NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 437

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SEQ ID NO 438
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 438

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SEQ ID NO 439
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 439

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SEQ ID NO 440
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 440

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FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

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SEQUENCE: 450

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 461

gtccccagtt gtatagggc tgc

<210> SEQ ID NO 462
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 462

gtcccccattt cccagaggg gsaat

<210> SEQ ID NO 463
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 463

```
gtccgggcca ggcacaaagtc
```

SEQ ID NO: 464
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 464

```
gtccggtctcg atgctgttccc
```

SEQ ID NO: 465
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 465

```
gtctatogga ggactgtgccc
```

SEQ ID NO: 466
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 466

```
gtctgcocca tgatctgcc
```

SEQ ID NO: 467
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
NAME/KEY: modified_base
LOCATION: (7)...
OTHER INFORMATION: 1
NAME/KEY: modified_base
LOCATION: (13)...
OTHER INFORMATION: 1
NAME/KEY: modified_base
LOCATION: (19)...
OTHER INFORMATION: 1

SEQUENCE: 467

```
gtgaatnggt tmcgcgggtc
```

SEQ ID NO: 469
LENGTH: 18
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 469

gtgccgggt ctcggggc

SEQ ID NO: 469
LENGTH: 10
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc.feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 469

gtgccgggt ctcggggc

SEQ ID NO: 470
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc.feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 470
gtgcgcggga gcgcgaactc

SEQ ID NO: 471
LENGTH: 26
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 471
gtgcgtgatca cgcatactc gtgcgg

SEQ ID NO: 472
LENGTH: 22
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 472
gtgcgtgcac ccgcataattt gg

SEQ ID NO: 473
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 473
gtgggtcacc tgcgtgcaccat

SEQ ID NO: 474
LENGTH: 22
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 474

gtttcgaggt ctccgggc

<210> SEQ ID NO 475
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 475

gttctcagat aacgcggaac cagcaacaga cacagaa

<210> SEQ ID NO 476
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 476

gttgaaccc ggaacatca t

<210> SEQ ID NO 477
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_difference
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 477

gttsgataca ggccagactt tgtg

<210> SEQ ID NO 478
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 478

gttttatat astttggg

<210> SEQ ID NO 479
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: biotinylated at 3' end
<210> SEQ ID NO 480
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: modified_base
<222> LOCATION: (2)...(2)
<223> OTHER INFORMATION: m5c
<221> NAME/KEY: modified_base
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: m5c
<221> NAME/KEY: modified_base
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: m5c
<221> NAME/KEY: modified_base
<222> LOCATION: (12)...(12)
<223> OTHER INFORMATION: m5c
<221> NAME/KEY: modified_base
<222> LOCATION: (14)...(14)
<223> OTHER INFORMATION: m5c
<400> SEQUENCE: 480
gnsgnsgnsgnsgnsgnsgnsgnscn

<210> SEQ ID NO 481
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone
<400> SEQUENCE: 481
taasgctt

<210> SEQ ID NO 482
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<400> SEQUENCE: 482
taagcgct

<210> SEQ ID NO 483
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<400> SEQUENCE: 483
taagctctgt caacgccagg
<210> SEQ ID NO 484
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)..(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 484

taccgagctt cgacgagatt tca 23

<210> SEQ ID NO 485
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)..(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 485

taccgcgtgc gaccctctt 18

<210> SEQ ID NO 486
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)..(0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 486

tacttcctgg atccctggcg 20

<210> SEQ ID NO 487
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 487

tagaaacagc atctctccttt tagggcagca ca 32

<210> SEQ ID NO 488
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)..(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 488

tagagctc 8

<210> SEQ ID NO 489
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> OTHER INFORMATION: Synthetic oligonucleotide
<222> NAME/KEY: misc_feature
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 489

tagacgttag cgtga

15

<210> SEQ ID NO 490
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 490
tatagtcct gagactgccc cacctttca acaacc

36

<210> SEQ ID NO 491
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 491
tatcggagga cttggcgcgcc g

21

<210> SEQ ID NO 492
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 492
tagcgcgc gcggactctat

20

<210> SEQ ID NO 493
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 493
tcaaatggtg gattttccca tgaagtct

27

<210> SEQ ID NO 494
<211> LENGTH: 7
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 494
tcaacgt

7
<210> SEQ ID NO 495
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 495

tcaacgtc

8

<210> SEQ ID NO 496
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: p-ethoxy backbone

<400> SEQUENCE: 496
tcaacgtt

8

<210> SEQ ID NO 497
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 497

tcaacgtt

8

<210> SEQ ID NO 498
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 499

tcaacgtt

8

<210> SEQ ID NO 499
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 499

tcaacgttaa cgttaacgtt

20

<210> SEQ ID NO 500
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone
<221> NAME/KEY: misc_feature
<222> LOCATION: (32)...(32)
<223> OTHER INFORMATION: biotinylated at 3' end

<400> SEQUENCE: 500

tcaacgttta cgttaacgtt aacgtaacg tt

<210> SEQ ID NO 501
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 501

tcaacggttga

<210> SEQ ID NO 502
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 502

tcaacggttga

<210> SEQ ID NO 503
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: biotinylated at 3' end

<400> SEQUENCE: 503

tcaacggttga

<210> SEQ ID NO 504
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: FITC labeled

<400> SEQUENCE: 504
<210> SEQ ID NO 505
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: p-ethoxy backbone

<400> SEQUENCE: 505
tcaagctt

---

<210> SEQ ID NO 506
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 506
tcaagctt

---

<210> SEQ ID NO 507
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (5) ...(5)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 507
tcaatggctga

---

<210> SEQ ID NO 508
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (5) ...(5)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 509
tcaangtt

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<210> SEQ ID NO 509
<211> LENGTH: 10
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: misc_feature
tcangttga

<210> SEQ ID NO 510
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 510

tcacggt

<210> SEQ ID NO 511
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 511

tcagctaac cctgac

<210> SEQ ID NO 512
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 512

tcagctaac ctctgac

<210> SEQ ID NO 513
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 513

tcagctaac gctgac

<210> SEQ ID NO 514
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 514

tcgact

SEQ ID NO 515
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 515

tcagaccacg tggtcgggtg ttctctga

SEQ ID NO 516
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 516

tcagaccacg tggtcgggtg ttctctga

SEQ ID NO 517
LENGTH: 8
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 517

tcagcgt

SEQ ID NO 518
LENGTH: 12
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 518

tcagctcgg cc

SEQ ID NO 519
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 519

tcagcttcgg taccttttca
<210> SEQ ID NO 520
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 520

tcaggaacc cgcaccagt ggtctga

<210> SEQ ID NO 521
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 521

tcaggaacc cgcaccagt ggtctga

<210> SEQ ID NO 522
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 522

tcaggggtg ggggaacctt

<210> SEQ ID NO 523
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified base
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 523

tcagngct

<210> SEQ ID NO 524
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 524

tcatcgat
<210> SEQ ID NO 525
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 525

tccagacgt tctgatgct

<210> SEQ ID NO 526
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 526

tccagtagt tctagttct

<210> SEQ ID NO 527
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 527

tccaccacgt ggctgatgct

<210> SEQ ID NO 529
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 529

tccaccacgt ggtctgatgct

<210> SEQ ID NO 530
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 530

tccagacgt ttctgaagtt
FEATURE:
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 530

ccagcggt gaagt

-continued

SEQUENCE: 531

ccagcggtt gaagt

SEQUENCE: 532

ccagcggttgaagt

SEQUENCE: 533

tccagctgc gcacat

SEQUENCE: 534

tccagacgt tccagtttct

SEQUENCE: 535

tccagacgt tccagtttct
-continued

<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 535

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<222> LOCATION: (0)...(0)
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<400> SEQUENCE: 536

tccaggacct ctctcaggtt 20

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<223> OTHER INFORMATION: phosphodiester backbone

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tcctacaagt gcctagctct

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NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 551
ctcgacgt tctgacgtct

SEQ ID NO 552
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 552
tctgacgg tctgacgtct

SEQ ID NO 553
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 553
tctgacgg tctgacgtct

SEQ ID NO 554
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 554
tctgacgg tctgacgtct

SEQ ID NO 555
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 555
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tccatgacgt cctgatgct

**Sequence 557**
tccatgacgt cctgatgct

**Sequence 558**
tccatgacgt tcctagcttt

**Sequence 559**
tccatgacgt tcctotocat gacgttcttc tcctagacgt tctctc

**Sequence 560**
tccatgacgt tcctagacgtt

**Sequence 561**
tccatgacgt tcctagacgt
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<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 562

tccatgacgt tccgacggtt

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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 563

tccatgacgt tccgacggtt

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<221> NAME/KEY: misc_feature
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<400> SEQUENCE: 564

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<400> SEQUENCE: 565

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<223> OTHER INFORMATION: phosphodiester backbone

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<223> OTHER INFORMATION: phosphorothioate backbone

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<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 569

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<400> SEQUENCE: 570

tccatgacgt tctgacggtt

20

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<212> TYPE: DNA
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<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 571

tccatgacgt tctgacgagg

20

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**OTHER INFORMATION:** Synthetic oligonucleotide
**NAME/KEY:** misc_feature
**LOCATION:** (0)...

**OTHER INFORMATION:** phosphodiester backbone
**NAME/KEY:** modified_base
**LOCATION:** (13)...

**OTHER INFORMATION:** m5c

**SEQUENCE:** 572

tccatgagct tcttgagctc

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**SEQ ID NO 573**
**LENGTH:** 20
**TYPE:** DNA
**ORGANISM:** Artificial Sequence

**FEATURE:**
**OTHER INFORMATION:** Synthetic oligonucleotide
**NAME/KEY:** misc_feature
**LOCATION:** (0)...

**OTHER INFORMATION:** phosphodiester backbone

**SEQUENCE:** 573

tccatgagct tcttgagctt

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**SEQ ID NO 574**
**LENGTH:** 20
**TYPE:** DNA
**ORGANISM:** Artificial Sequence

**FEATURE:**
**OTHER INFORMATION:** Synthetic oligonucleotide
**NAME/KEY:** misc_feature
**LOCATION:** (0)...

**OTHER INFORMATION:** phosphodiester backbone

**SEQUENCE:** 574

tccatgagct tcttgagctt

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**SEQ ID NO 575**
**LENGTH:** 20
**TYPE:** DNA
**ORGANISM:** Artificial Sequence

**FEATURE:**
**OTHER INFORMATION:** Synthetic oligonucleotide
**NAME/KEY:** misc_feature
**LOCATION:** (0)...

**OTHER INFORMATION:** p-ethoxy backbone

**SEQUENCE:** 575

tccatgagct tcttgagctc

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**LENGTH:** 20
**TYPE:** DNA
**ORGANISM:** Artificial Sequence

**FEATURE:**
**OTHER INFORMATION:** Synthetic oligonucleotide
**NAME/KEY:** misc_feature
**LOCATION:** (0)...

**OTHER INFORMATION:** phosphorothioate backbone

**SEQUENCE:** 576

tccatgagct tcttgagctc

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**SEQ ID NO 577**
**LENGTH:** 20
**TYPE:** DNA
**ORGANISM:** Artificial Sequence

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<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 577

tccatgagt tcttgagtct  

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 578

tccatgagt tcttgagtct

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<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: I

<400> SEQUENCE: 579

tccatgagt tccatgagt

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<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 581

tccatgagt tccatggtct

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ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...
OTHER INFORMATION: phosphodiester backbone
NAME/KEY: modified_base
LOCATION: (8)...
OTHER INFORMATION: m5c

SEQUENCE: 582

tccatgagt tcctgatgc

SEQ ID NO 583
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...
OTHER INFORMATION: phosphorothioate backbone
NAME/KEY: modified_base
LOCATION: (8)...
OTHER INFORMATION: m5c
NAME/KEY: modified_base
LOCATION: (17)...
OTHER INFORMATION: m5c

SEQUENCE: 583
tccatgagt tcctgagntt

SEQ ID NO 584
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 584
tccatgcgg tcctgagct

SEQ ID NO 585
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 585
tccatgcgg tcctgagct

SEQ ID NO 586
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 586
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<223> OTHER INFORMATION: phosphorothioate backbone
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tccatgag ctctggctct

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<400> SEQUENCE: 597

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<400> SEQUENCE: 598

tccagtctc tccgtagctc
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tccagtctc tccgtagctc
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<400> SEQUENCE: 600

tccagtctc tccgtagctc
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<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 601

tccagtctc tccgtagctc
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backbone with phosphorothioate at 5' and 3' ends

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<221> NAME/KEY: misc_feature
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<400> SEQUENCE: 605

 tcagtcgg toctgatgt
  20

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<223> OTHER INFORMATION: phosphodiester backbone
<226> NAME/KEY: modified_base
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<223> OTHER INFORMATION: m5c
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OTHER INFORMATION: phosphodiester backbone

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ORGANISM: Artificial Sequence
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LOCATION: (0) ...(0)
OTHER INFORMATION: phosphorothioate backbone

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LENGTH: 20

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NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 615

tccatgctg tctgctgct

SEQ ID NO 616
LENGTH: 20

ORGANISM: Artificial Sequence
FEATURE:
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 616

tccatgctg ttttgctgct

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LENGTH: 20

ORGANISM: Artificial Sequence
FEATURE:
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 617

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<223> OTHER INFORMATION: m5c

SEQUENCE: 618

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FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ... (0)
OTHER INFORMATION: phosphodiester backbone
NAME/KEY: modified_base
LOCATION: (8) ... (8)
OTHER INFORMATION: m5c

SEQUENCE: 619
tccatgtnng tcctgatgct

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FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ... (0)
OTHER INFORMATION: phosphodiester backbone
NAME/KEY: modified_base
LOCATION: (8) ... (8)
OTHER INFORMATION: m5c

SEQUENCE: 620
tccatgtnng tcctgatgct

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LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ... (0)
OTHER INFORMATION: phosphorothioate backbone
NAME/KEY: modified_base
LOCATION: (8) ... (8)
OTHER INFORMATION: m5c
NAME/KEY: modified_base
LOCATION: (17) ... (17)
OTHER INFORMATION: m5c

SEQUENCE: 621
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SEQ ID NO 622
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
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OTHER INFORMATION: phosphodiester backbone
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NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

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LENGTH: 19
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

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ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 651
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SEQ ID NO 652
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ORGANISM: Artificial Sequence
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OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 652
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LENGTH: 22
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 653
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SEQ ID NO 654
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 654

toctgaogtt gaagt

SEQ ID NO 655
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ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 655

toctgaogtt gaagt

SEQ ID NO 656
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 656

toctgaogtt gaagt

SEQ ID NO 657
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 657

toctgaogtt gaagt

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ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone
NAME/KEY: modified_base
LOCATION: (7) ...(7)
OTHER INFORMATION: m5c

SEQUENCE: 658

toctgaogtt gaagt

SEQ ID NO 659
LENGTH: 15
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ORGANISM: Artificial Sequence
FEATURE:
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NAME/KEY: misc_feature
LOCATION: (0) ...(0)
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<223> OTHER INFORMATION: phosphodiester backbone

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<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 677

tcttgctgctt cctgctgcttgaagcaggg

<210> SEQ ID NO 678
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 678

tcttgctgcttt caagctgcaggg

<210> SEQ ID NO 679
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 679

tcttgctgcttt cctgctgcttt

<210> SEQ ID NO 680
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
tctgtcgtt gaagst 15

<210> SEQ ID NO 681
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 681

<210> SEQ ID NO 682
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 682

tctgtcgtt ttttgtcgtt 20

<210> SEQ ID NO 683
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 683

tcttacgtt gaagst 15

<210> SEQ ID NO 684
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 684

tcttgtcgtt tctgtcgtt 20

<210> SEQ ID NO 685
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<400> SEQUENCE: 685
tgagcctc
<210> SEQ ID NO 686
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 686
tgagcctccccc
<210> SEQ ID NO 687
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 687
tgagacattgacacatctg
<210> SEQ ID NO 688
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 689
tgagcgttccccc
<210> SEQ ID NO 689
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 689
tgagcgtcgatggtgtgtttgacgtt
<210> SEQ ID NO 690
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 690
tgga
<210> SEQ ID NO 690
<211> LENGTH: 5
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 690
<210> SEQ ID NO 691
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 691

tcgccgttcc ccccccccc

<210> SEQ ID NO 692
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_difference
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 692

tcgtag

<210> SEQ ID NO 693
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 693

tcgctca

<210> SEQ ID NO 694
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 694

tcgctattc ccccccccc

<210> SEQ ID NO 695
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 695

tcgctgattc ccccccccc

<210> SEQ ID NO 696
<211> LENGTH: 20
<212> TYPE: DNA
ORGANISM: Artificial Sequence

FEATURE:

OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 696

tgctgctgt ccccccccc

SEQ ID NO 697
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 697

tgctgctgt ctccgt

SEQ ID NO 698
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 698

tgctgctgt ctcgctctct t

SEQ ID NO 699
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphodiester on 3' end

SEQUENCE: 699

tgctgctgt ctcgctctct t

SEQ ID NO 700
LENGTH: 21
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphodiester on 3' end

SEQUENCE: 700

tgctgctgt ctcgctctct t

SEQ ID NO 701
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
<220> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 701

tgctgctgt ctgcccttct tcttgcc

<210> SEQ ID NO 702
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 702

tgctgctgt tgcctctttct

<210> SEQ ID NO 703
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 703

tgctgctgt tgtgctttct

<210> SEQ ID NO 704
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 704

tgctgctgcc ccccccccccc

<210> SEQ ID NO 705
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 705

tgctgctcg ttcgctgtcg

<210> SEQ ID NO 706
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 706

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tcgctgctc ggtgctgctc gtt
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SEQ ID NO 707
LENGTH: 14
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 707

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tcgctgctc gtt
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SEQ ID NO 708
LENGTH: 14
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorodithioate backbone

SEQUENCE: 708

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tcgctgctc gtt
```

SEQ ID NO 709
LENGTH: 14
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorodithioate/phosphodiester backbone with phosphodiester on 3' end

SEQUENCE: 709

```
tcgctgctc gtt
```

SEQ ID NO 710
LENGTH: 14
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorodithioate/phosphodiester backbone with phosphodiester on 5' end

SEQUENCE: 710

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tcgctgctc gtt
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SEQ ID NO 711
LENGTH: 17
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone
<400> SEQUENCE: 711

tgctgctgcc cccccccc 17

<210> SEQ ID NO: 712
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 712

tgctgctgcc cccccccc 20

<210> SEQ ID NO: 713
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (16)...(16)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 713

tgctgctgcc cccccccc 20

<210> SEQ ID NO: 714
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphothioate backbone

<400> SEQUENCE: 714

tgctgctgcc cccccccc 20

<210> SEQ ID NO: 715
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 715

tgctgctgg tgcgctgg tgcgtt 26

<210> SEQ ID NO: 716
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone
SEQUENCE: 716

tcgctggttg gttttggttt gtt

SEQ ID NO 717
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 717
tcgctggttg gttttggttt gtt

SEQ ID NO 718
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 718
tcgctggttg gttttggttt gtt

SEQ ID NO 719
LENGTH: 22
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 719
tcgctggttg gtttttgcgtt tt

SEQ ID NO 720
LENGTH: 22
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

SEQUENCE: 720
tcgctggttg gtttttgcgtt tt

SEQ ID NO 721
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone
<400> SEQUENCE: 721
tcgtcgttgc tcgttcttga cgtt 24

<210> SEQ ID NO 722
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 722
tcgtcgttgc tcgtcgttgc tcgtt 26

<210> SEQ ID NO 723
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 723
tcgtcgttgc tcgttgtg ctt 23

<210> SEQ ID NO 724
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 724
tcgtcgttgc gcgttcttga cgtt 24

<210> SEQ ID NO 725
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 725
tcgtcgttgc gcgttcttgt cttt 24

<210> SEQ ID NO 726
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 726
tcgtcgttgc gcgtcgttgc 20
<210> SEQ ID NO 727
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 727

tgctgatgctcgtttagg gggg

<210> SEQ ID NO 728
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorodithioate backbone

<400> SEQUENCE: 729

tgctgatgctcgtttgct cgt

<210> SEQ ID NO 729
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 730

tgctgatgctcgtttgctt cgtt

<210> SEQ ID NO 730
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 731

tgctgatgctcgtttgctt cgtt

<210> SEQ ID NO 731
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 732

tgctgatgctcgtttgctt cgtt

<210> SEQ ID NO 732
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorodithioate backbone

SEQUENCE: 732

tgctggttt cgtggttttt cgtt  

SEQ ID NO: 733
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone
NAME/KEY: misc_feature
LOCATION: (24)...(24)
OTHER INFORMATION: biotinylated at 3' end

SEQUENCE: 733

tgctggttt cgtggttttt cgtt  

SEQ ID NO: 734
LENGTH: 32
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 734

tgctggttt cgtggttttt cgtt gg  

SEQ ID NO: 735
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 735

tgctggttt cgtggttttt cgtt  

SEQ ID NO: 736
LENGTH: 28
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 736

tgctggttt cgtggttttt cgtt gg  

SEQ ID NO: 737
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
<210> SEQ ID NO 738
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<222> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 738

tcgtctttt ttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttt

<210> SEQ ID NO 739
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<222> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 739

tcgtga

<210> SEQ ID NO 740
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<222> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 740

tcgtgg

<210> SEQ ID NO 741
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<222> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 741

tcgtngtttc 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<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

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<210> SEQ ID NO: 743
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 743
tctaaaaacc atctatcttt aacccct

<210> SEQ ID NO: 744
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 744
tctagcttt ttagctttcc

<210> SEQ ID NO: 745
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 745
tctatccac gttggttctcg ttag

<210> SEQ ID NO: 746
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 746
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<210> SEQ ID NO: 747
<211> LENGTH: 22
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone
tctccatct atggtttatat cg 22

<210> SEQ ID NO 748
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 749

tctccatgat ggttttatcgc 20

<210> SEQ ID NO 749
<211> LENGTH: 22
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<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 750

tctccacagc agcgagcgc at 22

<210> SEQ ID NO 750
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 751

tctccacagc agcgacat 18

<210> SEQ ID NO 751
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<212> TYPE: DNA
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<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 752

tctccacagc ggcgc at 18

<210> SEQ ID NO 752
<211> LENGTH: 17
<212> TYPE: DNA
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<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 753

tctccacagc ggccat 17

<210> SEQ ID NO 753
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 753

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<210> SEQ ID NO: 754
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 754

ttccccagctgcgccat

<210> SEQ ID NO: 755
<211> LENGTH: 18
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 755

ttccccagctgcccstat

<210> SEQ ID NO: 756
<211> LENGTH: 19
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 756

ttccccagctgcccat

<210> SEQ ID NO: 757
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 757

ttccccagctgcccatat

<210> SEQ ID NO: 758
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
Sequence 763

tctcccatcg tgcccag

Sequence 764

tctccgacg tgcgccat

Sequence 765

tctccgctcg tgcgccat

Sequence 766

tctccgctcg tgcgccat

Sequence 767

tctccgctcg tgcgccat

Sequence 769

tctccgctcg tgcgccat
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 769

cttgaagctca tctgaagtgg gctgaagtct 30

SEQ ID NO: 769
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5’ and 3’ ends

SEQUENCE: 769
tctgcggctgccggcatatat 20

SEQ ID NO: 770
LENGTH: 8
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 770
tcttgcga 8

SEQ ID NO: 771
LENGTH: 45
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 771
tctgcggatg ctaaggagcgt tacattgca caatcattsa aaggt 45

SEQ ID NO: 772
LENGTH: 27
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 772
tctttatagg tgaetcgaca cttggca 27

SEQ ID NO: 773
LENGTH: 15
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0) ...(0)
OTHER INFORMATION: phosphodiester backbone
NAME/KEY: modified.base
<222> LOCATION: (3)...(3)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 773

tongaagtt gaagtt 15

<210> SEQ ID NO 774
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 774
tgaagtgtt 8

<210> SEQ ID NO 775
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 775
tgcaatgtga ogtcctttag catt 23

<210> SEQ ID NO 776
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 776
tgcaagagt cgggttttcc ccaaccoccc c 31

<210> SEQ ID NO 777
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 777
tgcatacgct ctt 12

<210> SEQ ID NO 778
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends
<400> SEQUENCE: 779

tgcatacgct

<210> SEQ ID NO 779
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 779

tgcatacccc aggcaccacat

<210> SEQ ID NO 780
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 780

tgcatacgct acacagctct

<210> SEQ ID NO 781
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 781

tgcatacgct acacagctct

<210> SEQ ID NO 782
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 782

tgcatacgct acacagctct

<210> SEQ ID NO 783
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 783

tgcatacgct gcatacgctac acacagctct
<210> SEQ ID NO 784
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc.feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 784
tgccaagtgc tgaatcacta ataaga

<210> SEQ ID NO 785
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc.feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 785
tgcctcaaga ggaattttg tttcatacag

<210> SEQ ID NO 786
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc.feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 786
tgcgctct

<210> SEQ ID NO 787
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 787
tgtcagcgtg gctgtaacct

<210> SEQ ID NO 788
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc.feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 788
tgtcagcgtg gctgtaacct

<210> SEQ ID NO 789
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphodiester backbone

SEQUENCE: 789
tgtgctttcc ccccccccc 20

SEQ ID NO 790
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 790
tgtgctttcc ccccccccc 20

SEQ ID NO 791
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 791
tgtgcttttt tgtgcttttg gctt 24

SEQ ID NO 792
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide
NAME/KEY: misc_feature
LOCATION: (0)...(0)
OTHER INFORMATION: phosphorothioate backbone

SEQUENCE: 792
tgtgcttttt tgtgcttttg gctt 24

SEQ ID NO 793
LENGTH: 12
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 793
tggaaccttcc at 12

SEQ ID NO 794
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic oligonucleotide

SEQUENCE: 794
tggaaccttct atgtcgttcc 20
<210> SEQ ID NO 801
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 801

tgctggtgct gtt 13

<210> SEQ ID NO 802
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 802

tgctggtgct gtgtgtcgtg tgcgt 25

<210> SEQ ID NO 803
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 803

tgctggtgct ggtgtgctg t 21

<210> SEQ ID NO 804
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 804

ttcaccggtg taagcggttatt gtc 24

<210> SEQ ID NO 805
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 805

ttcaccgtt 8

<210> SEQ ID NO 806
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 806

ttcaccgtt 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 806

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ttaggacaa taccgctacc accg
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24

<210> SEQ ID NO 807
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 807

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ttaggacag gtcgtagggtg
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20

<210> SEQ ID NO 808
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorodithioate backbone

<400> SEQUENCE: 808

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ttaggggtgg ggttaggggtt
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20

<210> SEQ ID NO 809
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 809

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25

<210> SEQ ID NO 810
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 810

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ttcatgcttt gcasaatggc g
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21

<210> SEQ ID NO 811
<211> LENGTH: 43
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 811

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ttcatgcttt gcasaatggc g
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21
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<210> SEQ ID NO 812
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 812

ttcctgtctg ttcggctcgg

<210> SEQ ID NO 813
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphothioate/phosphodiester backbone with phosphothioate at 5' and 3' ends

<400> SEQUENCE: 813

ttcctgtctg gtcctgtat

<210> SEQ ID NO 814
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 814

ttcgccgcaaa tggcctcagg atgtac

<210> SEQ ID NO 815
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 815

ttcgctttta tctgagaacc atct

<210> SEQ ID NO 816
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 816

ttcctctctg cagagact

<210> SEQ ID NO 817
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphothioate/phosphodiester
backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 817
tccgcgcgag ctcctccacc

<210> SEQ ID NO 818
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 818
tccgcgcgag ctcctccacc

<210> SEQ ID NO 819
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 819
tccgctggttttgtcgtttttgtcgg

<210> SEQ ID NO 820
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 820
ttcctgctgttgcgtgcttttcggtttttttcggtagtac

<210> SEQ ID NO 821
<211> LENGTH: 16
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 821
ttgaaactgs gggtggsagc

<210> SEQ ID NO 822
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 822
ttgccccata ttttagaacc

<210> SEQ ID NO 823
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone

<400> SEQUENCE: 823

ttgggggggg tt

<210> SEQ ID NO 824
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 824

ttgtaccttc catgatggtt

<210> SEQ ID NO 825
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 825

tttatctttt ataaacataa cttaaaca

<210> SEQ ID NO 826
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 826

tttgaatctt cagcggcttc cagtgcc

<210> SEQ ID NO 827
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 827

tttgaatca ggactggtga ggttgag

<210> SEQ ID NO 828
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 828

tttgaattcc gtgtacagaa gcgagaagc
<210> SEQ ID NO 829
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: chimeric phosphorothioate/phosphodiester backbone with phosphorothioate at 5' and 3' ends

<400> SEQUENCE: 829

tttgaaacg ctggaccttc

<210> SEQ ID NO 830
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 830

tttggcgccg ctagacttas cctgagagat a

<210> SEQ ID NO 831
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 831

tttgggccca cgagagacag agacacttc

<210> SEQ ID NO 832
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 832

tttggcoccg cttctcggtt cttgacacg

<210> SEQ ID NO 833
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ... (0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 833

ttttotagag aggtgcaaca tgcctcgg

<210> SEQ ID NO 834
tttttgggggg ggggggttttt

<210> SEQ ID NO 835
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<240> SEQUENCE: 835

ttttttttttt ttttttttt

<210> SEQ ID NO 836
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: chimeric phosphothioate/phosphodiester backbone with phosphodiester on 3' end
<221> NAME/KEY: misc_difference
<222> LOCATION: (13)...(13)
<223> OTHER INFORMATION: FITC labeled
<240> SEQUENCE: 836

ttttttttttt ttttttttt

<210> SEQ ID NO 837
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone
<240> SEQUENCE: 837

ttttttttttt ttttttttt ttttttttt

<210> SEQ ID NO 838
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphorothioate backbone
<240> SEQUENCE: 838

ttttttttttt tttttttttt ttttttttttttt
<210> SEQ ID NO 839
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0)...(0)
<223> OTHER INFORMATION: phosphodiester backbone

<400> SEQUENCE: 839

ttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttt
<210> SEQ ID NO 844
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (2)...(2)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 844

tngtcgttcc ccccccccc

<210> SEQ ID NO 845
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (2)...(2)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 845

tngtcgtttttgt cgtt

<210> SEQ ID NO 846
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (2)...(2)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 846

tngtcgttcc ccccccccc

<210> SEQ ID NO 847
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
<221> NAME/KEY: misc_feature
<222> LOCATION: (0) ...(0)
<223> OTHER INFORMATION: phosphodiester backbone
<221> NAME/KEY: modified_base
<222> LOCATION: (2)...(2)
<223> OTHER INFORMATION: m5c
<221> NAME/KEY: modified_base
<222> LOCATION: (5)...(5)
<223> OTHER INFORMATION: m5c
<221> NAME/KEY: modified_base
<222> LOCATION: (13)...(13)
<223> OTHER INFORMATION: m5c
<221> NAME/KEY: modified_base
<222> LOCATION: (21)...(21)
<223> OTHER INFORMATION: m5c

<400> SEQUENCE: 847
We claim:

1. A method for treating a subject having a B-cell malignancy resistant to therapy with an antibody specific for a surface antigen selected from CD19, CD20, and CD22, wherein cells of the malignancy have low or no baseline expression of the surface antigen, the method comprising:
   - administering to the subject the immunostimulatory CpG oligonucleotide ODN 2006 (SEQ ID NO:729) comprising a backbone modification and an unmethylated C, in an effective amount to upregulate expression of the antigen by the cells of the lymphoma or leukemia; and
   - administering to the subject an antibody specific for the upregulated surface antigen, in an effective amount to treat the subject.

2. A method for treating a subject having a B-cell malignancy, wherein cells of the B-cell malignancy have low or no baseline expression of CD20, the method comprising:
   - administering to the subject the immunostimulatory CpG oligonucleotide ODN 2006 (SEQ ID NO:729) comprising a backbone modification and an unmethylated C, in an effective amount to upregulate expression of CD20 by the cells; and
   - administering to the subject an antibody specific for CD20, in an effective amount to treat the subject.

3. A method for treating a subject having a marginal zone lymphoma or B-cell chronic lymphocytic leukemia, wherein cells of the lymphoma or leukemia have low or no baseline expression of an antigen selected from CD19 and CD22, the method comprising:
   - administering to the subject the immunostimulatory CpG oligonucleotide ODN 2006 (SEQ ID NO:729) comprising a backbone modification and an unmethylated C, in an effective amount to upregulate expression of the surface antigen by the cells; and
   - administering to the subject an antibody specific for the upregulated surface antigen, in an amount effective to treat the subject.

* * * *