RNAI CONJUGATES AND USES THEREOF

CROSS-RELATED APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 63/157,465 filed March 5, 2021, and U.S. Provisional Patent Application Serial No. 63/214,153, filed June 23, 2021. The entire contents of which is incorporated herein by this reference.

TECHNICAL FIELD

[002] The disclosure relates to oligonucleotides or oligonucleotides linked to targeting moieties useful in the inhibition, remission, and/or controlling of cancer in patients. In certain embodiments, the disclosure relates to methods of administering to subjects in need thereof a therapeutically effective amount of one or more RNAi oligonucleotides, or one or more RNAi molecules, that inhibit signal transducer and activator of transcription 3 ("STAT3") expression in a subject.

BACKGROUND OF THE DISCLOSURE

[003] The growth and progression of cancer is influenced by many factors including the tumor microenvironment ("TME") which contains components which may control, influence, or enhance tumor development, including blood vessels, immune cells, fibroblasts, bone marrow-derived inflammatory cells, signaling molecules and the extracellular matrix (Yin *et al.*, INT J. CANCER (2019) 144(5):933-46). Despite the existing heterogeneity of various tumors, the development of a tumor is highly dependent upon the physiological state of the TME. Although tumors may come from a variety of anatomical locations and/or cell populations the tumor itself will have many common features that can be used to derive treatment protocols for the tumor. This is particularly true for the TME maturation of epithelial-derived tumors. Genetic alterations in tumor cells result in hyperplasia, uncontrolled growth, resistance to apoptosis, and a metabolic shift towards anaerobic glycolysis (the so-called "Warburg Effect"). These events create hypoxia, oxidative stress, and acidosis within the TME triggering an adjustment of the extracellular matrix (ECM) surrounding the altered or cancerous cells, a response from neighboring stromal cells (*e.g.,* fibroblasts) and immune cells (lymphocytes and macrophages), inducing angiogenesis and, ultimately, resulting in metastasis. The TME profile itself also

directly impacts the efficacy of anti-cancer therapies (Giraldo *et al.*, BR. J. CANCER (2019) 120: 45-53).

[004] Currently, chemotherapy is the leading cancer therapy worldwide, often combined with surgery, or surgery and radiotherapy, depending on tumor type and stage (Abbas *et al.*, AN OVERVIEW OF CANCER TREATMENT MODALITIES/INTECHOPEN, 2018). Since the discovery of several important mutations that contribute to carcinogenesis (*e.g.,* epidermal cell alterations (Yamaoka *et al.*, INT. J. MOL. SCI. (2017) 18(11): 2420)) these mutations and the proteins they represent have been extensively used as targets for the development of more selective drugs and drug combinations to treat cancer patients. Despite the effectiveness of these drugs, multidrug resistance (MDR) is often seen in patients, which often results in tumor relapse, limited therapeutic options and low quality of life for patients. In addition, cancer research has often been focused on tumor cells even though the effect of the TME and the 'normal' or non-cancerous cells within it that have been shown to play a key role in tumor progression, development and MDR (Klemm *et al.*, TRENDS CELL BIOL (2015) 25(4): 198-213).

[005] At a late stage in development for a solid tumor, the tumor microenvironment is highly complex and heterogeneous (Runa *et al.*, CURR MOL BIOL REP (2017) 3(4): 218-29). The interplay between cancer cells and neighboring cells, including stromal and immune system cells (which frequently appear due to inflammation at the tumor location) results in additional alterations in the TME as well as cellular components, the extracellular matrix, and the formation of vascularization systems, all of which contribute to the metastasis of the tumor (Runa *et al.*, CURR MOL BIOL REP (2017) 3(4): 218-29). During tumor growth, cancer cells and TME constituents are continually adapting to the environment conditions, influencing the overall tumor growth. Accordingly, novel therapies that target different facets of the TME that contribute to tumor growth are needed.

BRIEF SUMMARY OF THE DISCLOSURE

[006] The TME is a complex system of blood vessels, immune cells, fibroblasts, signaling molecules and the extracellular matrix that interact with tumor tissue. Tumor progression is influenced by interactions of cancer cells with their environment that ultimately determine whether the primary tumor is eradicated, metastasizes or establishes dormant micro metastases. The TME can also impact therapeutic responses and drug or treatment resistance. Cancer cells

debilitate antitumor immune responses and create an immunosuppressive environment. Thus, there exists an ongoing need to develop therapeutics capable of overcoming this immunosuppressive environment and/or sensitizing cancer cells to anticancer therapeutics to improve patient outcomes.

[007] The present disclosure provides novel nucleic acids, oligonucleotides or analogues thereof comprising targeting ligands such as hydrophobic ligands, including but not limited to adamantyl and lipid conjugates, which are useful to target immune cells in the TME for therapeutic intervention. The present disclosure relates to nucleic acid-ligand conjugates and oligonucleotide-ligand conjugates, which function to modulate the expression of a target gene in a cell (e.g., an immune cell in a tumor microenvironment), and methods of preparation and uses thereof. Without wishing to be bound by theory, attachment of lipophilic/hydrophobic moieties, such as fatty acids and adamantyl group, to these highly hydrophilic nucleic acids/oligonucleotides substantially enhance plasma protein binding and consequently circulation half-life. As demonstrated herein, incorporation of a hydrophobic moiety such as a lipid facilitates systemic delivery of the novel nucleic acids, oligonucleotides, or analogues thereof into immune cell populations in a tumor microenvironment.

[008] Suitable nucleic acid-ligand conjugates and oligonucleotide-ligand conjugates include nucleic acid inhibitor molecules, such as dsRNA inhibitor molecules, dsRNAi inhibitor molecules, antisense oligonucleotides, miRNA, ribozymes, antagomirs, aptamers, and single-stranded RNAi inhibitor molecules. In some aspects, the present disclosure provides nucleic acid-lipid conjugates, oligonucleotide-lipid conjugates, and analogues thereof, which find utility as modulators of intracellular RNA levels. Nucleic acid inhibitor molecules of the disclosure modulate RNA expression through a diverse set of mechanisms, for example by RNA interference (RNAi). An advantage of the nucleic acid-ligand conjugates, oligonucleotide-ligand conjugates and analogues thereof provided herein is that a broad range of pharmacological activities is possible, consistent with the modulation of intracellular RNA levels. In addition, the disclosure provides methods of using an effective amount of the conjugates described herein for the treatment or amelioration of a disease condition by modulating the intracellular RNA levels.

[009] In some aspects, the present disclosure relates to oligonucleotide-ligand conjugates comprising one or more nucleic acid-ligand conjugate units that modulate target gene expression in an immune cell in the tumor microenvironment *via* RNA interference (RNAi). In some

aspects, the present disclosure relates to oligonucleotide-ligand conjugates comprising one or more hydrophobic moiety ligand(s), including, but not limited to, lipid moieties, that modulate (*e.g.*, reduce or inhibit) target gene expression in an immune cell in the tumor microenvironment, compositions of said oligonucleotide-ligand conjugates, and methods of preparation and uses thereof. In some aspects, the oligonucleotide-ligand conjugates target a gene encoding a regulator of immune suppression, such that reducing or inhibiting expression of the regulator overcomes an immunosuppressive tumor microenvironment. In some embodiments, reducing or inhibiting expression of the regulator induces or enhances an antitumor immune response.

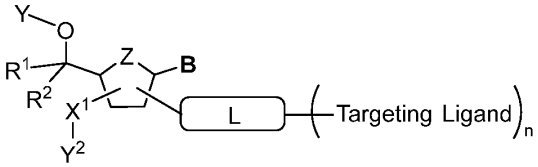
[0010] The present disclosure is based, at least in part, on the discovery of oligonucleotide-ligand conjugates that effectively reduce target gene expression in immune cells present within a tumor microenvironment. Without being bound by theory, as described herein, a hydrophobic moiety (*e.g.*, lipid) facilitates delivery and distribution of an RNAi oligonucleotide-lipid conjugate into immune cells, such as those expressing lipid trafficking receptors, of the tumor microenvironment, thereby increasing efficacy and durability of gene knockdown. Accordingly, the disclosure provides methods of treating cancer and/or reducing tumor growth by modulating target gene expression, e.g., of a gene encoding a regulator of immune suppression, in immune cells within a tumor microenvironment by administering the oligonucleotide ligand conjugates of the disclosure, and pharmaceutically acceptable compositions thereof, as described herein. The disclosure further provides methods of using the oligonucleotide ligand conjugates in the manufacture of a medicament for treating cancer and/or reducing tumor growth by modulating target gene expression in immune cells in a tumor microenvironment.

[0011] In some aspects, the disclosure provides a method of treating, ameliorating, or preventing cancer, and/or preventing metastasis of cancer in a subject in need thereof. The disclosure further provides RNAi oligonucleotide molecules that can limit, control, or eliminate the expression of key genes associated with cancer and/or an immune suppressive tumor microenvironment. Such RNAi oligonucleotide molecules are a variety of double-stranded RNAi oligonucleotides that target signal transducer and activator of transcription 3 (STAT3). In certain embodiments, the method comprises administering to the subject a therapeutically effective amount of a composition that inhibits STAT3 expression or activity in the subject. Such RNAi oligonucleotide molecules are used to treat a subject having cancer and associated pathologies and may thereby therapeutically benefit a subject suffering from carcinoma,

sarcoma, melanoma, lymphoma, and leukemia, prostate cancer, breast cancer, hepatocellular carcinoma (HCC), colorectal cancer, and glioblastoma.

[0012] STAT3 is an important transcription factor that is crucial for then maintenance of carcinogenesis and for chemoresistance to anticancer agents. STAT3 is found in the cytoplasm and is activated in response to stimuli from the cytokines. Activated STAT3 regulates the transcription of genes controlling cell survival and proliferation and regulates the expression of antiapoptotic and immune response genes. Constitutive activation of STAT3 is necessary for the proliferation and survival of different cancers (Groner, B. *et al*, **SEMINARS IN CELL & DEVELOPMENTAL BIOLOGY**, Vol. 19(4): 341-50 (2008)). Activation of STAT-3 provides an advantage for survival of the cancer cells. Like NF-κB, the inhibition of STAT-3 in different cancer types has been demonstrated to induce apoptosis and chemosensitization of cells (da Hora, C.C. *et al.* CELL DEATH DISCOV, Vol. 5(72) https://doi.org/10.1038/s41420-019-0155-9 (2019)). The mRNA sequence of human *STAT3* (NM_001369512.1) is set forth as SEQ ID NO:85 or SEQ ID NO: 1217 (NM_139276.3).

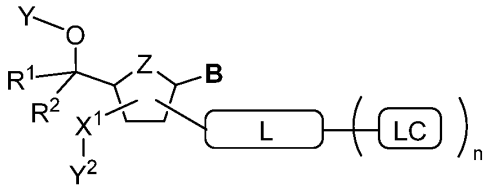
[0013] Accordingly, in one aspect, the disclosure provides an oligonucleotide-ligand conjugate comprising a nucleotide sequence that reduces expression of a target mRNA in an immune cell associated with a tumor microenvironment and one or more targeting ligands, wherein one or more nucleosides of the nucleotide sequence conjugated with one or more targeting ligands is represented by formula **I-a**:



I-a;

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

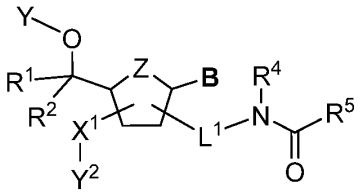
[0014] In another aspect, the present disclosure provides an oligonucleotide-ligand conjugate comprising a nucleotide sequence that reduces expression of a target mRNA in an immune cell associated with a tumor microenvironment and one or more targeting ligands, wherein one or more nucleosides of the nucleotide sequence conjugated with one or more targeting ligands is represented by formula **II-a**:



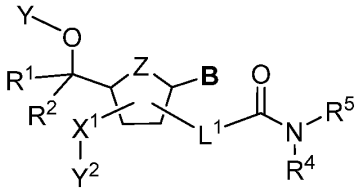
II-a.

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

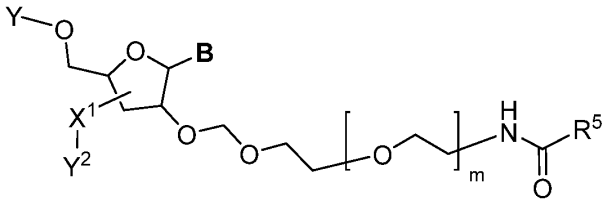
[0015] In certain embodiments, the oligonucleotide-ligand conjugates are represented by formula **II-b, II-c, II-Ib** or **II-Ic**:



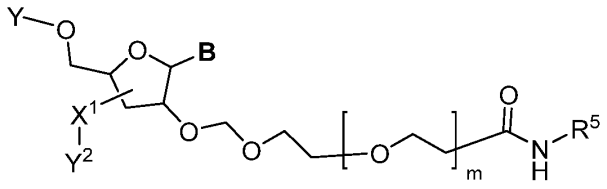
II-b



II-c



II-Ib

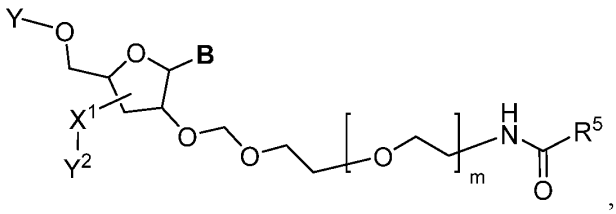


II-Ic

or a pharmaceutically acceptable salt thereof.

[0016] In any of the foregoing or related aspects, R^5 is a saturated or unsaturated, straight or branched C1-C50 hydrocarbon chain. In some aspects, R^5 is a saturated or unsaturated, straight or branched C8-C30 hydrocarbon chain. In some aspects, R^5 is a saturated or unsaturated, straight or branched C16 hydrocarbon chain. In some aspects, R^5 is a saturated or unsaturated, straight or branched C18 hydrocarbon chain.

[0017] In any of the foregoing or related aspects, the oligonucleotide-ligand conjugate comprises an antisense strand of 15 to 30 nucleotides and a sense strand of 15 to 40 nucleotide, wherein the sense and antisense strands form a duplex region, wherein the antisense strand comprises a region of complementarity to a target sequence expressed in an immune cell associated with a tumor microenvironment, wherein the sense strand comprises at its 3' end a stem-loop comprising a tetraloop comprising 4 nucleosides, wherein one or more of the 4 nucleosides conjugated with the targeting ligand is represented by formula II-Ib:



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wherein B is selected from an adenine and a guanine nucleobase, and wherein R^5 is a hydrocarbon chain. In some aspects, wherein the 4 nucleosides of the tetraloop are numbered 1-4 from 5' to 3', and wherein position 1 is represented by formula II-Ib. In other aspects, position 2 is represented by formula II-Ib. In yet other aspects, position 3 is represented by formula II-Ib. In further aspects, position 4 is represented by formula II-Ib.

[0018] In any of the foregoing or related aspects, the target mRNA encodes a regulator of immune suppression. In some aspects, the regulator of immune suppression is a checkpoint inhibitor polypeptide. In some aspects, the regulator of immune suppression is a transcription factor.

[0019] In any of the foregoing or related aspects, the immune cell associated with a tumor microenvironment is a myeloid cell. In some aspects, the immune cell associated with a tumor microenvironment is a T cell. In some aspects, the nucleotide sequence reduces expression of

the target mRNA in more than one immune cell associated with the tumor microenvironment. In some aspects, the immune cell is a myeloid cell or a T cell. In some aspects, the myeloid cell is a myeloid derived suppressor cell (MDSC). In some aspects, the MDSC is a granulocytic MDSC (G-MDSC) or monocytic MDSC (M-MDSC). In some aspects, the nucleotide sequence reduces expression of the target mRNA in G-MDSCs and M-MDSCs. In some aspects, the T cell is a CD8+ T cell or Treg cell.

[0020] In some aspects, the oligonucleotide-ligand conjugate comprises a single stranded oligonucleotide. In some aspects, the oligonucleotide-ligand conjugate comprises a double stranded oligonucleotide. In some aspects, the double stranded oligonucleotide comprises a sense strand and an antisense strand that form a duplex region, wherein the antisense strand comprises a region of complementarity to the target mRNA in the immune cell associated with a tumor microenvironment.

[0021] In another aspect, the present disclosure provides RNAi oligonucleotide molecules capable of inhibiting expression of STAT3. Such molecules can be used alone or in combination with a second therapeutic agent and can vary in dosage. In some embodiments, such RNAi oligonucleotide molecules are comprised of a sense strand and an antisense strand forming a double-stranded region.

[0022] In some aspects, an oligonucleotide for reducing STAT3 expression comprises an antisense strand of 15 to 30 nucleotides in length and a sense strand of 15 to 40 nucleotides in length, wherein the sense strand and antisense strand form a duplex region, wherein the antisense strand has a region of complementarity to a target mRNA sequence of *STAT3* as set forth in SEQ ID NO: 85 or SEQ ID NO: 1217, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the target sequence. In some aspects, the region of complementarity is fully complementary to the target sequence of *STAT3*.

[0023] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a region of complementarity at least 15 contiguous nucleotides in length to a target sequence selected from SEQ ID NOs: 89-280. In some aspects, the region of complementarity is selected from SEQ ID Nos: 89-280.

[0024] In some aspects, an oligonucleotide for reducing STAT3 expression comprises:

(i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *STAT3* mRNA target sequence, wherein the region of complementarity is selected from SEQ ID NOs: 89-280, and

(ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

[0025] In some aspects, the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequences of SEQ ID NOs: 9, 37, 65, or 69, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequences of SEQ ID NOs: 10, 38, 66, or 70. In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand and an antisense strand comprising the nucleotide sequences selected from:

(a) SEQ ID NOS: 9 and 10, respectively;

(b) SEQ ID NOs: 37 and 38, respectively;

(c) SEQ ID NOs: 65 and 66, respectively; and,

(d) SEQ ID NOs: 69 or 70, respectively.

[0026] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand comprising a nucleotide sequence selected from SEQ ID NOs: 857-946.

[0027] In some aspects, an oligonucleotide for reducing STAT3 expression comprises an antisense strand comprising a nucleotide sequence selected from SEQ ID NOs: 947-1036.

[0028] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand and an antisense strand comprising the nucleotide sequences selected from:

(a) SEQ ID NOs: 861 and 951, respectively;

(b) SEQ ID NOs: 857 and 947, respectively;

(c) SEQ ID NOs: 858 and 948, respectively;

(d) SEQ ID NOs: 859 and 949, respectively;

(e) SEQ ID NOs: 860 and 950, respectively;

(f) SEQ ID NOs: 862 and 952, respectively;

(g) SEQ ID NOs: 863 and 953, respectively;

(h) SEQ ID NOs: 864 and 954, respectively;

(i) SEQ ID NOs: 865 and 955, respectively;

(j) SEQ ID NOs: 866 and 956, respectively;

(k) SEQ ID NOs: 867 and 957, respectively;

(l) SEQ ID NOs: 868 and 958, respectively;

(m) SEQ ID NOs: 869 and 959, respectively;

(n) SEQ ID NOs: 870 and 960, respectively;

(o) SEQ ID NOs: 871 and 961, respectively;

(p) SEQ ID NOs: 872 and 962, respectively;

(q) SEQ ID NOs: 873 and 963, respectively;

(r) SEQ ID NOs: 874 and 964, respectively;

(s) SEQ ID NOs: 875 and 965, respectively;

(t) SEQ ID NOs: 876 and 966, respectively;

(u) SEQ ID NOs: 877 and 967, respectively;

(v) SEQ ID NOs: 878 and 968, respectively;

(w) SEQ ID NOs: 879 and 969, respectively;

(x) SEQ ID NOs: 880 and 970, respectively;

(y) SEQ ID NOs: 881and 971, respectively;

(z) SEQ ID NOs: 882 and 972, respectively;

(aa) SEQ ID NOs: 883 and 973, respectively;

(bb) SEQ ID NOs: 884 and 974, respectively;

(cc) SEQ ID NOs: 885 and 975, respectively;

(dd) SEQ ID NOs: 886 and 976, respectively;

(ee) SEQ ID NOs: 887 and 977, respectively;

(ff) SEQ ID NOs: 888 and 978, respectively;

(gg) SEQ ID NOs: 940 and 1030, respectively;

(hh) SEQ ID NOs: 896 and 986, respectively; and

(ii) SEQ ID NOs: 920 and 1010, respectively.

[0029] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand and an antisense strand comprising the nucleotide sequences selected from:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively.

[0030] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand and an antisense strand comprising the nucleotide sequences selected from:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively.

[0031] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand and an antisense strand comprising the nucleotide sequences selected from:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively.

[0032] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand comprising the nucleotide sequence of SEQ ID NO: 862 and an antisense strand comprising the nucleotide sequence of SEQ ID NO: 952.

[0033] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand comprising the nucleotide sequence of SEQ ID NO: 875 and an antisense strand comprising the nucleotide sequence of SEQ ID NO: 965.

[0034] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand comprising the nucleotide sequence of SEQ ID NO: 876 and an antisense strand comprising the nucleotide sequence of SEQ ID NO: 966.

[0035] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand comprising the nucleotide sequence of SEQ ID NO: 920 and an antisense strand comprising the nucleotide sequence of SEQ ID NO: 966.

[0036] In any of the foregoing or related aspects, the antisense strand is 19 to 27 nucleotides in length or 21 to 27 nucleotides in length. In some embodiments, the antisense strand is 22 nucleotides in length.

[0037] In any of the foregoing or related aspects, the sense strand is 19 to 40 nucleotides in length. In some embodiments, the sense strand is 36 nucleotides in length.

[0038] In any of the foregoing or related aspects, the oligonucleotide has a duplex region of at least 19 nucleotides in length. In any of the foregoing or related aspects, the oligonucleotide has a duplex region of at least 21 nucleotides in length. In some embodiments, the duplex region is 20 nucleotides in length.

[0039] In some embodiments, the region of complementarity to *STAT3* is at least 19 contiguous nucleotides in length. In some embodiments, the region of complementarity to *STAT3* is at least 21 contiguous nucleotides in length.

[0040] In any of the foregoing or related aspects, the oligonucleotide comprises on the sense strand at its 3′ end a stem-loop set forth as: S1-Loop-S2, wherein S1 is complementary to S2, and wherein Loop forms a loop between S1 and S2 of 3 to 5 nucleotides in length.

[0041] In some embodiments, an oligonucleotide for reducing STAT3 expression for treating or preventing cancer, and/or preventing metastasis of cancer, comprises an antisense strand and a sense strand, wherein the antisense strand is 21 to 27 nucleotides in length and has a region of complementarity to a target mRNA sequence of *STAT3* set forth in SEQ ID NO: 85 or SEQ ID NO: 1217 , wherein the sense strand comprises at its 3′ end a stem-loop set forth as: S1-Loop-S2, wherein S1 is complementary to S2, and wherein Loop forms a loop between S1 and S2 of 3 to 5 nucleotides in length, and wherein the antisense strand and the sense strand form a duplex structure of at least 19 nucleotides in length.

[0042] In some embodiments, Loop is a tetraloop. In some embodiments, Loop is 4 nucleotides in length. In some embodiments, Loop comprises a sequence GAAA.

[0043] In some embodiments, the oligonucleotide comprises an antisense strand which is 27 nucleotides in length and a sense strand which is 25 nucleotides in length. In some embodiments, the oligonucleotide comprises an antisense strand which is 22 nucleotides in length and a sense strand which is 36 nucleotides in length.

[0044] In any of the foregoing or related aspects, the duplex region of the oligonucleotide of the present disclosure comprises a 3′-overhang sequence on the antisense strand. In some

embodiments, the 3′-overhang sequence on the antisense strand is 2 nucleotides in length. In some embodiments, the 3’-overhang sequence is GG.

[0045] In some embodiments, the oligonucleotide comprises an antisense strand and a sense strand that are each in a range of 21 to 23 nucleotides in length. In some embodiments, the oligonucleotide comprises a duplex structure in a range of 19 to 21 nucleotides in length. In some such embodiments, the oligonucleotide comprises a 3′-overhang sequence of one or more nucleotides in length, wherein the 3′-overhang sequence is present on the antisense strand, the sense strand, or the antisense strand and sense strand. In some embodiments, the 3′-overhang sequence of 2 nucleotides in length, wherein the 3′-overhang sequence is on the antisense strand, and wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length, such that the sense strand and antisense strand form a duplex of 21 nucleotides in length.

[0046] In some embodiments, the oligonucleotide comprises at least one modified nucleotide. In some embodiments, the modified nucleotide comprises a 2′-modification. In some embodiments, all the nucleotides of the oligonucleotide are modified, for example with a 2’-modification. In some embodiments, about 10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprise a 2’-fluoro modification. In some embodiments, about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the antisense strand comprise a 2’-fluoro modification. In some embodiments, about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the oligonucleotide comprise a 2’-fluoro modification. In some embodiments, the sense strand comprises 36 nucleotides with positions 1-36 from 5’ to 3 ’, wherein positions 8-11 comprise a 2’-fluoro modification. In some embodiments, the antisense strand comprises 22 nucleotides with positions 1-22 from 5’ to 3’, and wherein positions 2, 3, 4, 5, 7, 10 and 14 comprise a 2’-fluoro modification. In some embodiments, the remaining nucleotides comprise a 2’-O-methyl modification.

[0047] In some embodiments, the oligonucleotide comprises at least one modified internucleotide linkage, preferably a phosphorothioate linkage.

[0048] In some embodiments, the 4′-carbon of the sugar of the 5′-nucleotide of the antisense strand comprises a phosphate analog, for example, an oxymethylphosphonate, vinylphosphonate or malonyl phosphonate.

[0049] In some embodiments, at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands, such as a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid.

[0050] In some embodiments the targeting ligand is a saturated fatty acid moiety. In some embodiments the saturated fatty acid moiety varies in length from C10 to C24. In some embodiments the saturated fatty acid moiety has a length of C16. In some embodiments the saturated fatty acid moiety has a length of C18. In some embodiments the saturated fatty acid moiety has a length of C22.

[0051] In some embodiments, the targeting ligand comprises a N-acetyl galactosamine (GalNAc) moiety. In some embodiments, the (GalNAc) moiety comprises a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety.

[0052] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand and an antisense strand comprising the nucleotide sequences selected from:

(a) SEQ ID NOs: 1041 and 1131, respectively;

(b) SEQ ID NOs: 1037 and 1127, respectively;

(c) SEQ ID NOs: 1038 and 1128, respectively;

(d) SEQ ID NOs: 1039 and 1129, respectively;

(e) SEQ ID NOs: 1040 and 1130, respectively;

(f) SEQ ID NOs: 1042 and 1132, respectively;

(g) SEQ ID NOs: 1043 and 1133, respectively;

(h) SEQ ID NOs: 1044 and 1134, respectively;

(i) SEQ ID NOs: 1045 and 1135, respectively;

(j) SEQ ID NOs: 1046 and 1136, respectively;

(k) SEQ ID NOs: 1047 and 1137, respectively;

(l) SEQ ID NOs: 1048 and 1138, respectively;

(m) SEQ ID NOs: 1049 and 1139, respectively;

(n) SEQ ID NOs: 1050 and 1140, respectively;

(o) SEQ ID NOs: 1051 and 1141, respectively;

(p) SEQ ID NOs: 1052 and 1142, respectively;

(q) SEQ ID NOs: 1053 and 1143, respectively;

(r) SEQ ID NOs: 1054 and 1144, respectively;

(s) SEQ ID NOs: 1055 and 1145, respectively;

(t) SEQ ID NOs: 1056 and 1146, respectively;

(u) SEQ ID NOs: 1057 and 1147, respectively;

(v) SEQ ID NOs: 1058 and 1148, respectively;

(w) SEQ ID NOs: 1059 and 1149, respectively;

(x) SEQ ID NOs: 1060 and 1150, respectively;

(y) SEQ ID NOs: 1061 and 1151, respectively;

(z) SEQ ID NOs: 1062 and 1152, respectively;

(aa) SEQ ID NOs: 1063 and 1153, respectively;

(bb) SEQ ID NOs: 1064 and 1154, respectively;

(cc) SEQ ID NOs: 1065 and 1155, respectively;

(dd) SEQ ID NOs: 1066 and 1156, respectively;

(ee) SEQ ID NOs: 1067 and 1157, respectively;

(ff) SEQ ID NOs: 1068 and 1158, respectively;

(gg) SEQ ID NOs: 1120 and 1210, respectively;

(hh) SEQ ID NOs: 1076 and 1166, respectively; and

(ii) SEQ ID NOs: 1100 and 1190, respectively.

[0053] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand and an antisense strand comprising the nucleotide sequences selected from:

(a) SEQ ID NOs: 1081 and 1171, respectively;

(b) SEQ ID NOs: 1090 and 1180, respectively;

(c) SEQ ID NOs: 1079 and 1169, respectively;

(d) SEQ ID NOs: 1076 and 1166, respectively;

(e) SEQ ID NOs: 1072 and 1162, respectively;

(f) SEQ ID NOs: 1070 and 1160, respectively; and

(g) SEQ ID NOs: 1069 and 1159, respectively.

[0054] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand and an antisense strand comprising the nucleotide sequences selected from:

(a) SEQ ID NOs: 1120 and 1210, respectively;

(b) SEQ ID NOs: 1117 and 1207, respectively; and

(c) SEQ ID NOs: 1119 and 1209, respectively.

[0055] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand and an antisense strand comprising the nucleotide sequences selected from:

(a) SEQ ID NOs: 1095 and 1185, respectively;

(b) SEQ ID NOs: 1104 and 1194, respectively;

(c) SEQ ID NOs: 1093 and 1183, respectively; and

(d) SEQ ID NOs: 1100 and 1190, respectively.

[0056] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand comprising the nucleotide sequence of SEQ ID NO: 1042 and an antisense strand comprising the nucleotide sequence of SEQ ID NO: 1132.

[0057] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand comprising the nucleotide sequence of SEQ ID NO: 1055 and an antisense strand comprising the nucleotide sequence of SEQ ID NO: 1145.

[0058] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand comprising the nucleotide sequence of SEQ ID NO: 1056 and an antisense strand comprising the nucleotide sequence of SEQ ID NO: 1146.

[0059] In some aspects, an oligonucleotide for reducing STAT3 expression comprises a sense strand comprising the nucleotide sequence of SEQ ID NO: 1100 and an antisense strand comprising the nucleotide sequence of SEQ ID NO: 1190.

[0060] In some embodiments, the targeting ligand is conjugated to one or more nucleotides of Loop of the stem loop. In some embodiments, up to 4 nucleotides of Loop of the stem-loop are each conjugated to a monovalent GalNAc moiety.

[0061] In some embodiments, the oligonucleotides of the present disclosure are RNAi oligonucleotides.

[0062] In some embodiments, the disclosure of the present disclosure is a pharmaceutical composition comprising one or more oligonucleotides and a pharmaceutically acceptable carrier, delivery agent or excipient.

[0063] In some aspects the oligonucleotide of the present disclosure is provided in the form of a kit for treating a cancer. In a further aspect, the oligonucleotide of the present disclosure is provided in the form of a kit for treating a disease, disorder or condition associated with STAT3 expression. In some embodiments, the kit comprises an oligonucleotide described herein, and a

pharmaceutically acceptable carrier. In some embodiments, the kit further includes a package insert comprising instructions for administration of the oligonucleotide to a subject having a cancer. In some embodiments, the kit further includes a package insert comprising instructions for administration of the oligonucleotide to a subject having a disease, disorder or condition associated with STAT3 expression.

[0064] In some embodiments, the present disclosure provides a method of delivering an oligonucleotide to a subject, the method comprising administering a pharmaceutical composition to a subject. In some embodiments, the present disclosure provides a method of delivering an oligonucleotide to an immune cell associated with a tumor microenvironment, comprising administering an oligonucleotide-ligand conjugate described herein.

[0065] In some embodiments the oligonucleotide-ligand conjugate is delivered to tumor associated cells. In some embodiments the oligonucleotide-ligand conjugate is delivered to immune cells. In some embodiments the immune cells are myeloid derived suppressor cells (MDSCs). In some embodiments, the immune cells are T cells.

[0066] In some embodiments the oligonucleotide described herein targets *STAT3*. In some embodiments the oligonucleotide targets *STAT3* and the siRNA also modulates PD-LI mRNA expression.

[0067] In some aspects, the present disclosure provides a method of reducing expression of a target mRNA in a cell, a population of cells associated with a tumor microenvironment in a subject by administering an oligonucleotide of the disclosure. In another aspect, the present disclosure provides a method of reducing STAT3 expression in a cell, a population of cells or a subject by administering an oligonucleotide of the disclosure. In some embodiments, a method of reducing STAT3 expression in a cell, a population of cells or a subject comprises the step of: contacting the cell or the population of cells or administering to the subject an effective amount of an oligonucleotide or oligonucleotides described herein, or a pharmaceutical composition thereof. In some embodiments, the method for reducing STAT3 expression comprises reducing an amount or a level of *STAT3* and *PD-L1* mRNA, an amount, or a level of STAT3 and PD-L1 protein, or both.

[0068] In some embodiments the present disclosure provides a pharmaceutical product for use as a therapeutic agent. In some embodiments a therapeutic agent is administered as a monotherapy and is an inhibitor of STAT3 expression.

[0069] In some embodiments, a method of treating human subjects that are resistant to anti-PD1 or anti-PD-L1 therapy is provided comprising administering any one of the STAT3 targeting oligonucleotides described herein. Subjects who are resistant to anti-PD1 or anti-PD-L1 include subject whose benefit from the anti-PD1 or anti-PD-L1 therapy remained diminished by at least one standard deviation as compared to a non-resistant control for greater than three months.

[0070] In some embodiments a therapeutic agent is administered as a monotherapy and is an inhibitor of STAT3 and PD-L1 expression. In some embodiments, the present disclosure provides a pharmaceutical product comprising at least a first and second therapeutic agent, wherein the first therapeutic agent is an inhibitor of STAT3. In some embodiments a therapeutic agent is administered prior to, or intermittently with, administration of a second therapeutic agent. In some embodiments, a first therapeutic agent is administered concurrently or simultaneously with a second therapeutic agent. In some embodiments, the present disclosure provides a pharmaceutical product comprising more than two therapeutic agents, wherein the first therapeutic agent is an inhibitor of STAT3.

[0071] In some aspects, the disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of an oligonucleotide-ligand conjugate described herein that targets a regulator of immune suppression, provided by the disclosure, in combination with one or more additional therapeutic agents or procedures. In some embodiments, the disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of an oligonucleotide that targets STAT3, provided by the disclosure, in combination with one or more additional therapeutic agents or procedures. In some aspects, the second therapeutic agent or procedure is selected from the group consisting of: a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy, gene therapy or a combination thereof.

[0072] In some embodiments, the disclosure provides a method of treating a subject having a disease, disorder or condition associated with STAT3 expression, the method comprising administering to the subject a therapeutically effective amount of an oligonucleotide or oligonucleotide-ligand conjugate described herein. In some embodiments, the oligonucleotide or

oligonucleotide-ligand conjugate is administered in combination with a second composition or therapeutic agent. In some embodiments, the second composition or therapeutic agent targets TGFB, CXCR2, CCR2, ARG1, PTGS2, SOCS1 or PD-L1.

[0073] In some embodiments, the one or more additional therapeutic agents is a PD-1 antagonist, a CTLA-4 inhibitor, a TGFB inhibitor, a CXCR2 inhibitor, a CCR2 antagonist, an ARG1 inhibitor, a PTGS2 inhibitor, a SOCS1 modulator or a combination thereof.

[0074] In some embodiments, the one or more additional therapeutic agents is a PD-1 antagonist.

[0075] In some embodiments, the PD-1 antagonist is selected from the group consisting of: PDR001, nivolumab, pembrolizumab, pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224. In some embodiments, the PD-1 antagonist is selected from the group consisting of: FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559.

[0076] In some embodiments, the one or more additional therapeutic agents is a CTLA-4 inhibitor. In some embodiments, the CTLA-4 inhibitor is Ipilimumab or Tremelimumab.

[0077] In some embodiments, the one or more additional therapeutic agents is a TGFB inhibitor. In some embodiments, the TGFB inhibitor is Frisolimumab, LY3022859 or PF-03446962.

[0078] In some embodiments, the one or more additional therapeutic agents is an ARG1 inhibitor. In some embodiments, the ARG1 inhibitor is CB-1158.

BRIEF DESCRIPTION OF THE DRAWINGS

[0079] **FIG. 1A** provides structures of RNAi oligonucleotide molecules having chemical modifications with GalNAc (top) or lipid (bottom) conjugated to the base molecule to generate oligonucleotide-ligand conjugates.

[0080] **FIG. 1B** provides structures of lipid tails suitable for conjugation to RNAi oligonucleotide molecules.

[0081] **FIG. 2A** is a graph representing remaining human *ALDH2* mRNA levels in human LS411N tumor xenograft epithelium from mice three days following treatment with 10mg/kg ALDH2 RNAi -GalXC lipid conjugates with varying acyl chain lengths and unsaturation.

[0082] **FIG. 2B** is a graph representing remaining mouse *Aldh2* mRNA levels in tumor microenvironment (TME) isolated from human LS411N tumor xenografts. TME was isolated

from mice three days following treatment with 10mg/kg ALDH2-GalXC lipid conjugates with varying acyl chain lengths and unsaturation

[0083] **FIG. 3A** is a graph demonstrating remaining human *ALDH2* mRNA following treatment with various doses of GalXC-ALDH2-C22 conjugate in human LS411N tumor xenograft epithelium. Samples were collected from mice on Days 3, 7, and 14 post-treatment.

[0084] **FIG. 3B** is a graph demonstrating remaining mouse *Aldh2* mRNA following treatment with various doses of GalXC-ALDH2-C22 conjugate in host mouse tissue in the tumor microenvironment collected from human LS411N tumors. Samples were collected on Days 3, 7, and 14 post-treatment.

[0085] **FIGs. 4A** and **4B** are graphs demonstrating remaining mouse *Aldh2* mRNA following treatment with 25mg/kg of GalXC-ALDH2-C22 conjugate in the tumor draining lymph nodes of human LS411N tumor xenograft bearing mice (**FIG. 4A**) and in lymph nodes of mice with no tumors (**FIG. 4B**).

[0086] **FIG. 5A** is a graph showing remaining mouse *Aldh2* mRNA levels following treatment with GalXC-ALDH2-C22 conjugate or PBS in murine tumor draining lymph nodes (TdLN) compared to non-TdLN over time in human LS411N tumor xenografts. Normalized mRNA is relative to a PBS treated mouse.

[0087] **FIG. 5B** provides graphs showing the *Pdl1* mRNA levels in murine tumor draining lymph nodes (TdLN) compared to Non-TdLN from LS411N tumor xenograft mice treated with GalXC-ALDH2-C22.

[0088] **FIG. 6** is a graph demonstrating the expression of *Arg1* in isolated tumor associated $CD11b^+$ myeloid derived suppressor cells (MDSCs) and normal spleen myeloid cells from human LS411N tumor xenografts treated with 25 mg/kg GalXC-ALDH2-C22. Three days after treatment, MDSCs and tumor cells were isolated from mice and measured using CDllb mRNA. BLOQ= below limit of quantification.

[0089] **FIGs. 7A** and **7B** are graphs showing the level of remaining mouse *Aldh2* mRNA in isolated CDllb+ MDSCs (**FIG. 7A**) and tumor cells (**FIG. 7B**) from mice with human LS411N tumor xenografts treated with GalXC-ALDH2-C22 conjugate.

[0090] **FIGs. 8A** and **8B** are graphs demonstrating remaining mouse *Aldh2* mRNA from bulk tumor (**FIG. 8A**), and liver (**FIG. 8B**) of Pan02 xenografts. Mice were treated with 25mg/kg of the specified GalXC-ALDH2-lipid conjugate and mRNA was measured on day 3.

[0091] **FIGs. 8C** and **8D** are graphs demonstrating remaining mouse *Aldh2* mRNA from bulk tumor (**FIG. 8C**) and tumor draining lymph node (TdLN) from mice with Pan02 xenografts on day 7 and day 14 after treatment with 25mg/kg of the specified GalXC-ALDH2-lipid conjugate.

[0092] **FIG. 9** provides graphs showing expression of differentiating mRNA markers (*Ly6G, Cxcr2, Slc27a2, and Ptgs2)* in G-MDSC isolated from TME of untreated (control) PAN02 tumors.

[0093] **FIG. 10** provides graphs showing the expression of differentiating mRNA markers (*Ly6G, Cxcr2, Slc27a2, and Ptgs2)* in M-MDSC isolated from TME.

[0094] **FIGs. 11** and **12** provide graphs showing the differential expression of lipid trafficking receptors in G-MDSC and M-MDSC in untreated (control) tissue.

[0095] **FIGs. 13A** and **13B** provide graphs showing remaining mouse *Aldh2* mRNA levels after treatment with 25 mg/kg of GalXC-ALDH2-C18 conjugate in isolated G-MDSCs and M-MDSCs from Pan02 (**FIG. 13A)** and B16F10 (**FIG. 13B**) TME. Mice were randomized into groups once tumors reached 300-500mm then treated on day 1 and tissue was collected for analysis on day 3.

[0096] **FIGs. 13C** and **13D** provide graphs showing remaining mouse *Aldh2* mRNA levels after treatment with 50 mg/kg GalXC-ALDH2-C18 conjugate in G-MDSCs and M-MDSCs from Pan02 TME of mice on days 3 (**FIG. 13C**) and 7 (**FIG. 13D**).

[0097] **FIGs. 14A - 14C** are graphs showing the relative expression of *Stat3* in G-MDSC (**FIG. 14A**), M-MDSC (**FIG. 14B**) and TdLN (**FIG. 14C**) from Pan02 xenografts implanted in mice.

[0098] **FIGs. 15A** and **15B** are graphs showing remaining mouse *Stat3* mRNA levels in the livers of mice treated with GalXC-STAT3-conjugates (GalNAc conjugates) targeting different regions of *Stat3* mRNA. Mice were administered a single dose (3mg/kg) (**FIG. 15A**) and multi dose to determine dose responsiveness (**FIG. 15B**). Arrows indicate constructs selected for further study.

[0099] **FIGs. 16A** and **16B** are graphs showing mouse *Stat3* mRNA expression after treatment with GalXC-STAT3-C18 conjugates in G-MDSCs and M-MDSCs derived from Pan02 xenografts implanted in mice. Tumors were dosed at 25 mg/kg (**FIG. 16A**) and 50 mg/kg (**FIG. 16B**).

[00100] **FIGs. 17A** and **17B** are graphs showing mouse *Stat3* mRNA expression after treatment of Pan02 xenograft mice with GalXC-STAT3-C18 conjugates in bulk tumor (TME) (**FIG. 17A**) and TdLNs (**FIG. 17B**) at doses of 25 and 50 mg/kg.

[00101] **FIG. 18A** provides graphs showing the effect of GalXC-STAT3-C18-4123 on *Stat3* and *Pdl1* mRNA levels in G/M-MDSCs in TME and TdLNs of Pan02 xenograft mice on day 3 after a dose of 25 or 50 mg/kg of conjugate.

[00102] **FIG. 18B** provides graphs showing the effect of GalXC-STAT3-C18-4123 on *Stat3* and *Pdl1* mRNA levels in TdLN of Pan02 xenograft mice on day 7 after a 25mg/kg dose of conjugate.

[00103] **FIGs. 19A** and **19B** are graphs showing the *in vivo* effect of subcutaneous treatment with a total dose of 50 mg/kg GalXC-STAT3-C18-4123 on tumor volume in immunocompetent mice bearing Pan02 murine pancreatic tumors. Mice were treated with either four 12.5 mg/kg (**FIG. 19A**) or two 25mg/kg (**FIG. 19B**) doses of conjugate.

[00104] **FIG. 20** provides a graph depicting the percent (%) of human *STAT3* mRNA remaining in Huh7 cells endogenously expressing human *STAT3*, after 24-hour treatment with 1nM of DsiRNA targeting various regions of the *STAT3* gene. 192 DsiRNAs were designed and screened. Two primer pairs were used. Expression was normalized between samples using the HPRT and SFRS9 housekeeping genes (Forward 1- SEQ ID NO: 1219, Reverse 1- SEQ ID NO: 1220; Probe 1- SEQ ID NO: 1221; Forward 2- SEQ ID NO: 1222, Reverse 2- SEQ ID NO: 1223; Probe 2- SEQ ID NO: 1224).

[00105] **FIGs. 21A** and **21B** provide graphs depicting the percent (%) of human *STAT3* mRNA remaining in Huh7 cells endogenously expressing human *STAT3*, after 24-hour treatment with 0.05nM, 0.3nM, or 1nM of DsiRNA targeting various regions of the *STAT3* gene. 48 GalNAc-conjugated *STAT3* oligonucleotides s were assayed in **FIG. 21A** and 34 of those oligonucleotides were selected for further testing *in vivo* (**FIG. 21B**).

[00106] **FIGs. 22A** and **22B** provide graphs depicting the percent (%) of human *STAT3* mRNA remaining in liver of mice exogenously expressing human *STAT3* (hydrodynamic injection model) after treatment with GalNAc-conjugated *STAT3* oligonucleotides. Mice were dosed subcutaneously with 1mg/kg of the indicated GalNAc-*STAT3* oligonucleotides formulated in PBS. Three days post-dose mice were hydrodynamically injected (HDI) with a DNA plasmid encoding human *STAT3*. The level of human *STAT3* mRNA was determined from livers

collected 18 hours after injection. Arrows indicate oligonucleotides selected for dose response analysis. Hs/Mf = human/monkey common sequence; Hs/Mm= human/mouse common sequence; Hs/Mf/Mm= human/monkey/mouse triple common sequence.

[00107] **FIG. 23** provides a graph depicting the dose response of GalNAc-conjugated *STAT3* oligonucleotides. The percent (%) of human *STAT3* mRNA remaining in liver of mice exogenously expressing *STAT3* (HDI model) after treatment with human GalNAc-conjugated *STAT3* oligonucleotides at three doses (0.3mg/kg, 1mg/kg,) was measured. The level of human *STAT3* mRNA was determined from livers collected 18 hours after injection with plasmid encoding human *STAT3*. Arrows indicate oligonucleotides selected for dose response analysis. Hs/Mf = human/monkey common sequence; Hs/Mm= human/mouse common sequence.

[00108] **FIG. 24** provides a graph depicting the normalized (to Ppib) relative mouse *STAT3* mRNA remaining in liver of mice endogenously expressing mouse *STAT3* after treatment with GalNAc-conjugated *STAT3* oligonucleotides. Mice were dosed subcutaneously with 3mg/kg of the indicated GalNAc-*STAT3* oligonucleotides formulated in PBS. Five days post-dose liver was collected and the level of mouse *STAT3* mRNA was determined. Arrows indicate top oligonucleotides and those selected for dose response study.

[00109] **FIG. 25** provides a graph depicting the normalized (to Ppib) relative mouse *STAT3* mRNA remaining in liver of mice endogenously expressing mouse *STAT3* after treatment with GalNAc-conjugated *STAT3* oligonucleotides. Mice were dosed subcutaneously with 3mg/kg of the indicated GalNAc-*STAT3* oligonucleotides formulated in PBS. Five days post-dose liver was collected and the level of mouse *STAT3* mRNA was determined. Arrows indicate oligonucleotides selected for dose response study.

[00110] **FIGs. 26A** and **26B** provide graphs depicting the dose response of GalNAc-conjugated *STAT3* oligonucleotides. The percent (%) of mouse *STAT3* mRNA remaining in liver of mice endogenously expressing *STAT3* after treatment with human GalNAc-conjugated *STAT3* oligonucleotides at three doses (0.3mg/kg, 1mg/kg, and 3mg/kg) was measured. The level of mouse *STAT3* mRNA was determined from livers collected 5 days later. TC = triple common (mouse/human/monkey); Hs_Mm = human/mouse.

[00111] **FIG. 27** provides a graph depicting the percent (%) of human *STAT3* mRNA remaining in liver of mice exogenously expressing human *STAT3* (hydrodynamic injection model) after treatment with GalNAc-conjugated *STAT3* oligonucleotides. Mice were dosed

subcutaneously with 1mg/kg of the indicated GalNAc-*STAT3* oligonucleotides formulated in PBS. Three days post-dose mice were hydrodynamically injected (HDI) with a DNA plasmid encoding human *STAT3*. The level of human *STAT3* mRNA was determined from livers collected 18 hours after injection. Arrows indicate oligonucleotides selected for dose response study.

[00112] **FIG. 28** provides a graph depicting the dose response of GalNAc-conjugated *STAT3* oligonucleotides. The percent (%) of human *STAT3* mRNA remaining in liver of mice exogenously expressing human *STAT3* (hydrodynamic injection model) after treatment with GalNAc-conjugated *STAT3* oligonucleotides. Mice were dosed subcutaneously with three doses (0.3mg/kg, 1mg/kg, and 3mg/kg) of the indicated GalNAc-*STAT3* oligonucleotides formulated in PBS. Three days post-dose mice were hydrodynamically injected (HDI) with a DNA plasmid encoding human *STAT3*. The level of human *STAT3* mRNA was determined from livers collected 18 hours after injection. TC = triple common (mouse/human/monkey); Hs_Mm = human/mouse; Hs = human.

[00113] **FIG. 29** provides a graph depicting the dose response of GalNAc-conjugated STAT3 oligonucleotides. The percent (%) of human *STAT3* mRNA remaining in liver of mice exogenously expressing human *STAT3* (hydrodynamic injection model) after treatment with GalNAc-conjugated *STAT3* oligonucleotides. Mice were dosed subcutaneously with two doses (0.3mg/kg and 1mg/kg) of the indicated GalNAc-*STAT3* oligonucleotides formulated in PBS. Three days post-dose mice were hydrodynamically injected (HDI) with a DNA plasmid encoding human *STAT3*. The level of human *STAT3* mRNA was determined from livers collected 18 hours after injection.

[00114] **FIG. 30** provides a graph depicting the percent (%) remaining human *STAT1* mRNA in Huh7 cells endogenously expressing *STAT3* and *STAT1* treated with GalNAc-conjugated *STAT3* oligonucleotides. Cells were treated for 24 hours with three doses (0.05nM, 0.3nM, and 1nM) of oligonucleotide.

DETAILED DESCRIPTION

[00115] The present disclosure now will be described more fully hereinafter with reference to the accompanying drawings, in which illustrative embodiments of the disclosure are shown. The disclosure may, however, be embodied in many different forms and should not be construed as

limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the disclosure to those skilled in the art.

[0006] In some aspects, the disclosure provides oligonucleotide-ligand conjugates (e.g., RNAi oligonucleotide-lipid conjugates) that reduce expression of a target gene (e.g., encoding a regulator of immune suppression) in immune cells within a tumor microenvironment. In other aspects, the disclosure provides methods of treating a disease or disorder (e.g., cancer) using the oligonucleotide-ligand conjugates, or pharmaceutically acceptable compositions thereof, described herein. In other aspects, the disclosure provides methods of using the oligonucleotide-ligand conjugates described herein in the manufacture of a medicament for treating cancer. In other aspects, the oligonucleotide-ligand conjugates provided herein are used to treat cancer by modulating (e.g., inhibiting or reducing) expression of a target gene encoding a regulator of immune suppression in an immune cell in the tumor microenvironment. In some aspects, the disclosure provides methods of treating cancer by reducing expression of a target encoding a regulator of immune suppression in an immune cell in the tumor microenvironment.

Definitions

[00116] The publications discussed throughout the text are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior disclosure.

[00117] As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items. Further, the singular forms and the articles "a", "an" and "the" are intended to include the plural forms as well, unless expressly stated otherwise. It will be further understood that the terms: includes, comprises, including and/or comprising, when used in this specification, specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof. Further, it will be understood that when an element, including component or subsystem, is referred to and/or shown as being connected or coupled to another element, it can be directly connected or coupled to the other element or intervening elements may be present.

[00118] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice of the disclosed methods and compositions, exemplary methods, and materials are described herein.

[00119] General texts which describe molecular biological techniques useful herein, including the use of vectors, promoters and many other relevant topics, include Berger and Kimmel, GUIDE TO MOLECULAR CLONING TECHNIQUES, METHODS IN ENZYMOLOGY, volume 152, (Academic Press, Inc., San Diego, Calif.) ("Berger"); Sambrook *et al.*, MOLECULAR CLONING--A LABORATORY MANUAL, 2d ed., Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, 1989 ("Sambrook") and CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, F.M. Ausubel *et al.*, eds., **CURRENT PROTOCOLS, A JOINT VENTURE BETWEEN GREENE PUBLISHING ASSOCIATES, INC. AND JOHN WILEY AND SONS, INC.,** (supplemented through 1999) ("Ausubel"). Examples of protocols sufficient to direct persons of skill through *in vitro* amplification methods, including the polymerase chain reaction (PCR), the ligase chain reaction(LCR), Q.beta.-replicase amplification and other RNA polymerase mediated techniques (*e.g.,* NASBA), *e.g.,* for the production of the homologous nucleic acids of the disclosure are found in Berger, Sambrook, and Ausubel, as well as in Mullis *et al.*, (1987) U.S. Pat. No. 4,683,202; Innis *et al.*, eds. (1990); PCR PROTOCOLS: A GUIDE TO METHODS AND APPLICATIONS (Academic Press Inc. San Diego, Calif.) ("Innis"); Arnheim and Levinson (Oct. 1, 1990) Cand EN 36-47; J. NIH RES. (1991) 3:81-94; Kwoh *et al.*, (1989) PROC. NATL. ACAD. SCI. USA 86: 1173; Guatelliet *et al.,* (1990) PROC. NAT'L. ACAD. SCI. USA 87: 1874; Lomell *et al.*, (1989) J. CLIN. CHEM 35: 1826; Landegren *et al.*, (1988) SCIENCE 241: 1077-80; Van Brunt (1990) BIOTECHNOLOGY 8: 291-94; Wu and Wallace (1989) GENE 4:560; Barringer *et al.*, (1990) GENE 89:117; and, Sooknanan and Malek(1995) BIOTECHNOLOGY 13: 563-564. Improved methods for cloning *in vitro* amplified nucleic acids are described in Wallace *et al.*, U.S. Pat. No.5,426,039. Improved methods for amplifying large nucleic acids by PCR are summarized in Cheng *et al.*, (1994) NATURE 369: 684-85 and the references cited therein, in which PCR amplicons of up to 40 kb are generated.

[00120] As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example,

reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

[00121] Ranges can be expressed herein as from "about" one value, and/or to "about" another value. When such a range is expressed, another embodiment includes from the one value and/or to the other value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are several values disclosed herein, and that each value is also herein disclosed as "about" that value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that when a value is disclosed that "less than or equal to" the value, "greater than or equal to the value" and possible ranges between values are also disclosed, as appropriately understood by the skilled artisan. For example, if the value "10" is disclosed the "less than or equal to 10" as well as "greater than or equal to 10" is also disclosed. It is also understood that the throughout the application, data is provided in several different formats, and that this data, represents endpoints and starting points, and ranges for any combination of the data points. For example, if a particular datapoint "10" and a particular data point 15 are disclosed, it is understood that greater than, greater than or equal to, less than, less than or equal to, and equal to 10 and 15 are considered disclosed as well as between 10 and 15. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[00122] In this specification and in the claims, which follow, reference will be made to several terms which shall be defined to have the following meanings:

[00123] The term "cancer" or "tumor" includes, but is not limited to, solid tumors and blood borne tumors. These terms include diseases of the skin, tissues, organs, bone, cartilage, blood, and vessels. These terms further encompass primary and metastatic cancers.

[00124] The term “PD-1” refers to a protein found on T cells that helps keep the immune responses in check. When PD-1 is bound to another protein called PD-L1, it helps keep T cells from killing other cells, including cancer cells. Some anticancer drugs, called immune checkpoint inhibitors, are used to block PD-1. When this protein is prevented from acting on T cells, they can act to kill cancer cells.

[00125] The term "STAT3" refers to Signal transducer and activator of transcription 3 (STAT3) which is a transcription factor which in humans is encoded by the STAT3 gene (STAT3 Human (Hs) NM_001369512.1 Genbank RefSeq #, or NM_139276.3). STAT3 mediates the expression of a variety of genes in response to cell stimuli, and thus plays a key role in many cellular processes such as cell growth and apoptosis, as well as the growth and progression of cancer.

[00126] The term "TGF-β" refers to Transforming growth factor beta (TGF-β) which is a cytokine involved in immune and stem cell regulation and differentiation. TGF-β is an important cytokine with identified roles in many pathologies including cancer, infectious disease, and autoimmunity. Its immunosuppressive functions in the tumor microenvironment contribute to oncogenesis (Massague *et al.*, CELL, 103 (2): 295-309 (2000)).

[00127] The term "CXCR2" refers to C-X-C motif chemokine receptor 2 (CXCR2) which is a receptor for interleukin 8 (IL-8) and a member of the G-protein-coupled receptor family. CXCR2 can mediate neutrophil migration to areas of inflammation.

[00128] The term "CCR2" refers to C-C chemokine receptor type 2 (CCR2) which is a receptor for monocyte chemoattractant protein 1. The inflammatory response in some cancers can be partially mediated by the activities of monocyte chemoattractant protein 1.

[00129] The term "ARG1" refers to Arginase-1 (ARG1) which is an enzyme that converts L-arginine to urea and L-ornithine. L-arginine and its downstream metabolites contribute to a suppressive tumor microenvironment through modulation of T-cell activity (Kim *et al.*, FRONTIERS IN ONCOLOGY, 8:67 (2018)).

[00130] The term "PTGS2" refers to Prostaglandin-endoperoxide synthase 2 (PTGS2) which is also known as cyclooxygenase-2 or COX-2. PTGS2 is a key enzyme in prostaglandin synthesis. Prostaglandins can inhibit anti-tumor activities of some immune cells, contributing to a suppressive tumor microenvironment.

[00131] The term "CTLA-4" refers to Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or cluster of differentiation 152 (CD152) which is a protein found on T cells that helps keep the immune responses in check. CTLA-4 was the first immune checkpoint target and CTLA-4 inhibitors have been developed as breakthrough anti-cancer treatments.

[00132] The term “SOCS1” refers to Suppressor of cytokine signaling 1 (SOCS1) which is a member of the STAT-induced STAT inhibitor (SSI) family. SOCS1 is a cytokine-inducible negative regulator of cytokine signaling.

[00133] As used herein, the term "cold tumor" or "non-inflamed tumor" refers to a tumor or tumor microenvironment wherein there is minimal to no presence of anti-tumor immune cells, such as tumor infiltrating lymphocytes (TILs), and/or contain cell subsets associated with immune suppression including regulatory T cells (Treg), myeloid-derived suppressor cells (MDSCs) and M2 macrophages. Specifically, in some embodiments, a cold tumor is characterized by a low number or even absence of infiltration of anti-tumor immune cells that such cells may be present but remain stuck in the surrounding stroma, thus unable to colonize the tumor microenvironment to provide their antitumor functions.

[00134] As used herein, “complementary” refers to a structural relationship between two nucleotides (*e.g.*, on two opposing nucleic acids or on opposing regions of a single nucleic acid strand) that permits the two nucleotides to form base pairs with one another. For example, a purine nucleotide of one nucleic acid that is complementary to a pyrimidine nucleotide of an opposing nucleic acid may base pair together by forming hydrogen bonds with one another. In some embodiments, complementary nucleotides can base pair in the Watson-Crick manner or in any other manner that allows for the formation of stable duplexes. In some embodiments, two nucleic acids may have regions of multiple nucleotides that are complementary with each other to form regions of complementarity, as described herein.

[00135] As used herein, “species cross-reactive oligonucleotide” refers to an oligonucleotide capable of inhibiting expression of a target mRNA in more than one species. For example, in some embodiments a species cross-reactive oligonucleotide is capable of inhibiting expression of a target mRNA in human and non-human primates. Example species include but is not limited to human, non-human primates, mouse, and rat. In some embodiments, species cross-reactive oligonucleotides are capable of targeting and inhibiting mRNA in at least two, at least three, or at least four species.

[00136] As used herein, “deoxyribonucleotide” refers to a nucleotide having a hydrogen in place of a hydroxyl at the 2′ position of its pentose sugar when compared with a ribonucleotide. A modified deoxyribonucleotide is a deoxyribonucleotide having one or more modifications or

substitutions of atoms other than at the 2′ position, including modifications or substitutions in or of the sugar, phosphate group or base.

[00137] As used herein, “double-stranded RNA” or “dsRNA” refers to an RNA oligonucleotide that is substantially in a duplex form. In some embodiments, the complementary base-pairing of duplex region(s) of a dsRNA oligonucleotide is formed between antiparallel sequences of nucleotides of covalently separate nucleic acid strands. In some embodiments, complementary base-pairing of duplex region(s) of a dsRNA formed between antiparallel sequences of nucleotides of nucleic acid strands that are covalently linked. In some embodiments, complementary base-pairing of duplex region(s) of a dsRNA is formed from single nucleic acid strand that is folded (*e.g.*, *via* a hairpin) to provide complementary antiparallel sequences of nucleotides that base pair together. In some embodiments, a dsRNA comprises two covalently separate nucleic acid strands that are fully duplexed with one another. However, in some embodiments, a dsRNA comprises two covalently separate nucleic acid strands that are partially duplexed (*e.g.*, having overhangs at one or both ends). In some embodiments, a dsRNA comprises antiparallel sequence of nucleotides that are partially complementary, and thus, may have one or more mismatches, which may include internal mismatches or end mismatches.

[00138] As used herein, “duplex,” in reference to nucleic acids (*e.g.*, oligonucleotides), refers to a structure formed through complementary base pairing of two antiparallel sequences of nucleotides.

[00139] As used herein, “excipient” refers to a non-therapeutic agent that may be included in a composition, for example, to provide or contribute to a desired consistency or stabilizing effect.

[00140] As used herein, the term "hot tumor" or "inflamed tumor" refers to a tumor or tumor microenvironment wherein there is a considerable presence of anti-tumor immune cells especially TILs and thus are typically immuno-stimulatory.

[00141] As used herein, “loop” refers to an unpaired region of a nucleic acid (*e.g.*, oligonucleotide) that is flanked by two antiparallel regions of the nucleic acid that are sufficiently complementary to one another, such that under appropriate hybridization conditions (*e.g.*, in a phosphate buffer, in a cells), the two antiparallel regions, which flank the unpaired region, hybridize to form a duplex (referred to as a “stem”). The loop may refer to a loop

comprising four nucleotides as a tetraloop (tetraL). The loop may refer to a loop comprising three nucleotides as a triloop (triL).

[00142] As used herein, "modified internucleotide linkage" refers to an internucleotide linkage having one or more chemical modifications when compared with a reference internucleotide linkage comprising a phosphodiester bond. In some embodiments, a modified nucleotide is a non-naturally occurring linkage. Typically, a modified internucleotide linkage confers one or more desirable properties to a nucleic acid in which the modified internucleotide linkage is present. For example, a modified nucleotide may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, *etc*.

[00143] As used herein, "modified nucleotide" refers to a nucleotide having one or more chemical modifications when compared with a corresponding reference nucleotide selected from: adenine ribonucleotide, guanine ribonucleotide, cytosine ribonucleotide, uracil ribonucleotide, adenine deoxyribonucleotide, guanine deoxyribonucleotide, cytosine deoxyribonucleotide and thymidine deoxyribonucleotide. In some embodiments, a modified nucleotide is a non-naturally occurring nucleotide. In some embodiments, a modified nucleotide has one or more chemical modification in its sugar, nucleobase and/or phosphate group. In some embodiments, a modified nucleotide has one or more chemical moieties conjugated to a corresponding reference nucleotide. Typically, a modified nucleotide confers one or more desirable properties to a nucleic acid in which the modified nucleotide is present. For example, a modified nucleotide may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, *etc*.

[00144] As used herein, "nicked tetraloop structure" refers to a structure of a RNAi oligonucleotide that is characterized by separate sense (passenger) and antisense (guide) strands, in which the sense strand has a region of complementarity with the antisense strand, and in which at least one of the strands, generally the sense strand, has a tetraloop configured to stabilize an adjacent stem region formed within the at least one strand.

[00145] As used herein, "oligonucleotide" refers to a short nucleic acid (*e.g.*, less than about 100 nucleotides in length). An oligonucleotide may be single stranded (ss) or double-stranded (ds). An oligonucleotide may or may not have duplex regions. An oligonucleotide may comprise deoxyribonucleotides, ribonucleosides, or a combination of both. In some

embodiments, a double-stranded oligonucleotide comprising ribonucleotides is referred to as "dsRNA". As a set of non-limiting examples, an oligonucleotide may be, but is not limited to, a small interfering RNA (siRNA), microRNA (miRNA), short hairpin RNA (shRNA), dicer substrate interfering RNA (dsiRNA), antisense oligonucleotide, short siRNA or ss siRNA. In some embodiments, a double-stranded RNA (dsRNA) is an RNAi oligonucleotide.

[00146] The terms "RNAi oligonucleotide conjugate" and "oligonucleotide-ligand conjugate" are used interchangeably and refer to an oligonucleotide comprising one or more nucleotides conjugated with one or more targeting ligands.

[00147] As used herein, "overhang" refers to terminal non-base pairing nucleotide(s) resulting from one strand or region extending beyond the terminus of a complementary strand with which the one strand or region forms a duplex. In some embodiments, an overhang comprises one or more unpaired nucleotides extending from a duplex region at the 5′ terminus or 3′ terminus of a dsRNA. In certain embodiments, the overhang is a 3′ or 5′ overhang on the antisense strand or sense strand of a dsRNA.

[00148] As used herein, "phosphate analog" refers to a chemical moiety that mimics the electrostatic and/or steric properties of a phosphate group. In some embodiments, a phosphate analog is positioned at the 5′ terminal nucleotide of an oligonucleotide in place of a 5′-phosphate, which is often susceptible to enzymatic removal. In some embodiments, a 5′ phosphate analog contains a phosphatase-resistant linkage. Examples of phosphate analogs include, but are not limited to, 5′ phosphonates, such as 5′ methylene phosphonate (5′-MP) and 5′-(E)-vinylphosphonate (5′-VP). In some embodiments, an oligonucleotide has a phosphate analog at a 4′-carbon position of the sugar (referred to as a "4′-phosphate analog") at a 5′-terminal nucleotide. An example of a 4′-phosphate analog is oxymethylphosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (*e.g.*, at its 4′-carbon) or analog thereof. *See*, *e.g.*, US Provisional Patent Application Nos. 62/383,207 (filed on 2 September 2016) and 62/393,401 (filed on 12 September 2016). Other modifications have been developed for the 5′ end of oligonucleotides (*see*, *e.g.*, Intl. Patent Application No. WO 2011/133871; US Patent No. 8,927,513; and Prakash *et al.*, (2015) NUCLEIC ACIDS RES. 43:2993-3011).

[00149] As used herein, "reduced expression" of a gene (*e.g.*, *STAT3*) refers to a decrease in the amount or level of RNA transcript (*e.g.*, *STAT3* mRNA) or protein encoded by the gene and/or a decrease in the amount or level of activity of the gene in a cell, a population of cells, a

sample, or a subject, when compared to an appropriate reference (*e.g.*, a reference cell, population of cells, sample, or subject). For example, the act of contacting a cell with an oligonucleotide herein (*e.g.*, an oligonucleotide comprising an antisense strand having a nucleotide sequence that is complementary to a nucleotide sequence comprising *STAT3* mRNA) may result in a decrease in the amount or level of *STAT3* mRNA, protein and/or activity (*e.g.*, *via* degradation of *STAT3* mRNA by the RNAi pathway) when compared to a cell that is not treated with the dsRNA. Similarly, and as used herein, "reducing expression" refers to an act that results in reduced expression of a gene (*e.g.*, *STAT3*). As used herein, "reduction of STAT3 expression" refers to a decrease in the amount or level of *STAT3* mRNA, STAT3 protein and/or STAT3 activity in a cell, a population of cells, a sample or a subject when compared to an appropriate reference (*e.g.*, a reference cell, population of cells, sample, or subject).

[00150] As used herein, "region of complementarity" refers to a sequence of nucleotides of a nucleic acid (*e.g.*, a dsRNA) that is sufficiently complementary to an antiparallel sequence of nucleotides to permit hybridization between the two sequences of nucleotides under appropriate hybridization conditions (*e.g.*, in a phosphate buffer, in a cell, *etc.*). In some embodiments, an oligonucleotide herein comprises a targeting sequence having a region of complementary to a mRNA target sequence.

[00151] As used herein, "ribonucleotide" refers to a nucleotide having a ribose as its pentose sugar, which contains a hydroxyl group at its 2′ position. A modified ribonucleotide is a ribonucleotide having one or more modifications or substitutions of atoms other than at the 2′ position, including modifications or substitutions in or of the ribose, phosphate group or base.

[00152] As used herein, "RNAi oligonucleotide" refers to either (a) a dsRNA having a sense strand (passenger) and antisense strand (guide), in which the antisense strand or part of the antisense strand is used by the *Argonaute* 2 (Ago2) endonuclease in the cleavage of a target mRNA or (b) a ss oligonucleotide having a single antisense strand, where that antisense strand (or part of that antisense strand) is used by the Ago2 endonuclease in the cleavage of a target mRNA.

[00153] As used herein, "strand" refers to a single, contiguous sequence of nucleotides linked together through internucleotide linkages (*e.g.*, phosphodiester linkages or phosphorothioate linkages). In some embodiments, a strand has two free ends (*e.g.*, a 5′ end and a 3′ end).

[00154] As used herein, "subject" means any mammal, including mice, rabbits, non-human primates (NHP), and humans. In one embodiment, the subject is a human or NHP. Moreover, "individual" or "patient" may be used interchangeably with "subject."

[00155] As used herein, "synthetic" refers to a nucleic acid or other molecule that is artificially synthesized (*e.g.*, using a machine (*e.g.*, a solid-state nucleic acid synthesizer)) or that is otherwise not derived from a natural source (*e.g.*, a cell or organism) that normally produces the molecule.

[00156] As used herein, "targeting ligand" refers to a molecule or "moiety" (*e.g.*, a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid) that selectively binds to a cognate molecule (*e.g.*, a receptor) of a tissue or cell of interest and/or that is conjugatable to another substance for purposes of targeting the other substance to the tissue or cell of interest. For example, in some embodiments, a targeting ligand may be conjugated to an oligonucleotide for purposes of targeting the oligonucleotide to a specific tissue or cell of interest. In some embodiments, a targeting ligand selectively binds to a cell surface receptor. Accordingly, in some embodiments, a targeting ligand when conjugated to an oligonucleotide facilitates delivery of the oligonucleotide into a particular cell through selective binding to a receptor expressed on the surface of the cell and endosomal internalization by the cell of the complex comprising the oligonucleotide, targeting ligand and receptor. In some embodiments, a targeting ligand is conjugated to an oligonucleotide *via* a linker that is cleaved following or during cellular internalization such that the oligonucleotide is released from the targeting ligand in the cell.

[00157] As used herein, "loop", "triloop", or "tetraloop" refers to a loop that increases stability of an adjacent duplex formed by hybridization of flanking sequences of nucleotides. The increase in stability is detectable as an increase in melting temperature (T_m) of an adjacent stem duplex that is higher than the T_m of the adjacent stem duplex expected, on average, from a set of loops of comparable length consisting of randomly selected sequences of nucleotides. For example, a loop (e.g., a tetraloop or triloop) can confer a T_m of at least about 50°C, at least about 55°C, at least about 56°C, at least about 58°C, at least about 60°C, at least about 65°C or at least about 75°C in 10 mM $NaHPO_4$ to a hairpin comprising a duplex of at least 2 base pairs (bp) in length. In some embodiments, a loop (*e.g.*, a tetraloop) may stabilize a bp in an adjacent stem duplex by stacking interactions. In addition, interactions among the nucleotides in a tetraloop include, but are not limited to, non-Watson-Crick base pairing, stacking interactions, hydrogen

bonding and contact interactions (Cheong *et al.,* (1990) NATURE 346:680-82; Heus and Pardi (1991) SCIENCE 253:191-94). In some embodiments, a loop comprises or consists of 3 to 6 nucleotides and is typically 4 to 5 nucleotides. In certain embodiments, a loop comprises or consists of 3, 4, 5 or 6 nucleotides, which may or may not be modified (*e.g.*, which may or may not be conjugated to a targeting moiety). In some embodiments, a tetraloop comprises or consists of 3 to 6 nucleotides and is typically 4 to 5 nucleotides. In certain embodiments, a tetraloop comprises or consists of 3, 4, 5 or 6 nucleotides, which may or may not be modified (*e.g.*, which may or may not be conjugated to a targeting moiety). In one embodiment, a loop consisting of 4 nucleotides is a tetraloop. Any nucleotide may be used in the loop (*e.g.,* a tetraloop) and standard IUPAC-IUB symbols for such nucleotides may be used as described in Cornish-Bowden ((1985) NUCLEIC ACIDS RES. 13:3021-3030). For example, the letter "N" may be used to mean that any base may be in that position, the letter "R" may be used to show that A (adenine) or G (guanine) may be in that position, and "B" may be used to show that C (cytosine), G (guanine), or T (thymine) may be in that position. Examples of tetraloops include the UNCG family of tetraloops (*e.g.*, UUCG), the GNRA family of tetraloops (*e.g.*, GAAA), and the CUUG tetraloop (Woese *et al.,* (1990) PROC. NATL. ACAD. SCI. USA 87:8467-71; Antao *et al.,* (1991) NUCLEIC ACIDS RES. 19:5901-05). Examples of DNA tetraloops include the d(GNNA) family of tetraloops (*e.g.*, d(GTTA), the d(GNRA)) family of tetraloops, the d(GNAB) family of tetraloops, the d(CNNG) family of tetraloops, and the d(TNCG) family of tetraloops (*e.g.*, d(TTCG)). (*See*, *e.g.*, Nakano *et al.,* (2002) BIOCHEM. 41:4281-92; Shinji *et al.,* (2000) NIPPON KAGAKKAI KOEN YOKOSHU 78:731). In some embodiments, the tetraloop is contained within a nicked tetraloop structure.

[00158] As used herein, "treat" or "treating" refers to the act of providing care to a subject in need thereof, for example, by administering a therapeutic agent (*e.g.*, an oligonucleotide herein) to the subject, for purposes of improving the health and/or well-being of the subject with respect to an existing condition (*e.g.*, a disease, disorder) or to prevent or decrease the likelihood of the occurrence of a condition. In some embodiments, treatment involves reducing the frequency or severity of at least one sign, symptom or contributing factor of a condition (*e.g.*, disease, disorder) experienced by a subject.

[00159] As used herein, the term "tumor microenvironment" relates to the cellular environment in which any given tumor exists, including the tumor stroma, surrounding blood

vessels, immune cells, fibroblasts, other cells, signaling molecules, and the ECM. It is understood that the tumor microenvironment harbors and/or surrounds the tumor cells with which it interacts.

Oligonucleotide Conjugates for Delivery to Immune Cells in the Tumor Microenvironment

[00160] The tumor microenvironment (TME) plays a key role in sustaining tumor growth, invasion, and ultimately metastasis. The complex TME is comprised in part by immune cells, fibroblasts, and blood vessels. The immune cell composition in the TME is typically categorized as a "cold" or "hot" tumor. Cold tumors have a dampened immune response due at least in part to the presence of myeloid-derived suppressor cells (MDSC) and T regulatory cells (Tregs). Both MDSCs and Tregs dampen the ability of T-cells to infiltrate the tumor and induce an anti-tumor response. Hot tumors show infiltration of cancer-fighting T cells demonstrating a combative anti-tumor response. Cold tumors are generally less responsive to immunotherapy treatments compared to hot tumors. Therapies to convert the tumor immune environment from a cold to hot environment are needed.

mRNA Target Sequences

[00161] In some embodiments, the oligonucleotide-ligand conjugate is targeted to an mRNA target sequence in an immune cell associated with a tumor microenvironment *via* the targeting ligand. In some embodiments, the oligonucleotide-ligand conjugate, or a portion, fragment, or strand thereof (*e.g.*, an antisense strand or a guide strand of a double-stranded oligonucleotide) binds or anneals to a target mRNA sequence, thereby reducing expression of the target mRNA. In some embodiments, the oligonucleotide-ligand conjugate is targeted to an mRNA target sequence in an immune cell associated with a tumor microenvironment *via* the targeting ligand for the purpose of reducing expression of the target mRNA *in vivo*. In some embodiments, the amount or extent of reduction of expression of the target mRNA by an oligonucleotide-ligand conjugate correlates with the potency of the oligonucleotide-ligand conjugate. In some embodiments, the amount or extent of reduction of expression of the target mRNA by an oligonucleotide-ligand conjugate correlates with the amount or extent of therapeutic benefit in a subject or patient having cancer treated with the oligonucleotide-ligand conjugate.

[00162] Through examination of the nucleotide sequence of target mRNAs, including mRNAs of multiple different species (*e.g.,* human, cynomolgus monkey, mouse, and rat) and as a result of *in vitro* and *in vivo* testing, it has been discovered that certain target mRNA sequences are more amenable than others to oligonucleotide-mediated reduction and are thus useful as target sequences for the oligonucleotide-ligand conjugate herein. In some embodiments, a sense strand of an oligonucleotide-ligand conjugate (*e.g.,* RNAi oligonucleotide-lipid conjugate), or a portion or fragment thereof, described herein, comprises a nucleotide sequence that is similar (*e.g.,* having no more than 4 mismatches) or is identical to a target mRNA sequence. In some embodiments, a portion or region of the sense strand of a double-stranded oligonucleotide described herein comprises a target mRNA sequence.

[00163] In some embodiments, the oligonucleotide-ligand conjugate targets an mRNA encoding a regulator of immune suppression expressed by an immune cell in a TME. In some embodiments, the regulator of immune suppression directly or indirectly impacts immune regulation. For example, in some embodiments, the regulator of immune suppression is a regulatory protein, an enzymatic protein, or a signaling protein. In some embodiments, the regulator of immune suppression is a polypeptide that controls immune signaling. In some embodiments, the regulator of immune suppression is an enzyme involved in processing a polypeptide involved in immune regulation. In some embodiments, the regulator of immune suppression is a checkpoint inhibitor polypeptide. In some embodiments, the regulator of immune suppression is a transcription factor. In some embodiments, the regulator of immune suppression is a cytokine. In some embodiments, the regulator of immune suppression is a chemokine receptor.

[00164] Both wild-type and mutated genes encoding immune regulators are capable of modifying the immune response in the TME or tumor draining lymph node (TdLN). In some embodiments, the oligonucleotide-ligand conjugate targets a wild-type mRNA encoding a regulator of immune suppression expressed by an immune cell in a TME. In some embodiments, the oligonucleotide-ligand conjugate targets a wild-type mRNA encoding a regulator of immune suppression expressed by an immune cell in a TdLN. In some embodiments, the oligonucleotide-ligand conjugate targets a mutated mRNA encoding a regulator of immune suppression expressed by an immune cell in a TME. In some embodiments, the oligonucleotide-ligand conjugate targets a mutated mRNA encoding a regulator of immune suppression expressed by an

immune cell in a TdLN. Mutated mRNA molecules produce misfolded proteins or hyperactive proteins.

[00165] In some embodiments, the oligonucleotide-ligand conjugate directly or indirectly reduces expression of proteins that contribute to the suppressive function of M-MDSC's. In some embodiments, the oligonucleotide-ligand conjugate directly or indirectly reduces expression of proteins that contribute to the suppressive function of G-MDSC's.

[00166] In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% in an immune cell of the TME. In some embodiments, the oligonucleotide-ligand conjugate reduces expression of the regulator of immune suppression by about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90% in an immune cell of the TME.

[00167] In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% in an immune cell of the TdLN. In some embodiments, the oligonucleotide-ligand conjugate reduces expression of the regulator of immune suppression by about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90% in an immune cell of the TdLN.

Immune Cells in a Tumor Microenvironment

[00168] In some aspects, the disclosure provides oligonucleotide-ligand conjugates that reduce expression of a target mRNA expressed in an immune cell present in a tumor and/or tumor microenvironment. In some embodiments, the oligonucleotide-ligand conjugate targets a suppressive immune cell in the tumor microenvironment. In some embodiments, the targeting ligand of the conjugate delivers the oligonucleotide to an immune cell present in a tumor.

[00169] In healthy individuals, immature myeloid cells produced from bone marrow differentiate into mature granulocytes, macrophages or dendritic cells and go on to become part of the innate immune system (Weiskopf *et al.*, MICROBIOL SPECTR. Oct; 4(5) (2016)). In pathological conditions such as cancer, a partial block in the differentiation of immature myeloid cells into mature myeloid cells can result in an expansion of the population of immature myeloid cells (Gabrilovitch *et al.*, NAT REV IMMUNOL. Mar; 9(3): 162–74 (2009)) incapable of assisting

in cancer monitoring or removal. Under the influence of GM-CSF secreted by cancer cells, these excess myeloid cells are recruited from bone marrow to the tumor site (Schmid and Varner. JOURNAL OF ONCOLOGY (2010)). Once within the TME, the myeloid cell population expands, and the cells exert immune suppressive functions that enables them to suppress T cells and NK cells through different mechanisms (Yang *et al.*, FRONT. IN IMMUNOL. 11:1371 (2020)) directly inhibiting a response to the cancer tumor.

[00170] Myeloid derived suppressor cells (MDSCs) contribute to immunotherapeutic resistance by actively inhibiting anti-tumor T-cell proliferation and cytotoxic activity, as well as by promoting expansion of immunosuppressive T regulatory cells (Gabrilovich *et al.*, NAT REV IMMUNOL (2009) 9(3): 162-74, Law *et al.*, CELLS (2020) 9: 561). In this way MDSCs can inhibit or attenuate the host immune response against a tumor. In addition, these MDSCs can also assist in cell dissemination through the promotion of angiogenesis, EMT and MET transition as well as in the secretion of tumorigenic factors. (Law *et al.*, CELLS (2020) 9: 561). Given their importance in the development, maintenance, and assistance in the expansion of tumors with which they are associated MDSCs are potential therapeutic targets for many tumor types if they can be attacked specifically. MDSCs can also be found in tumor draining lymph nodes (TdLN) where they can have a suppressive effect on naïve T cells also found in tumor draining lymph nodes (Swatz *et al.*, NAT REV CANCER (2012) 12: 210-19). Suppression of naïve T cells can then set the stage for tumors to metastasize into the lymph nodes and beyond (Swatz *et al.*, NAT REV CANCER (2012) 12: 210-19). Collectively, MDSCs are characterized by the co-expression of cell surface or mRNA markers CD11b (a marker for the myeloid cells of the macrophage lineage) and Gr-1(a marker for the myeloid lineage differentiation antigen) and denoted as $CD11b^{+}Gr\text{-}1^{+}$ cells. Gr-1 is further comprised of 2 components Ly6G and Ly6C. MDSCs consist of two subsets: Granulocytic MDSC (G-MDSC), further characterized as $CD11b^{+}Ly6G^{+}Ly6C^{lo}$, and monocytic MDSC (M-MDSC) characterized as $CD11b^{+}Ly6G^{-}Ly6C^{hi}$. mRNA markers *Ly6G, CxCr2, Slc27a2* and *Ptgs2* are preferentially expressed by G-MDSCs and not by M-MDSCs. Expression of specific markers such as *CxCr2, Scl27a2* and *Ptgs2* suggest the recruitment and suppression activity of G-MDSCs in the TME. Likewise, mRNA markers *Ly6C, Scarb1*, *Ldlr* and *Arg1* are highly expressed by M-MDSCs compared to G-MDSCs. Higher expression of lipid trafficking receptors such as Scarb1 and Ldlr in M-MDSCs may play key role in lipid uptake.

[00171] In some embodiments, the oligonucleotide-ligand conjugate targets a tumor resident immune cell. In some embodiments, the oligonucleotide-ligand conjugate targets an immune cell in the tumor draining lymph node (TdLN). In some embodiments, the oligonucleotide-ligand conjugate targets an mRNA in a tumor resident immune cell. In some embodiments, the oligonucleotide-ligand conjugate targets an mRNA in an immune cell in the tumor draining lymph node (TdLN).

[00172] In some embodiments, the immune cell is a suppressive myeloid cell. In some embodiments, the immune cell is a myeloid derived suppressor cell (MDSC). In some embodiments, the MDSC is a granulocytic MDSC (G-MDSC). In some embodiments, the MDSC is a monocytic MDSC (M-MDSC).

[00173] In some embodiments, the immune cell is a T-cell. In some embodiments, the T cell is a CD8+ T cell. In some embodiments, the T-cell is a Treg cell.

[00174] In some embodiments, the oligonucleotide-ligand conjugate reduces a target mRNA in a tumor resident and/or tumor draining lymph node MDSC. In some embodiments, the oligonucleotide conjugate reduces a target mRNA in a tumor resident and/or tumor draining lymph node G-MDSC. In some embodiments, the oligonucleotide-ligand conjugate reduces a target mRNA in a tumor resident and/or tumor draining lymph node M-MDSC. In some embodiments, the oligonucleotide-ligand conjugate reduces a target mRNA in a tumor resident and/or tumor draining lymph node Treg cell. In some embodiments, the oligonucleotide-ligand conjugate reduces a target mRNA in more than one type tumor resident and/or tumor draining lymph node immune cell. For example, in some embodiments, the oligonucleotide-ligand conjugate reduces a target mRNA in a MDSC (e.g., M-MDSC and/or G-MDSC) and a T cell (e.g., CD8+ T cell and/or Treg cell).

[00175] In some embodiments, the immunosuppressive activity of the immune cell (e.g. MDSC or Treg cell) is reduced after contact with the oligonucleotide-ligand conjugate. Immunosuppressive activity is measured using known methods in the art. In one such method, Arginase I levels are measured in isolated tumor immune cells compared to control immune cells. High Arginase I levels in tumor resident immune cells (e.g. myeloid cells) is indicative of an immunosuppressive environment. Additionally, in some embodiments the number of immune suppressive tumor resident cells indicates the level of suppressive activity. In some

embodiments, T-cell suppression assays and/or cytokine release assays are used to measure the suppressive activity of an immune cell.

Cancers

[00176] In some embodiments, the oligonucleotide-ligand conjugate described herein targets immune cells in a tumor. In some embodiments, the tumor is a primary tumor. In some embodiments, the tumor is a metastatic tumor. In some embodiments, the tumor is a refractory tumor. In some embodiments, the tumor is a Stage I, Stage II, Stage III, or Stage IV tumor. In some embodiments, the tumor is a solid-tumor. Solid-tumors refer to conditions where the cancer forms a mass

[00177] In some embodiments, the cancer is a thyroid cancer, papillary thyroid carcinoma, head and neck cancer, liver cancer, colorectal cancer, pancreatic cancer, breast cancer, ovarian cancer, lung cancer, carcinoma, blastoma, medulloblastoma, retinoblastoma, sarcoma, liposarcoma, synovial cell sarcoma, neuroendocrine tumors, carcinoid tumors, gastrinoma, islet cell cancer, mesothelioma, schwannoma, acoustic neuroma, meningioma, adenocarcinoma, lymphoid malignancies, squamous cell cancer, epithelial squamous cell cancer, small-cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer, gastrointestinal cancer, glioblastoma, cervical cancer, bladder cancer, hepatoma, metastatic breast cancer, colon cancer, rectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, Merkel cell cancer, testicular cancer, esophageal cancer, or tumors of the biliary tract. In some embodiments, the cancer is refractory to anti-PD1, anti-PDL1 and/or anti-CTLA4 therapy. In some embodiments, the cancer is a pancreatic cancer or lung cancer. In some embodiments, the cancer comprises tumors with immunosuppressive tumor microenvironments.

[00178] In some embodiments, the oligonucleotide-ligand conjugate is delivered to the tumor and reduces a target mRNA's expression in a tumor resident immune cell.

[00179] In some embodiments, the oligonucleotide-ligand conjugate reduces tumor volume. Tumor volume is measured using methods know to one of skill in the art. For example, extracted tumors are measured manually using calipers. Other methods include imagine methods

such as ultrasound and MRI. In some embodiments, the oligonucleotide conjugate reduces tumor volume by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% compared to an untreated tumor.

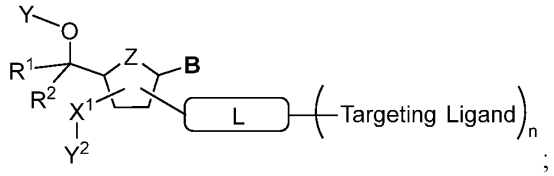
[00180] Tumor draining lymph nodes (TdLN) are the generally the first site of metastasis for cancer. In some embodiments, the oligonucleotide conjugate targets immune cells in the tumor draining lymph node. In some embodiments, the tumor draining lymph node is the subsegmental, segmental, lobar, interlobar, hilar, mediastinal, supratrochlear, deltoideopectoral, lateral, pectoral, subscapular, intermediate, subclavicular, superficial inguinal, deep inguinal, popliteal, facial buccinators, facial nasolabial, prostate, mandibular, submental, occipital, mastoid/retroauricular, parotid, deep preauricular, deep infra-auricular, deep intraglandular, deep cervical, deep anterior cervical, pretracheal, paratracheal, prelaryngeal, thyroid, deep lateral cervical, superior deep cervical, inferior deep cervical, retropharyngeal, jugulodigastric, anterior cervical, lateral cervical, supraclavicular, retroaortic, lateral aortic, celiac, gastric, hepatic, splenic, superior mesenteric, mesenteric, ileocolic, mesocolic, inferior mesenteric, or pararectal lymph node. In some embodiments, the tumor draining lymph node is a primary tumor draining lymph node. In some embodiments, the tumor draining lymph node is a lymph node that drains a tumor metastasis.

[00181] In some embodiments, the oligonucleotide-ligand conjugate does not target immune cells in the non-TdLN. In some embodiments, the oligonucleotide-ligand conjugate does not target cancer cells.

[00182] In some embodiments, the oligonucleotide-ligand conjugate targets immune cells in both the tumor and tumor draining lymph nodes. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA in immune cells in a TdLN by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%.

Structure of Oligonucleotide-Targeting Ligand Conjugates

[00183] In some embodiments, an oligonucleotide-ligand conjugate described herein comprises a nucleotide sequence and one or more targeting ligands, wherein the nucleotide sequence comprises one or more nucleosides (nucleic acids) conjugated with one or more targeting ligands represented by formula **I-a**:



;

I-a

or a pharmaceutically acceptable salt thereof,

wherein:

B is a nucleobase or hydrogen;

R^1 and R^2 are independently hydrogen, halogen, R^A, -CN, -S(O)R, $-S(O)_2R$, $-Si(OR)_2R$, $-Si(OR)R_2$, or $-SiR_3$; or

R^1 and R^2 on the same carbon are taken together with their intervening atoms to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

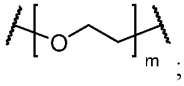
each R is independently hydrogen, a suitable protecting group, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same atom are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, silicon, and sulfur;

each targeting ligand is selected from lipid conjugate moiety (LC), carbohydrate, amino sugar or GalNAc; and wherein each LC is independently a lipid conjugate moiety comprising a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -Cy-, -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, $-S(O)_2-$, -P(O)OR-, -P(S)OR-;

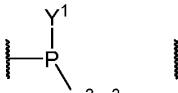
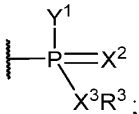
each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

n is 1-10;

L is a covalent bond or a bivalent saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -Cy-, -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -S(O)$_2$-, -P(O)OR-, -P(S)OR-, -$V^1CR^2W^1$-, or  ;

m is 1-50;

X^1, V^1 and W^1 are independently -$C(R)_2$-, -OR, -O-, -S-, -Se-, or -NR-;

Y is hydrogen, a suitable hydroxyl protecting group,  , or  ;

R^3 is hydrogen, a suitable protecting group, a suitable prodrug, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

X^2 is O, S, or NR;

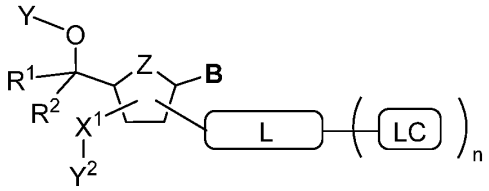
X^3 is -O-, -S-, -BH_2-, or a covalent bond;

Y^1 is a linking group attaching to the 2′- or 3′-terminal of a nucleoside, a nucleotide, or an oligonucleotide;

Y^2 is hydrogen, a suitable protecting group, a phosphoramidite analogue, an internucleotide linking group attaching to the 5′-terminal of a nucleoside, a nucleotide, or an oligonucleotide, or a linking group attaching to a solid support; and

Z is -O-, -S-, -NR-, or $-CR_2-$.

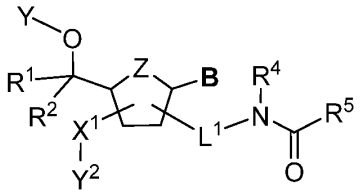
[00184] In some embodiments, the oligonucleotide-ligand conjugate comprises one or more nucleic acids conjugated with targeting ligands represented by formula **II-a**:



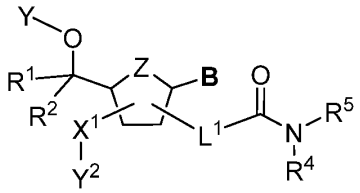
II-a.

or a pharmaceutically acceptable salt thereof.

[00185] In some embodiments, the oligonucleotide-ligand conjugate comprises one or more nucleic acids conjugated with targeting ligands represented by formula **II-b** or **II-c**:



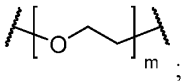
II-b



II-c

or a pharmaceutically acceptable salt thereof, wherein:

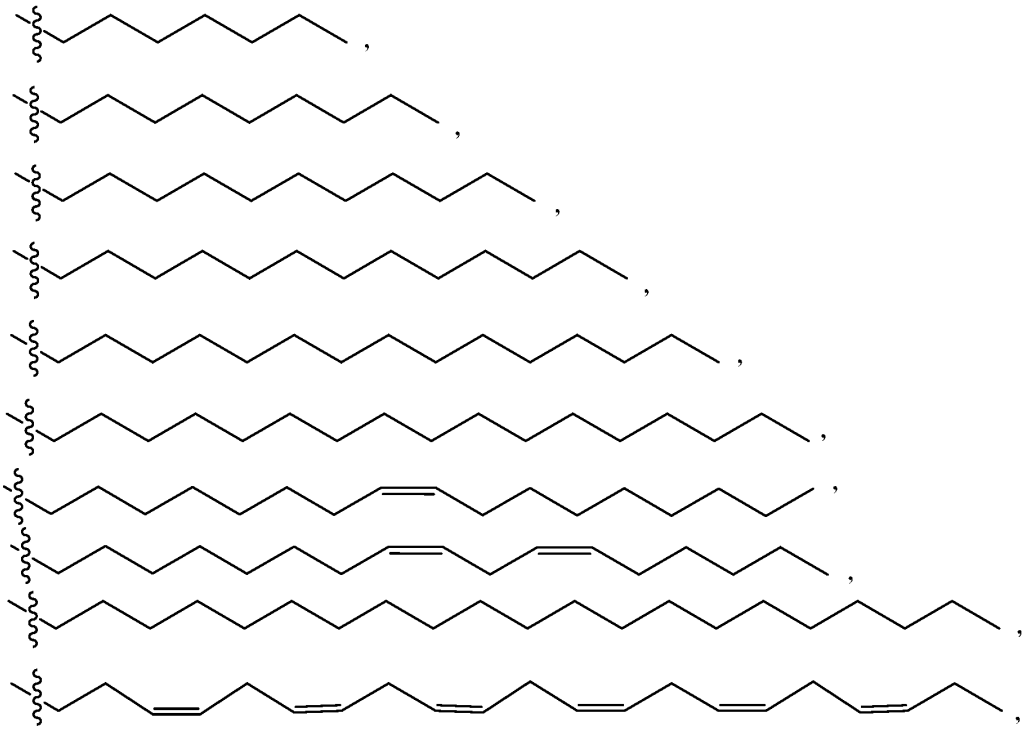
L^1 is a covalent bond, a monovalent or a bivalent saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are

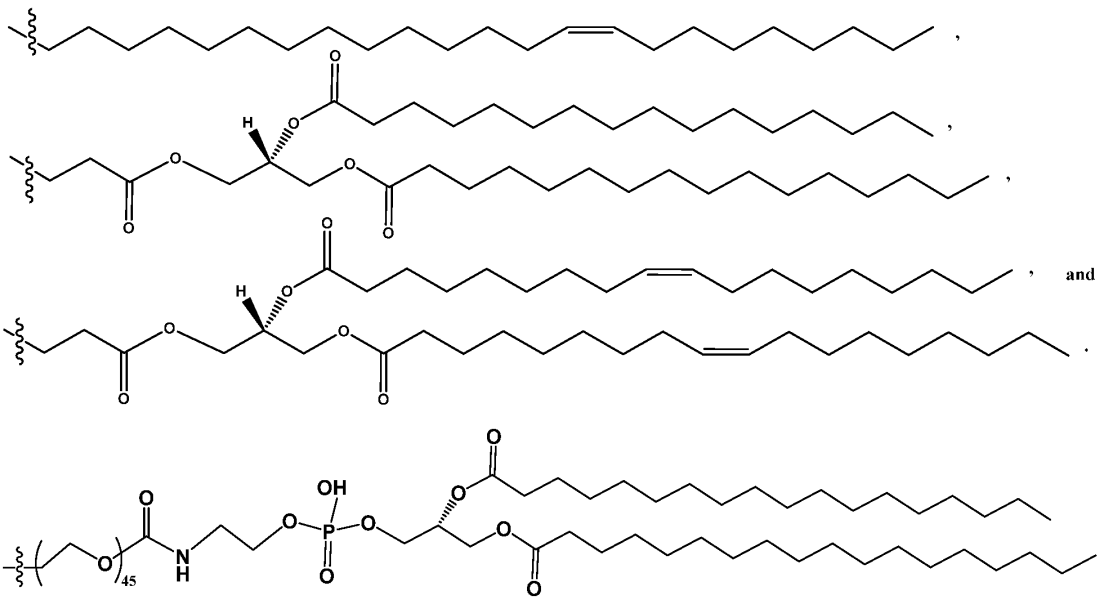
independently replaced by -Cy-, -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, -P(S)OR-, or  ;

R^4 is hydrogen, R^A, or a suitable amine protection group; and

R^5 is adamantyl, or a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, or -P(S)OR.

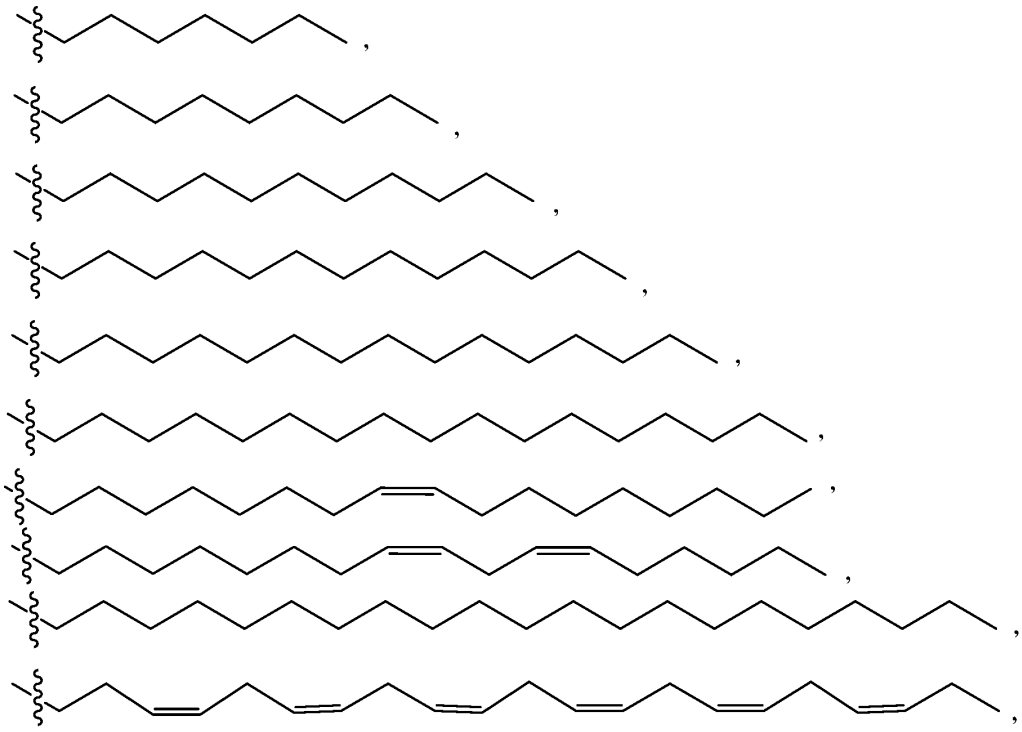
[00186] In some embodiments, R^5 is selected from

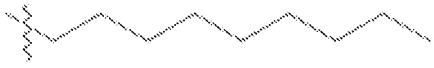
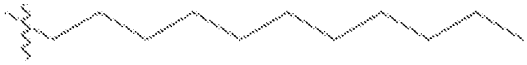
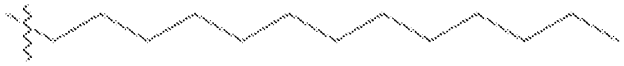
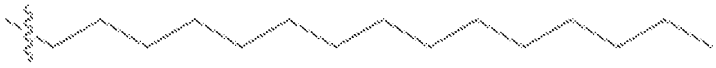
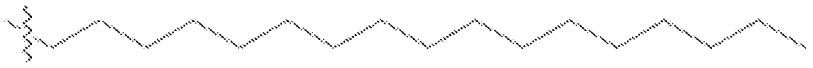
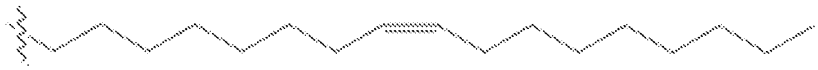
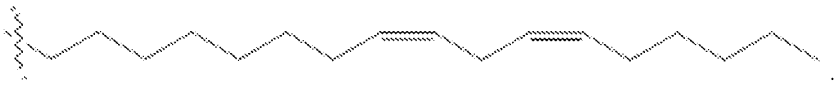
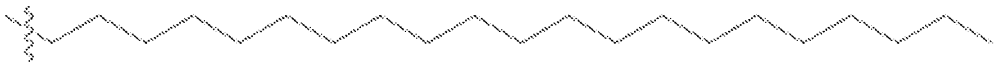




and

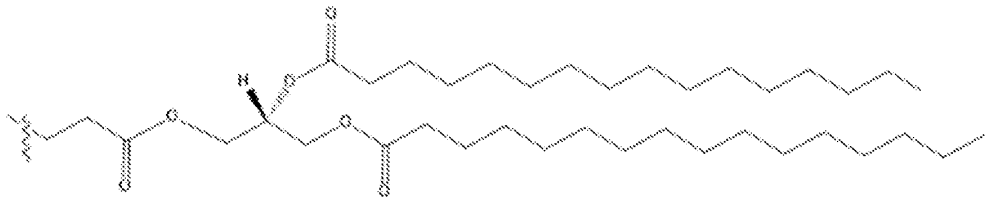
[00187] In some embodiments, R^5 is selected from:



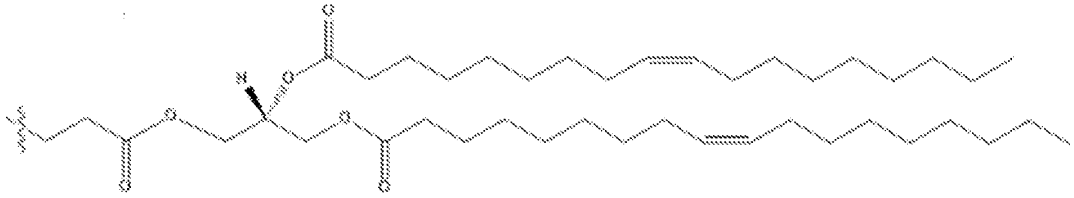
[00188] In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is

. In some embodiments, R^5 is . In some embodiments, R^5 is . In some embodiments, R^5 is

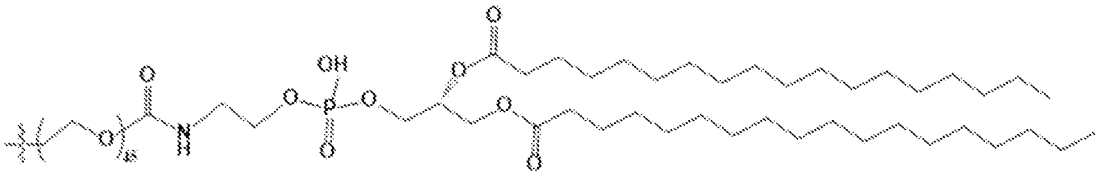
.



. In some embodiments, R^5 is

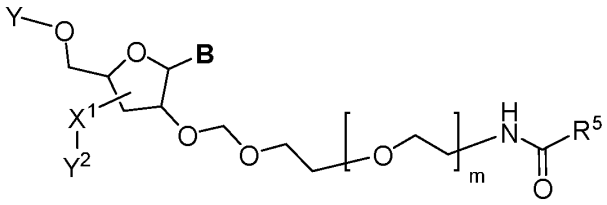


. In some embodiments, R^5 is

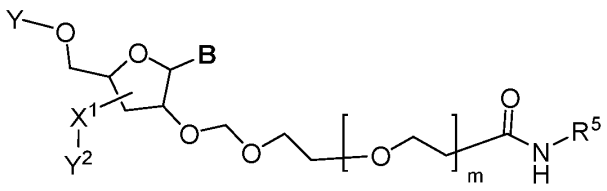


.

[00189] In some embodiments, the oligonucleotide-ligand conjugate comprises one or more nucleic acids conjugated with targeting ligands represented by formula **II-Ib** or **II-Ic**:



II-Ib



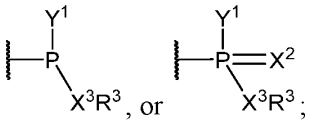
II-Ic

or a pharmaceutically acceptable salt thereof; wherein

B is a nucleobase or hydrogen;

m is 1-50;

X^1 is -O-, or -S-;

Y is hydrogen,  , or ;

R^3 is hydrogen, or a suitable protecting group;

X^2 is O, or S;

X^3 is -O-, -S-, or a covalent bond;

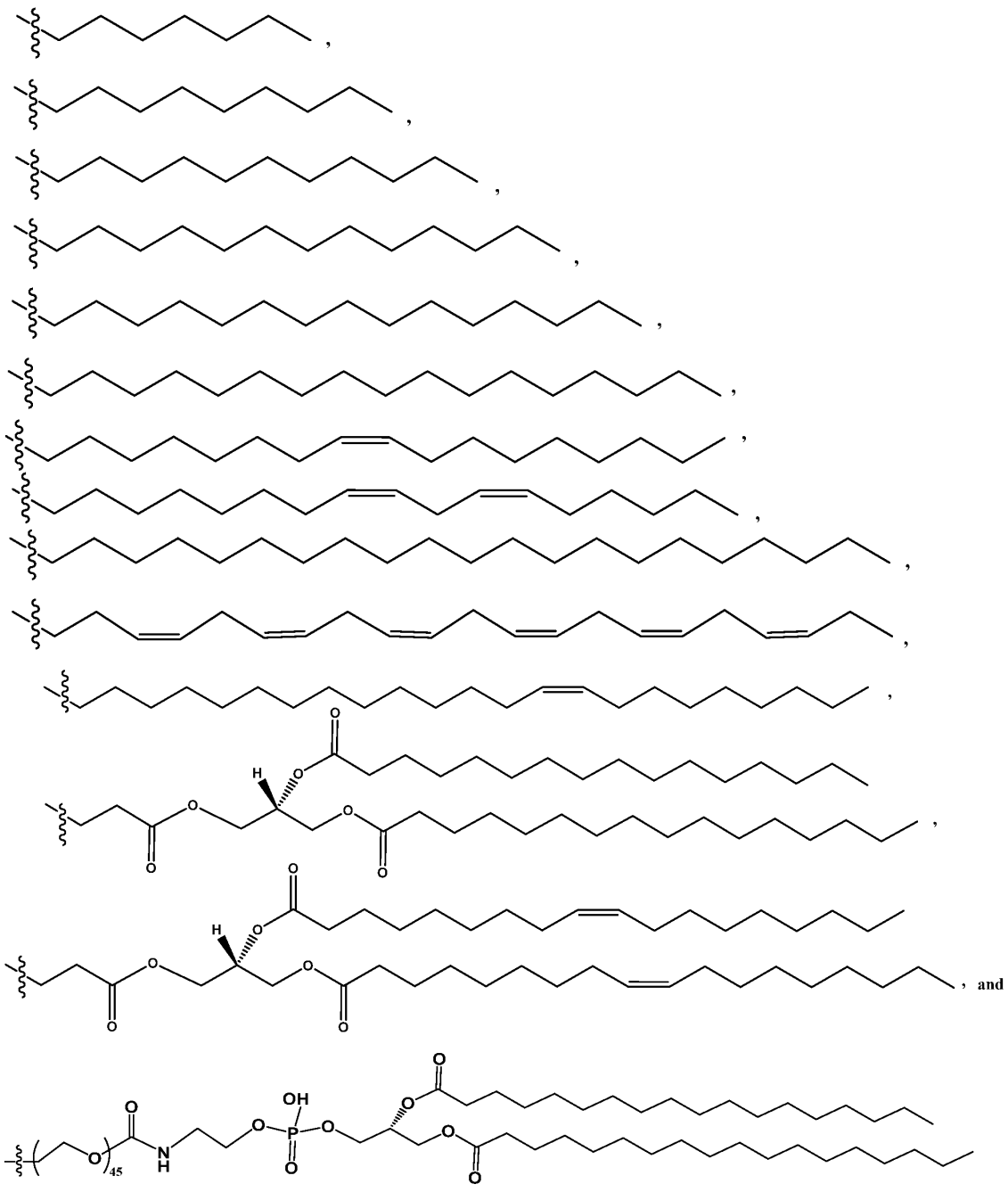
Y^1 is a linking group attaching to the 2′- or 3′-terminal of a nucleoside, a nucleotide, or an oligonucleotide;

Y^2 is hydrogen, a phosphoramidite analogue, an internucleotide linking group attaching to the 5′-terminal of a nucleoside, a nucleotide, or an oligonucleotide, or a linking group attaching to a solid support;

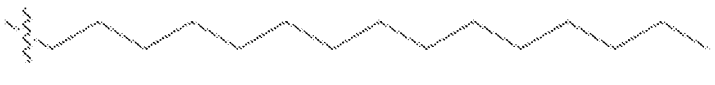
R^5 is adamantyl, or a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, or -P(S)OR-; and

R is hydrogen, a suitable protecting group, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

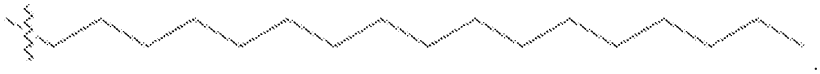
[00190] In some embodiments, R^5 is selected from



[00191] In some embodiments, R^5 is



[00192] In some embodiments, R^5 is



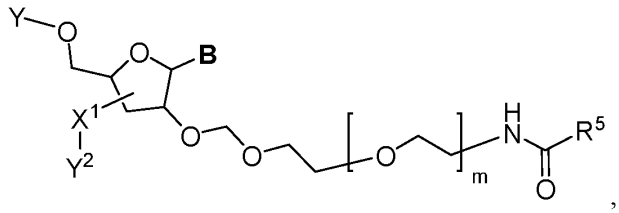
[00193] In some embodiments, the nucleotide sequence of the oligonucleotide comprises 1-10 targeting ligands. In some embodiments, the nucleotide sequence comprises 1, 2 or 3 targeting ligands.

[00194] In some embodiments, the oligonucleotide of the oligonucleotide-ligand conjugate is a double-stranded molecule. In some embodiments, the oligonucleotide is an RNAi molecule. In some embodiments, the double stranded oligonucleotide comprises a stem loop. In some embodiments, the ligand is conjugated to any of the nucleotides in the stem loop. In some embodiments, the ligand is conjugated to the first nucleotide from 5' to 3', in the stem loop. In some embodiments, the ligand is conjugated to the second nucleotide from 5' to 3' in the stem loop. In some embodiments, the ligand is conjugated to the third nucleotide from 5' to 3' in the stem loop. In some embodiments, the ligand is conjugated to the fourth nucleotide from 5' to 3' in the stem loop. In some embodiments, the ligand is conjugated to one, two, three, or four of the nucleotides in the stem loop. In some embodiments, the ligand is conjugated to three of the nucleotides in the stem loop.

[00195] In some embodiments, the oligonucleotide-ligand conjugate comprises a sense strand of 36 nucleotides with positions numbered 1-36 from 5' to 3'. In some embodiments, the oligonucleotide-ligand conjugate comprises a lipid conjugated to position 27 of a 36-nucleotide sense strand. In some embodiments, the oligonucleotide-ligand conjugate comprises a lipid conjugated to position 28 of a 36-nucleotide sense strand. In some embodiments, the oligonucleotide conjugate comprises a lipid conjugated to position 29 of a 36-nucleotide sense strand. In some embodiments, the oligonucleotide conjugate comprises a lipid conjugated to position 30 of a 36-nucleotide sense strand.

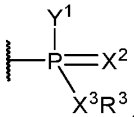
[00196] In some embodiments, an oligonucleotide-ligand conjugate comprises an antisense strand of 15 to 30 nucleotides and a sense strand of 15 to 40 nucleotide, wherein the sense and antisense strands form a duplex region, wherein the antisense strand comprises a

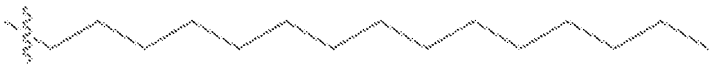
region of complementarity to a target sequence expressed in an immune cell associated with a tumor microenvironment, wherein the sense strand comprises at its 3' end a stem-loop comprising a tetraloop comprising 4 nucleosides, wherein one or more of the 4 nucleosides is represented by formula II-Ib:



,

wherein B is selected from an adenine and a guanine nucleobase, and wherein R^5 is a hydrocarbon chain. In some embodiments, m is 1, X1 is O, Y2 is an internucleotide linking group attaching to the 5' terminal of a nucleoside,

Y is represented by  , Y1 is a linking group attaching to the 2' or 3' terminal of a nucleotide, X2 is O, X3 is O, and R3 is H. In some embodiments, the hydrocarbon chain is a C8-C30 hydrocarbon chain. In some embodiments, the hydrocarbon chain is a C16 hydrocarbon chain. In some embodiments, the C16 hydrocarbon chain is represented by

 . In some embodiments, the 4 nucleosides of the tetraloop are numbered 1-4 from 5' to 3' and position 1 is represented by formula II-Ib. In some embodiments, position 2 is represented by formula II-Ib. In some embodiments, position 3 is represented by formula II-Ib. In some embodiments, position 4 is represented by formula II-Ib. In some embodiments, the sense strand is 36 nucleotides with positions numbered 1-36 from 5' to 3', wherein the stem-loop comprises nucleotides at positions 21-36, and wherein one or more nucleosides at positions 27-30 are represented by formula II-Ib. In some embodiments, the antisense strand is 22 nucleotides.

[00197] In some aspects, the disclosure provides oligonucleotide-ligand conjugates for targeting a target mRNA (*e.g.*, a target mRNA regulating immune suppression) and inhibiting or reducing target gene expression (*e.g.*, *via* the RNAi pathway), wherein the oligonucleotide-ligand conjugate is a double-stranded (ds) nucleic acid molecule comprising a sense strand (also

referred to herein as a passenger strand) and an antisense strand (also referred to herein as a guide strand). In some embodiments, the sense strand and antisense strand are separate strands and are not covalently linked. In some embodiments, the sense strand and antisense strand are covalently linked. In some embodiments, the sense strand and antisense strand form a duplex region, wherein the sense strand and antisense strand, or a portion thereof, binds or anneals to one another in a complementary manner (*e.g.*, by Watson-Crick base pairing).

[00198] In some embodiments, the sense strand has a first region (R1) and a second region (R2), wherein R2 comprises a first subregion (S1), a loop (L), such as a tetraloop (tetraL) or triloop (triL), and a second subregion (S2), wherein L or triL is located between S1 and S2, and wherein S1 and S2 form a second duplex (D2). D2 may have various lengths. In some embodiments, D2 is about 1-6 bp in length. In some embodiments, D2 is 2-6, 3-6, 4-6, 5-6, 1-5, 2-5, 3-5 or 4-5 bp in length. In some embodiments, D2 is 1, 2, 3, 4, 5 or 6 bp in length. In some embodiments, D2 is 6 bp in length.

[00199] In some embodiments, R1 of the sense strand and the antisense strand form a first duplex (D1). In some embodiments, D1 is at least about 15 (*e.g.*, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20 or at least 21) nucleotides in length. In some embodiments, D1 is in the range of about 12 to 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 27, 15 to 22, 18 to 22, 18 to 25, 18 to 27, 18 to 30 or 21 to 30 nucleotides in length). In some embodiments, D1 is at least 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 20, at least 25, or at least 30 nucleotides in length). In some embodiments, D1 is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length. In some embodiments, D1 is 19 nucleotides in length. In some embodiments, D1 is 20 nucleotides in length. In some embodiments, D1 comprising the sense strand and antisense strand does not span the entire length of the sense strand and/or antisense strand. In some embodiments, D1 comprising the sense strand and antisense strand spans the entire length of either the sense strand or antisense strand or both. In certain embodiments, D1 comprising the sense strand and antisense strand spans the entire length of both the sense strand and the antisense strand.

[00200] It should be appreciated that, in some embodiments, sequences presented in the Sequence Listing may be referred to in describing the structure of an oligonucleotide (e.g., a oligonucleotide-ligand conjugate) or other nucleic acid. In such embodiments, the actual oligonucleotide or other nucleic acid may have one or more alternative nucleotides (*e.g.*, an RNA

counterpart of a DNA nucleotide or a DNA counterpart of an RNA nucleotide) and/or one or more modified nucleotides and/or one or more modified internucleotide linkages and/or one or more other modification when compared with the specified sequence while retaining essentially same or similar complementary properties as the specified sequence.

[00201] In some embodiments, an oligonucleotide-ligand conjugate herein comprises a 25-nucleotide sense strand and a 27-nucleotide antisense strand that when acted upon by a Dicer enzyme results in an antisense strand that is incorporated into the mature RISC. In some embodiments, the sense strand of the oligonucleotide-ligand conjugate is longer than 27 nucleotides (*e.g.*, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 nucleotides). In some embodiments, the sense strand of the oligonucleotide-ligand conjugate is longer than 25 nucleotides (*e.g.*, 26, 27, 28, 29 or 30 nucleotides).

[00202] In some embodiments, the oligonucleotide-ligand conjugates herein have one 5′ end that is thermodynamically less stable when compared to the other 5′ end. In some embodiments, an asymmetric oligonucleotide-ligand conjugate is provided that comprises a blunt end at the 3′ end of a sense strand and a 3′-overhang at the 3′ end of an antisense strand. In some embodiments, the 3′-overhang on the antisense strand is about 1-8 nucleotides in length (*e.g.*, 1, 2, 3, 4, 5, 6, 7 or 8 nucleotides in length). Typically, an oligonucleotide-ligand conjugate has a two-nucleotide overhang on the 3′ end of the antisense (guide) strand. However, other overhangs are possible. In some embodiments, an overhang is a 3′-overhang comprising a length of between 1 and 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5 or 6 nucleotides. However, in some embodiments, the overhang is a 5′-overhang comprising a length of between 1 and 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5 or 6 nucleotides.

[00203] In some embodiments, two terminal nucleotides on the 3′ end of an antisense strand are modified. In some embodiments, the two terminal nucleotides on the 3′ end of the antisense strand are complementary with the target mRNA (*e.g.*, a target mRNA regulating immune suppression). In some embodiments, the two terminal nucleotides on the 3′ end of the antisense strand are not complementary with the target mRNA. In some embodiments, the two terminal nucleotides on the 3’ end of the antisense strand of an oligonucleotide-ligand conjugate herein are unpaired. In some embodiments, the two terminal nucleotides on the 3’ end of the

antisense strand of an oligonucleotide-ligand conjugate herein comprise an unpaired GG. In some embodiments, the two terminal nucleotides on the 3' end of the antisense strand of an oligonucleotide-ligand conjugate herein are not complementary to the target mRNA. In some embodiments, two terminal nucleotides on each 3′ end of an oligonucleotide-ligand conjugate are GG. Typically, one or both of the two terminal GG nucleotides on each 3′ end of a double-stranded oligonucleotide (*e.g.*, an RNAi oligonucleotide conjugate) is not complementary with the target mRNA.

[00204] In some embodiments, there is one or more (*e.g.*, 1, 2, 3, 4 or 5) mismatch(s) between a sense and antisense strand. If there is more than one mismatch between a sense and antisense strand, they may be positioned consecutively (*e.g.*, 2, 3 or more in a row), or interspersed throughout the region of complementarity. In some embodiments, the 3′ end of the sense strand contains one or more mismatches. In one embodiment, two mismatches are incorporated at the 3′ end of the sense strand. In some embodiments, base mismatches, or destabilization of segments at the 3′ end of the sense strand of an oligonucleotide-ligand conjugate herein improves or increases the potency and/or efficacy of the oligonucleotide-ligand conjugate.

[00205] In some embodiments, the targeting ligand is a GalNAc as described herein. In some embodiments, the targeting ligand is a carbohydrate. In some embodiments, the targeting ligand is an amino sugar.

[00206] In some embodiments, the oligonucleotide-ligand conjugate comprises two or more targeting ligands, wherein the targeting ligands are different. In some embodiments, the oligonucleotide-ligand conjugate comprises two or more targeting ligands, wherein the targeting ligands are the same.

Exemplary Oligonucleotides

[00207] In some embodiments, the oligonucleotide-ligand conjugate comprises an oligonucleotide conjugated with a fatty acid. In some embodiments, the fatty acid is a saturated fatty acid. In some embodiments, the fatty acid is an unsaturated fatty acid. In some embodiments, the oligonucleotide is conjugated with a lipid. In some embodiments, the lipid is a carbon chain. In some embodiments, the carbon chain is saturated. In some embodiments, the carbon chain is unsaturated. In some embodiments, the oligonucleotide is conjugated with a 16-

carbon (C16) lipid. In some embodiments, the C16 lipid comprises at least one double bond. In some embodiments, the oligonucleotide is conjugated with an 18-carbon (C18) lipid. In some embodiments, the C18 lipid comprises at least one double bond. In some embodiments, the oligonucleotide is conjugated with a 22-carbon (C22) lipid. In some embodiments, the C22 lipid comprises at least one double bond. In some embodiments, the oligonucleotide is conjugated with a 24-carbon (C24) lipid. In some embodiments, the C24 lipid comprises at least one double bond.

[00208] In some embodiments, the oligonucleotide of the oligonucleotide-ligand conjugate comprises a loop wherein at least one nucleotide of the loop is conjugated with a C16 lipid. In some embodiments, the second nucleotide of the loop is conjugated with a C16 lipid. In some embodiments, the oligonucleotide of the oligonucleotide-ligand conjugate comprises a loop wherein at least one nucleotide of the loop is conjugated with a C18 lipid. In some embodiments, the second nucleotide of the loop is conjugated with a C18 lipid. In some embodiments, the oligonucleotide of the oligonucleotide-ligand conjugate comprises a loop wherein at least one nucleotide of the loop is conjugated with a C22 lipid. In some embodiments, the second nucleotide of the loop is conjugated with a C22 lipid. In some embodiments, the oligonucleotide of the oligonucleotide-ligand conjugate comprises a loop wherein at least one nucleotide of the loop is conjugated with a C24 lipid. In some embodiments, the second nucleotide of the loop is conjugated with a C24 lipid.

[00209] In some embodiments, the oligonucleotide of the oligonucleotide-ligand conjugate comprises a tetraloop wherein at least one nucleotide of the tetraloop is conjugated with a C16 lipid. In some embodiments, the second nucleotide of the tetraloop is conjugated with a C16 lipid. In some embodiments, the oligonucleotide of the oligonucleotide-ligand conjugate comprises a tetraloop wherein at least one nucleotide of the tetraloop is conjugated with a C18 lipid. In some embodiments, the second nucleotide of the tetraloop is conjugated with a C18 lipid. In some embodiments, the oligonucleotide of the oligonucleotide-ligand conjugate comprises a tetraloop wherein at least one nucleotide of the tetraloop is conjugated with a C22 lipid. In some embodiments, the second nucleotide of the tetraloop is conjugated with a C22 lipid. In some embodiments, the oligonucleotide of the oligonucleotide-ligand conjugate comprises a tetraloop wherein at least one nucleotide of the tetraloop is conjugated

with a C24 lipid. In some embodiments, the second nucleotide of the tetraloop is conjugated with a C24 lipid.

[00210] In some embodiments, an oligonucleotide-ligand conjugate comprises a nucleotide sequence having at least one modified nucleoside. In some embodiments, an oligonucleotide-ligand conjugate comprises an antisense strand and a sense strand, wherein each strand comprises at least one modified nucleoside.

[00211] In some embodiments, the oligonucleotide-ligand conjugate is represented by the following formula:

Sense Strand:

[mXs][mX][mX][mX][mX][mX][mX][fX][fX][fX][fX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademX-TL] [mX] [mX] [mX] [mX] [mX] [mX][mX][mX]

Hybridized to

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fX][fX][fX][mX][fX][mX][mX] [fX][mX][mX][mX][fX][mX][mX][mX][mX][mX][mXs][mXs][mX]

Or

Sense Strand:

[mXs][mX][mX][mX][mX][mX][mX][fX][fX][fX][fX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademX-C#] [mX] [mX] [mX] [mX] [mX] [mX][mX][mX]

Hybridized to

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fX][fX][fX][mX][fX][mX][mX] [fX][mX][mX][mX][fX][mX][mX][mX][mX][mX][mXs][mXs][mX]

[00212] In some embodiments, the oligonucleotide-ligand conjugate is represented by the following formula:

Sense Strand:

[mXs][mX][mX][mX][mX][mX][mX][fX][fX][fX][fX][mX][mX][mX][mX][mX][mX][mX]

][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademX-TL] [mX] [mX] [mX] [mX] [mX] [mX][mX][mX]

Hybridized to

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fXs][fX][fX][mX][fX][mX][mX] [fX][mX][mX][mX][fX][mX][mX][mX][mX][mX][mXs][mXs][mX]

Or

Sense Strand:

[mXs][mX][mX][mX][mX][mX][mX][fX][fX][fX][fX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademX-C#] [mX] [mX] [mX] [mX] [mX] [mX][mX][mX]

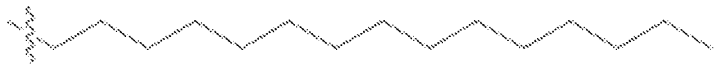
Hybridized to

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fXs][fX][fX][mX][fX][mX][mX] [fX][mX][mX][mX][fX][mX][mX][mX][mX][mX][mXs][mXs][mX]

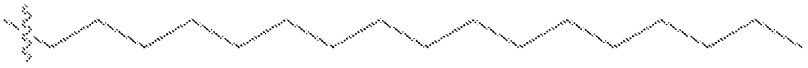
Table 1. Modification Key

[MePhosphonate-4O-mX]	4'-O-monomethylphosphonate-2'-O-methyl modified nucleotide
ademX-TL	2′-aminodiethoxymethanol-nucleotide-targeting ligand (*i.e.*, a targeting ligand attached to a nucleotide)
ademX-C#	2′-aminodiethoxymethanol-nucleotide-hydrocarbon chain (*e.g.,* a C16 or C18 lipid conjugate attached to a nucleotide)
[mXs]	2'-*O*-methyl modified nucleotide with a phosphorothioate linkage to the neighboring nucleotide
[fXs]	2'- fluoro modified nucleotide with a phosphorothioate linkage to the neighboring nucleotide
[mX]	2'-*O*-methyl modified nucleotide with phosphodiester linkages to neighboring nucleotides
[fX]	2'- fluoro modified nucleotide with phosphodiester linkages to neighboring nucleotides

[00213] In some embodiments, the oligonucleotide of the oligonucleotide-ligand conjugate is conjugated to a C16 lipid as shown in:



[00214] In some embodiments, the oligonucleotide of the oligonucleotide-ligand conjugate is conjugated to a C18 lipid as shown in:



[00215] In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA in immune cells of the TME or TdLN but does not reduce mRNA in tumor epithelial cells.

Methods of Use

i. Reducing Target Gene Expression

[00216] In some embodiments, the disclosure provides methods for contacting or delivering to an immune cell or population of immune cells of a tumor microenvironment (e.g., tumor resident immune cells) an effective amount of any of the oligonucleotide-ligand conjugates herein to reduce target gene expression (*e.g.*, reduce expression of a target gene encoding a regulator of immune suppression). In some embodiments, a reduction of target gene expression is determined by measuring a reduction in the amount or level of target mRNA, protein encoded by the target mRNA, or target gene (mRNA or protein) activity in a cell. The methods include those described herein and known to one of ordinary skill in the art.

[00217] Methods provided herein are useful in any appropriate tumor resident immune cell type. In some embodiments, a cell is any cell that expresses the target mRNA. In some embodiments, the cell is a primary cell obtained from a subject. In some embodiments, the primary cell has undergone a limited number of passages such that the cell substantially maintains is natural phenotypic properties. In some embodiments, a cell to which the oligonucleotide-ligand conjugate is delivered is *ex vivo* or *in vitro* (*i.e.*, can be delivered to a cell in culture or to an organism in which the cell resides).

[00218] In some embodiments, the oligonucleotide-ligand conjugates disclosed herein are delivered to an immune cell or population of immune cells of a tumor microenvironment using a nucleic acid delivery method known in the art including, but not limited to, injection of a solution or pharmaceutical composition containing the oligonucleotide-ligand conjugate, bombardment by particles covered by the oligonucleotide-ligand conjugate, exposing the cell or

population of cells to a solution containing the oligonucleotide-ligand conjugate, or electroporation of cell membranes in the presence of the oligonucleotide-ligand conjugate. Other methods known in the art for delivering oligonucleotides to cells may be used, such as lipid-mediated carrier transport, chemical-mediated transport, and cationic liposome transfection such as calcium phosphate, and others.

[00219] In some embodiments, reduction of target gene expression is determined by an assay or technique that evaluates one or more molecules, properties or characteristics of a cell or population of cells associated with target gene expression, or by an assay or technique that evaluates molecules that are directly indicative of target gene expression in a cell or population of cells (*e.g.*, target mRNA or protein). In some embodiments, the extent to which an oligonucleotide-ligand conjugate provided herein reduces target gene expression (e.g., reduces expression of a target gene encoding a regulator of immune suppression) is evaluated by comparing target gene expression in a cell or population of cells contacted with the oligonucleotide-ligand conjugate to a control cell or population of cells (*e.g.*, a cell or population of cells not contacted with the oligonucleotide-ligand conjugate or contacted with a control oligonucleotide-ligand conjugate). In some embodiments, a control amount or level of target gene expression in a control cell or population of cells is predetermined, such that the control amount or level need not be measured in every instance the assay or technique is performed. The predetermined level or value can take a variety of forms. In some embodiments, a predetermined level or value can be single cut-off value, such as a median or mean.

[00220] Measuring mRNA in the immune cells can be done using techniques known to those of skill in the art. For example, after a tumor is extracted, the tissue is manually or chemically dissociated into single cells. MACS sorting is then used to isolate the cells of interest (e.g. MDSCs) which are collected and prepared for RNA analysis. In some embodiments, the oligonucleotide conjugate reduces target mRNA expression in immune cells of the TME or TdLN for one day to at least 4 weeks. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in immune cells of the TME or TdLN for one day, three days, 7 days, 14 days, 21 days, 28 days, or 34 days. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in immune cells of the TME or TdLN for at least 1-4 weeks. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in immune cells of the TME or TdLN for up to 2 weeks. In

some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in immune cells of the TME or TdLN for up to 4 weeks.

[00221] In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in M-MDSCs for one day to at least 4 weeks. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in M-MDSCs for one day, three days, 7 days, 14 days, 21 days, 28 days, or 34 days. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in in M-MDSCs for at least 1-4 weeks. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in in M-MDSCs for up to 2 weeks. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in immune cells of the in M-MDSCs for up to 4 weeks.

[00222] In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in G-MDSCs for one day to at least 4 weeks. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in G-MDSCs for one day, three days, 7 days, 14 days, 21 days, 28 days, or 34 days. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in in G-MDSCs for at least 1-4 weeks. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in in G-MDSCs for up to 2 weeks. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in immune cells of the in G-MDSCs for up to 4 weeks.

[00223] In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in Tregs for one day to at least 4 weeks. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in Tregs for one day, three days, 7 days, 14 days, 21 days, 28 days, or 34 days. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in in M-MDSCs for at least 1-4 weeks. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in in Tregs for up to 2 weeks. In some embodiments, the oligonucleotide-ligand conjugate reduces target mRNA expression in immune cells of the in Tregs for up to 4 weeks.

[00224] In some embodiments, contacting or delivering an oligonucleotide-ligand conjugate described herein to an immune cell or a population of immune cells of a tumor microenvironment (e.g., a tumor resident immune cell) results in a reduction in target gene

expression. In some embodiments, the reduction in target gene expression is relative to a control amount or level of target gene expression in a cell or population of cells not contacted with the oligonucleotide-ligand conjugate or contacted with a control oligonucleotide-ligand conjugate. In some embodiments, the reduction in target gene expression is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower relative to a control amount or level of target gene expression. In some embodiments, the reduction in target gene expression in an immune cell in the TME is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower relative to a control amount or level of target gene expression. In some embodiments, the reduction in target gene expression in an immune cell in the TdLN is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower relative to a control amount or level of target gene expression. In some embodiments, the reduction in target gene expression in an M-MDSC is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower relative to a control amount or level of target gene expression. In some embodiments, the reduction in target gene expression in an G-MDSC is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower relative to a control amount or level of target gene expression. In some embodiments, the reduction in target gene expression in an Treg is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40%

or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower relative to a control amount or level of target gene expression. In some embodiments, the control amount or level of target gene expression is an amount or level of target mRNA and/or protein in a cell or population of cells that has not been contacted with an oligonucleotide-ligand conjugate herein. In some embodiments, the effect of delivery of an oligonucleotide-ligand conjugate to an immune cell or a population of immune cells of a tumor microenvironment (e.g., a tumor resident immune cell) according to a method herein is assessed after any finite period or amount of time (*e.g.*, minutes, hours, days, weeks, months). For example, in some embodiments, target gene expression is determined in an immune cell or a population of immune cells of a tumor microenvironment (e.g., a tumor resident immune cell) at least about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 24 hours; or at least about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, about 49 days, about 56 days, about 63 days, about 70 days, about 77 days, or about 84 days or more after contacting or delivering the oligonucleotide-ligand conjugate to the cell or population of cells. In some embodiments, target gene expression is determined in an immune cell or a population of immune cells of a tumor microenvironment (e.g., a tumor resident immune cell) at least about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months or more after contacting or delivering the oligonucleotide-ligand conjugate to the cell or population of cells.

[00225] Reducing the activity of immunosuppressive cells in a tumor, such as Tregs or MDSCs is a potential strategy to convert cold tumors into hot tumors. In some embodiments, the oligonucleotide-ligand conjugate converts a cold tumor into a hot tumor. In some embodiments, the oligonucleotide-ligand conjugate enhances anti-tumorigenic immune activity by reducing immunosuppressive activity. In some embodiments, the oligonucleotide-ligand conjugate enhances anti-tumorigenic T-cell activity by reducing the activity of immunosuppressive cells (*e.g.* MDSCs).

[00226] In some embodiments, the oligonucleotide-ligand conjugate enhances anti-tumorigenic activity by reducing the immunosuppressive activity of MDSCs. In some embodiments, the oligonucleotide-ligand conjugate enhances anti-tumorigenic activity by

reducing the immunosuppressive activity of M-MDSCs. In some embodiments, the oligonucleotide-ligand conjugate enhances anti-tumorigenic activity by reducing the immunosuppressive activity of G-MDSCs. In some embodiments, the oligonucleotide-ligand conjugate enhances anti-tumorigenic activity by reducing the immunosuppressive activity of Tregs. In some embodiments, methods for measuring anti-tumorigenic activity include, but are not limited to, measuring the number of tumor infiltrating lymphocytes in the tumor.

[00227] In some embodiments, the oligonucleotide-ligand conjugate reduces the immunosuppressive activity of M-MDSCs to a sufficient amount to convert a cold tumor into a hot tumor. In some embodiments, the oligonucleotide-ligand conjugate reduces the immunosuppressive activity of G-MDSCs to a sufficient amount to convert a cold tumor into a hot tumor. In some embodiments, the oligonucleotide-ligand conjugate reduces the immunosuppressive activity of Tregs to a sufficient amount to convert a cold tumor into a hot tumor. Methods for determine whether a cold tumor has been converted to a hot tumor include, but are not limited to, measuring the response of the tumor to an immunotherapy (e.g., checkpoint inhibitor polypeptide).

ii. Treatment Methods and Medical Use

[00228] In some aspects, the disclosure provides oligonucleotide-ligand conjugates for use, or adaptable for use, to treat a subject (*e.g.*, a human) with cancer that would benefit from reducing a target gene (e.g., a target gene encoding a regulator of immune suppression). In some respects, the disclosure provides oligonucleotide-ligand conjugates for use, or adapted for use, to treat a subject having cancer. In some respects, the disclosure provides oligonucleotide-ligand conjugates for use, or adapted for use, to treat a subject having cancer associated with an immunosuppressive TME. The disclosure also provides oligonucleotide-ligand conjugates for use, or adaptable for use, in the manufacture of a medicament or pharmaceutical composition for treating cancer. In some embodiments, the oligonucleotide-ligand conjugates for use, or adaptable for use, target a regulator of immune suppression (*e.g.*, a transcription factor or checkpoint inhibitor polypeptide). In some embodiments, the oligonucleotide-ligand conjugates for use, or adaptable for use, target a regulator of immune suppression and reduce the amount or level of the regulator's mRNA, or the regulator's protein and/or activity.

[00229] As detailed below, the methods also may include steps such as measuring or obtaining a baseline value for a marker of a regulator of immune suppression, and then comparing such obtained value to one or more other baseline values or values obtained after being administered the oligonucleotide to assess the effectiveness of treatment.

[00230] In some embodiments, the disclosure provides oligonucleotide-ligand conjugates for reducing immune suppression in a tumor microenvironment. In some embodiments, reduction of immune suppression is determined by an appropriate assay or technique to evaluate one or more properties or characteristics of immune suppression in a tumor (*e.g.* the presence of suppressive cells such as MDSCs) or by an assay or technique that evaluates molecules that are directly indicative of immune suppression (*e.g.*, high Arg1 expression). In some embodiments, the extent to which an oligonucleotide-ligand conjugate herein reduces immune suppression is evaluated by comparing immune suppression in the TME contacted with the oligonucleotide-ligand conjugate to an appropriate control (*e.g.*, an appropriate tumor not contacted with the oligonucleotide or contacted with a control oligonucleotide). In some embodiments, an appropriate control level of mRNA expression into protein may be a predetermined level or value, such that a control level need not be measured every time. The predetermined level or value can take a variety of forms. In some embodiments, a predetermined level or value can be single cut-off value, such as a median or mean.

[00231] In some embodiments, administration of an oligonucleotide-ligand conjugate herein results in a reduction in target mRNA in a tumor resident immune cell. In some embodiments, the reduction in target mRNA is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower when compared with an appropriate control level of mRNA. The appropriate control level may be a level of mRNA expression and/or protein translation in a cell or population of cells that has not been contacted with an oligonucleotide-ligand conjugate herein. In some embodiments, the effect of delivery of an oligonucleotide-ligand conjugate to a cell according to a method herein is assessed after a finite period. For example, levels of mRNA may be analyzed in a cell at least about 8 hours, about 12 hours, about 18 hours, about 24 hours; or at least about 1, 2, 3, 4, 5, 6, 7 or even up to 14 days after introduction of the oligonucleotide-ligand conjugate into the tumor.

[00232] In some embodiments, an oligonucleotide-ligand conjugate is delivered in the form of a transgene that is engineered to express in a cell the oligonucleotide-ligand conjugate or strands comprising the oligonucleotide-ligand conjugate (*e.g.*, its sense and antisense strands). In some embodiments, an o oligonucleotide-ligand conjugate is delivered using a transgene engineered to express any oligonucleotide-ligand conjugate disclosed herein. Transgenes may be delivered using viral vectors (*e.g.*, adenovirus, retrovirus, vaccinia virus, poxvirus, adeno-associated virus, or herpes simplex virus) or non-viral vectors (*e.g.*, plasmids or synthetic mRNAs). In some embodiments, transgenes can be injected directly to a subject.

[00233] In some aspects, the disclosure provides methods of treating a subject having, suspected of having, or at risk of developing a cancer. In some embodiments, the disclosure provides methods of treating or attenuating the onset or progression of cancer using the oligonucleotide-ligand conjugates described herein. In some embodiments of the methods herein, a subject is treated by administering a therapeutically effective amount of any one or more of the oligonucleotide-ligand conjugates herein. In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

[00234] In some embodiments of the methods herein, one or more oligonucleotide-ligand conjugates herein, or a pharmaceutical composition comprising one or more oligonucleotide-ligand conjugates, is administered to a subject having cancer. In some embodiments, the oligonucleotide-ligand conjugate reduces a target mRNA in a tumor (e.g., in an immune cell in a tumor microenvironment). In some embodiments, the amount of target mRNA and/or protein is reduced in the subject.

[00235] In some embodiments of the methods herein, an oligonucleotide-ligand conjugate herein, or a pharmaceutical composition comprising the oligonucleotide-ligand conjugate, is administered to a subject having cancer and expression of a target gene (e.g., regulator of immune suppression) is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to expression of the target prior to administration of one or more oligonucleotide-ligand conjugates or pharmaceutical composition. In some embodiments, the target mRNA is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about

99% or greater than 99% when compared to the target mRNA expression in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide-ligand conjugate or pharmaceutical composition or receiving a control oligonucleotide-ligand conjugate or pharmaceutical composition or treatment.

[00236] In some embodiments of the methods herein, an oligonucleotide-ligand conjugate or oligonucleotide-ligand conjugates herein, or a pharmaceutical composition comprising the oligonucleotide-ligand conjugate (s), is administered to a subject having cancer such that an amount or level of target mRNA (e.g., gene encoding a regulator of immune suppression) is reduced in tumor resident immune cells of the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of target mRNA prior to administration of the oligonucleotide-ligand conjugate or pharmaceutical composition. In some embodiments of the methods herein, an oligonucleotide-ligand conjugate or oligonucleotide-ligand conjugates herein, or a pharmaceutical composition comprising the oligonucleotide-ligand conjugate (s), is administered to a subject having cancer such that an amount or level of target mRNA (e.g., gene encoding a regulator of immune suppression) is reduced in TdLN immune cells of the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of target mRNA prior to administration of the oligonucleotide-ligand conjugate or pharmaceutical composition. In some embodiments, an amount or level of target mRNA is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of target mRNA in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide-ligand conjugate or oligonucleotide-ligand conjugates or pharmaceutical composition or receiving a control oligonucleotide-ligand conjugate or oligonucleotide-ligand conjugates, pharmaceutical composition or treatment.

[00237] In some embodiments of the methods herein, an oligonucleotide-ligand conjugate or oligonucleotide-ligand conjugates herein, or a pharmaceutical composition comprising the oligonucleotide-ligand conjugate(s), is administered to a subject having cancer with an immune

suppressive environment such that an amount or level of a target protein regulating immune suppression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of protein regulating immune suppression prior to administration of the oligonucleotide-ligand conjugate or pharmaceutical composition. In some embodiments, an amount or level of protein regulating immune suppression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of protein regulating immune suppression in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide-ligand conjugate(s) or pharmaceutical composition or receiving a control oligonucleotide-ligand conjugate(s), or pharmaceutical composition or treatment.

[00238] In some embodiments of the methods herein, an oligonucleotide-ligand conjugate or oligonucleotide-ligand conjugates herein, or a pharmaceutical composition comprising the oligonucleotide-ligand conjugate or oligonucleotide-ligand conjugates, is administered to a subject having cancer with an immunosuppressive TME such that an amount or level of an mRNA or protein regulating immune suppression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of the mRNA or protein regulating immune suppression prior to administration of the oligonucleotide-ligand conjugate or pharmaceutical composition. In some embodiments, an amount or level of target mRNA regulating immune suppression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of target mRNA in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide-ligand conjugate or pharmaceutical composition or receiving a control oligonucleotide-ligand conjugate, pharmaceutical composition or treatment.

[00239] Because of their high specificity, the oligonucleotide-ligand conjugates herein specifically target mRNAs of target genes of diseased cells and tissues. In some embodiments,

the oligonucleotide-ligand conjugate delivers the oligonucleotide to a target cell. In some embodiments, the target cell is an immune cell found in a tumor microenvironment. In some embodiments, the target cell is an immune cell found in an immune suppressive tumor microenvironment. In some embodiments, the oligonucleotide-ligand conjugate delivers the oligonucleotide to one or more MDSC cell populations. In some embodiments, the oligonucleotide-ligand conjugate delivers the oligonucleotide to a G-MDSC. In some embodiments, the oligonucleotide-ligand conjugate delivers the oligonucleotide to a M-MDSC. In some embodiments, the oligonucleotide-ligand conjugate delivers the oligonucleotide to a G-MDSC and a M-MDSC. In some embodiments, the oligonucleotide-ligand conjugate delivers the oligonucleotide to a T cell in a tumor microenvironment. In some embodiments, the oligonucleotide-ligand conjugate delivers the oligonucleotide nucleotide to a Treg cell.

[00240] As described herein, the oligonucleotide-ligand conjugate for targeting an mRNA encoding a regulator of immune suppression is capable of converting a cold tumor to a hot tumor. Hot tumors enable other therapeutic approaches to be more effective at treating disease. Therefore, in some embodiments, an oligonucleotide-ligand conjugate described herein is administered in combination with a second therapeutic agent. In some embodiments, the second therapeutic agent is selected from, but not limited to a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy, or a combination thereof.

[00241] Methods described herein typically involve administering to a subject in an effective amount of an oligonucleotide-ligand conjugate or oligonucleotide-ligand conjugates, that is, an amount capable of producing a desirable therapeutic result. A therapeutically acceptable amount may be an amount that can therapeutically treat a disease or disorder. The appropriate dosage for any one subject will depend on certain factors, including the subject's size, body surface area, age, the particular composition to be administered, the active ingredient(s) in the composition, time and route of administration, general health, and other drugs being administered concurrently.

[00242] In some embodiments, a subject is administered any one of the compositions herein either enterally (*e.g.*, orally, by gastric feeding tube, by duodenal feeding tube, *via* gastrostomy or rectally), parenterally (*e.g.*, subcutaneous injection, intravenous injection or infusion, intra-

arterial injection or infusion, intraosseous infusion, intramuscular injection, intracerebral injection, intracerebroventricular injection, intrathecal), topically (*e.g.*, epicutaneous, inhalational, *via* eye drops, or through a mucous membrane), or by direct injection into a target organ (*e.g.*, the liver of a subject). In some embodiments, an oligonucleotide-ligand conjugate or pharmaceutical composition thereof is administered intravenously or subcutaneously.

[00243] As a non-limiting set of examples, in some embodiments, the oligonucleotide-ligand conjugates herein are administered quarterly (once every three months), bi-monthly (once every two months), monthly or weekly. For example, the oligonucleotide-ligand conjugates may be administered every week or at intervals of two, or three weeks. Alternatively, the oligonucleotide-ligand conjugates may be administered daily. In some embodiments, a subject is administered one or more loading doses of the oligonucleotide-ligand conjugate followed by one or more maintenance doses of the oligonucleotide-ligand conjugate.

[00244] In some embodiments the oligonucleotide-ligand conjugate herein are administered alone or in combination. In some embodiments the oligonucleotides herein are administered in combination concurrently, sequentially (in any order), or intermittently. For example, two oligonucleotide-ligand conjugates may be co-administered concurrently. Alternatively, one oligonucleotide-ligand conjugate may be administered and followed any amount of time later (e.g., one hour, one day, one week or one month) by the administration of a second oligonucleotide-ligand conjugate.

[00245] In some embodiments, the subject to be treated is a human or non-human primate or other mammalian subject. Other exemplary subjects include domesticated animals such as dogs and cats; livestock such as horses, cattle, pigs, sheep, goats, and chickens; and animals such as mice, rats, guinea pigs, and hamsters.

Types of Oligonucleotides

[00246] A variety of oligonucleotide types and/or structures are useful for targeting a target sequence in the methods herein including, but not limited to, RNAi oligonucleotides, antisense oligonucleotides, miRNAs, *etc.* Any of the oligonucleotide types described herein or elsewhere are contemplated for use as a framework to incorporate a targeting sequence herein.

[00247] In some embodiments, the oligonucleotides herein inhibit expression of a target sequence by engaging with RNA interference (RNAi) pathways upstream or downstream of

Dicer involvement. For example, RNAi oligonucleotides have been developed with each strand having sizes of about 19-25 nucleotides with at least one 3′ overhang of 1 to 5 nucleotides (*see*, *e.g.*, US Patent No. 8,372,968). Longer oligonucleotides also have been developed that are processed by Dicer to generate active RNAi products (*see*, *e.g.*, US Patent No. 8,883,996). Further work produced extended dsRNAs where at least one end of at least one strand is extended beyond a duplex targeting region, including structures where one of the strands includes a thermodynamically-stabilizing tetraloop structure (*see*, *e.g.*, US Patent Nos. 8,513,207 and 8,927,705, as well as Intl. Patent Application Publication No. WO 2010/033225). Such structures may include ss extensions (on one or both sides of the molecule) as well as ds extensions.

[00248] In some embodiments, the oligonucleotides herein engage with the RNAi pathway downstream of the involvement of Dicer (*e.g.*, Dicer cleavage). In some embodiments, the oligonucleotides described herein are Dicer substrates. In some embodiments, upon endogenous Dicer processing, double-stranded nucleic acids of 19-23 nucleotide sin length capable of reducing target mRNA expression are produced. In some embodiments, the oligonucleotide has an overhang (*e.g.*, of 1, 2, or 3 nucleotides in length) in the 3′ end of the sense strand. In some embodiments, the oligonucleotide (*e.g.*, siRNA) comprises a 21-nucleotide guide strand that is antisense to a target RNA and a complementary passenger strand, in which both strands anneal to form a 19-bp duplex and 2 nucleotide overhangs at either or both 3′ ends. Longer oligonucleotide designs also are available including oligonucleotides having a guide strand of 23 nucleotides and a passenger strand of 21 nucleotides, where there is a blunt end on the right side of the molecule (3′ end of passenger strand/5′ end of guide strand) and a two nucleotide 3′-guide strand overhang on the left side of the molecule (5′ end of the passenger strand/3′ end of the guide strand). In such molecules, there is a 21 bp duplex region. *See*, *e.g.*, US Patent Nos. 9,012,138; 9,012,621 and 9,193,753.

[00249] In some embodiments, the oligonucleotides herein comprise sense and antisense strands that are both in the range of about 17 to 26 (*e.g.*, 17 to 26, 20 to 25 or 21-23) nucleotides in length. In some embodiments, the oligonucleotides herein comprise sense and antisense strands that are both in the range of about 17 to 36 (*e.g.*, 17 to 36, 20 to 25 or 21-23) nucleotides in length. In some embodiments, the oligonucleotides described herein comprise an antisense strand of 19-30 nucleotides in length and a sense strand of 19-50 nucleotides in length, wherein

the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhand of 1-4 nucleotides at the 3' terminus of the antisense strand. In some embodiments, an oligonucleotide herein comprises a sense and antisense strand that are both in the range of about 19-22 nucleotides in length. In some embodiments, the sense and antisense strands are of equal length. In some embodiments, an oligonucleotide comprises sense and antisense strands, such that there is a 3′-overhang on either the sense strand or the antisense strand, or both the sense and antisense strand. In some embodiments, for oligonucleotides that have sense and antisense strands that are both in the range of about 21-23 nucleotides in length, a 3′ overhang on the sense, antisense, or both sense and antisense strands is 1 or 2 nucleotides in length. In some embodiments, the oligonucleotide has a guide strand of 22 nucleotides and a passenger strand of 20 nucleotides, where there is a blunt end on the right side of the molecule (3′ end of passenger strand/5′ end of guide strand) and a 2 nucleotide 3′-guide strand overhang on the left side of the molecule (5′ end of the passenger strand/3′ end of the guide strand). In such molecules, there is a 20 bp duplex region.

[00250] Other oligonucleotide designs for use with the compositions and methods herein include: 16-mer siRNAs (*see*, *e.g.*, NUCLEIC ACIDS IN CHEMISTRY AND BIOLOGY. Blackburn (ed.), Royal Society of Chemistry, 2006), shRNAs (*e.g.*, having 19 bp or shorter stems; (*see*, *e.g.*, Moore *et al.,* (2010) METHODS MOL. BIOL. 629:141-58), blunt siRNAs (*e.g.*, of 19 bps in length; *see*, *e.g.*, Kraynack and Baker (2006) *RNA* 12:163-76), asymmetrical siRNAs (aiRNA; *see*, *e.g.*, Sun *et al.,* (2008) NAT. BIOTECHNOL. 26:1379-82), asymmetric shorter-duplex siRNA (*see*, *e.g.*, Chang *et al.,* (2009) MOL. THER. 17:725-32), fork siRNAs (*see*, *e.g.*, Hohjoh (2004) FEBS LETT. 557:193-98), ss siRNAs (Elsner (2012) NAT. BIOTECHNOL. 30:1063), dumbbell-shaped circular siRNAs (*see*, *e.g.*, Abe *et al.,* (2007) J. AM. CHEM. SOC. 129:15108-09), and small internally segmented interfering RNA (siRNA; *see*, *e.g.*, Bramsen *et al.,* (2007) NUCLEIC ACIDS RES. 35:5886-97). Further non-limiting examples of an oligonucleotide structures that may be used in some embodiments to reduce or inhibit the expression of STAT3 are microRNA (miRNA), short hairpin RNA (shRNA) and short siRNA (*see*, *e.g.*, Hamilton *et al.,* (2002) EMBO J. 21:4671-79; *see also*, US Patent Application Publication No. 2009/0099115).

[00251] Still, in some embodiments, an oligonucleotide for reducing or inhibiting expression of a target sequence herein is ss. Such structures may include but are not limited to ss

RNAi molecules. Recent efforts have demonstrated the activity of ss RNAi molecules (*see*, *e.g.*, Matsui *et al.*, (2016) MOL. THER. 24:946-55). However, in some embodiments, oligonucleotides herein are antisense oligonucleotides (ASOs). An antisense oligonucleotide is a ss oligonucleotide that has a nucleobase sequence which, when written in the 5′ to 3′ direction, comprises the reverse complement of a targeted segment of a particular nucleic acid and is suitably modified (*e.g.*, as a gapmer) to induce RNaseH-mediated cleavage of its target RNA in cells or (*e.g.*, as a mixmer) to inhibit translation of the target mRNA in cells. ASOs for use herein may be modified in any suitable manner known in the art including, for example, as shown in US Patent No. 9,567,587 (including, *e.g.*, length, sugar moieties of the nucleobase (pyrimidine, purine), and alterations of the heterocyclic portion of the nucleobase). Further, ASOs have been used for decades to reduce expression of specific target genes (*see*, *e.g.*, Bennett *et al.*, (2017) ANNU. REV. PHARMACOL. 57:81-105).

[00252] In some embodiments, the antisense oligonucleotide shares a region of complementarity with a target mRNA. In some embodiments, the antisense oligonucleotide is 15-50 nucleotides in length. In some embodiments, the antisense oligonucleotide is 15-25 nucleotides in length. In some embodiments, the antisense oligonucleotide is 22 nucleotides in length. In some embodiments, the antisense oligonucleotide is at least 15 contiguous nucleotides in length. In some embodiments, the antisense oligonucleotide is at least 19 contiguous nucleotides in length. In some embodiments, the antisense oligonucleotide is at least 20 contiguous nucleotides in length. In some embodiments, the antisense oligonucleotide differs by 1, 2, or 3 nucleotides from the target sequence.

Double-Stranded Oligonucleotides

[00253] In some embodiments, the disclosure provides double-stranded dsRNAs for targeting and inhibiting expression of a target sequence (*e.g.*, *via* the RNAi pathway) comprising a sense strand (also referred to herein as a passenger strand) and an antisense strand (also referred to herein as a guide strand). In some embodiments, the sense strand and antisense strand are separate strands and are not covalently linked. In some embodiments, the sense strand and antisense strand are covalently linked. In some embodiments, the sense strand and antisense strand form a duplex region, wherein the sense strand and antisense strand, or a portion thereof, binds with one another in a complementary fashion (e.g., by Watson-Crick base pairing).

[00254] In some embodiments, the sense strand has a first region (R1) and a second region (R2), wherein R2 comprises a first subregion (S1), a loop (L), such as a tetraloop (tetraL) or triloop (triL), and a second subregion (S2), wherein L, tetraL, or triL is located between S1 and S2, and wherein S1 and S2 form a second duplex (D2). D2 may have various length. In some embodiments, D2 is about 1-6 bp in length. In some embodiments, D2 is 2-6, 3-6, 4-6, 5-6, 1-5, 2-5, 3-5 or 4-5 bp in length. In some embodiments, D2 is 1, 2, 3, 4, 5 or 6 bp in length. In some embodiments, D2 is 6 bp in length.

[00255] In some embodiments, R1 of the sense strand and the antisense strand form a first duplex (D1). In some embodiments, D1 is at least about 15 (*e.g.*, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20 or at least 21) nucleotides in length. In some embodiments, D1 is in the range of about 12 to 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 27, 15 to 22, 18 to 22, 18 to 25, 18 to 27, 18 to 30 or 21 to 30 nucleotides in length). In some embodiments, D1 is at least 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 20, at least 25, or at least 30 nucleotides in length). In some embodiments, D1 is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length. In some embodiments, D1 is 20 nucleotides in length. In some embodiments, D1 comprising sense strand and antisense strand does not span the entire length of the sense strand and/or antisense strand. In some embodiments, D1 comprising the sense strand and antisense strand spans the entire length of either the sense strand or antisense strand or both. In certain embodiments, D1 comprising the sense strand and antisense strand spans the entire length of both the sense strand and the antisense strand.

[00256] It should be appreciated that, in some embodiments, sequences presented in the Sequence Listing may be referred to in describing the structure of an oligonucleotide or other nucleic acid. In such embodiments, the actual oligonucleotide or other nucleic acid may have one or more alternative nucleotides (*e.g.*, an RNA counterpart of a DNA nucleotide or a DNA counterpart of an RNA nucleotide) and/or one or more modified nucleotides and/or one or more modified internucleotide linkages and/or one or more other modification when compared with the specified sequence while retaining essentially same or similar complementary properties as the specified sequence.

[00257] In some embodiments, a double-stranded RNA (dsRNA) herein comprises a 25-nucleotide sense strand and a 27-nucleotide antisense strand that when acted upon by a Dicer enzyme results in an antisense strand that is incorporated into the mature RISC. In some

embodiments, the sense strand of the dsRNA is longer than 27 nucleotides (*e.g.*, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 nucleotides). In some embodiments, the sense strand of the dsRNA is longer than 27 nucleotides (*e.g.*, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides). In some embodiments, the sense strand of the dsRNA is longer than 25 nucleotides (*e.g.*, 26, 27, 28, 29 or 30 nucleotides).

[00258] In some embodiments, oligonucleotides herein have one 5′ end that is thermodynamically less stable when compared to the other 5′ end. In some embodiments, an asymmetry oligonucleotide is provided that includes a blunt end at the 3′ end of a sense strand and a 3′-overhang at the 3′ end of an antisense strand. In some embodiments, the 3′-overhang on the antisense strand is about 1-8 nucleotides in length (*e.g.*, 1, 2, 3, 4, 5, 6, 7 or 8 nucleotides in length). Typically, an oligonucleotide for RNAi has a two-nucleotide overhang on the 3′ end of the antisense (guide) strand. However, other overhangs are possible. In some embodiments, an overhang is a 3′-overhang comprising a length of between 1 and 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5 or 6 nucleotides. However, in some embodiments, the overhang is a 5′-overhang comprising a length of between 1 and 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5 or 6 nucleotides.

[00259] In some embodiments, two terminal nucleotides on the 3′ end of an antisense strand are modified. In some embodiments, the two terminal nucleotides on the 3′ end of the antisense strand are complementary with the target mRNA. In some embodiments, the two terminal nucleotides on the 3′ end of the antisense strand are not complementary with the target mRNA. In some embodiments, the two terminal nucleotides on the 3′ end of the antisense strand of an oligonucleotide herein comprise an unpaired GG. In some embodiments, the two (2) terminal nucleotides on the 3′ end of an antisense strand of an oligonucleotide herein are not complementary to the target mRNA. In some embodiments, two terminal nucleotides on each 3′ end of an oligonucleotide in the nicked tetraloop structure are GG. In some embodiments, one or both of the two (2) terminal GG nucleotides on each 3′ end of an oligonucleotide herein is not complementary with the target mRNA. Typically, one or both two terminal GG nucleotides on each 3′ end of an oligonucleotide is not complementary with the target.

[00260] In some embodiments, there is one or more (*e.g.*, 1, 2, 3, 4 or 5) mismatch between a sense and antisense strand. If there is more than one mismatch between a sense and antisense strand, they may be positioned consecutively (*e.g.*, 2, 3 or more in a row), or interspersed throughout the region of complementarity. In some embodiments, the 3′ end of the sense strand contains one or more mismatches. In one embodiment, two mismatches are incorporated at the 3′ end of the sense strand. In some embodiments, base mismatches, or destabilization of segments at the 3′ end of the sense strand of the oligonucleotide improved the potency of synthetic duplexes in RNAi, possibly through facilitating processing by Dicer.

a. Antisense Strands

[00261] In some embodiments, a dsRNA comprises an antisense strand of up to about 40 nucleotides in length (*e.g.*, up to 40, up to 35, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17 or up to 12 nucleotides in length). In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) comprises an antisense strand of up to about 50 nucleotides in length (*e.g.*, up to 50, up to 40, up to 35, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17 or up to 12 nucleotides in length). In some embodiments, an oligonucleotide may have an antisense strand of at least about 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 19, at least 21, at least 22, at least 25, at least 27, at least 30, at least 35 or at least 38 nucleotides in length). In some embodiments, an oligonucleotide may have an antisense strand in a range of about 12 to about 40 (*e.g.*, 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 22, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40 or 32 to 40) nucleotides in length. In some embodiments, an oligonucleotide comprises antisense strand of 15 to 30 nucleotides in length. In some embodiments, an oligonucleotide may have an antisense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 nucleotides in length.

[00262] In some embodiments, an antisense strand of an oligonucleotide may be referred to as a "guide strand." For example, if an antisense strand can engage with RNA-induced silencing complex (RISC) and bind to an *Argonaute* protein such as Ago2, or engage with or bind to one or more similar factors, and direct silencing of a target gene, it may be referred to as a guide strand. In some embodiments, a sense strand complementary to a guide strand may be referred to as a "passenger strand."

b. Sense Strands

[00263] In some embodiments, an oligonucleotide comprises a sense strand (or passenger strand) of up to about 40 nucleotides in length (*e.g.*, up to 40, up to 36, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17 or up to 12 nucleotides in length). In some embodiments, an oligonucleotide may have a sense strand of at least about 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 19, at least 21, at least 25, at least 27, at least 30, at least 36 or at least 38 nucleotides in length). In some embodiments, an oligonucleotide may have a sense strand in a range of about 12 to about 40 (*e.g.*, 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 21, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40 or 32 to 40) nucleotides in length. In some embodiments, an oligonucleotide herein comprises a sense strand of 15 to 50 nucleotides in length. In some embodiments, an oligonucleotide herein comprises a sense strand of 18 to 36 nucleotides in length. In some embodiments, an oligonucleotide may have a sense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 nucleotides in length. In some embodiments, an oligonucleotide comprises a sense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40,41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides in length. In some embodiments, an oligonucleotide herein comprises a sense strand of 36 nucleotides in length.

[00264] In some embodiments, an oligonucleotide provided herein *(e.g.,* an RNAi oligonucleotide) comprises a sense strand comprising a stem-loop structure at the 3′ end of the sense strand. In some embodiments, the stem-loop is formed by intrastrand base pairing. In some embodiments, a sense strand comprises a stem-loop structure at its 5′ end. In some embodiments, the stem of the stem-loop comprises a duplex of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 2 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 3 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 4 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 5 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 6 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 7 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 8 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 9

nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 10 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 11 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 12 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 13 nucleotides in length. In some embodiments, the stem of the stem-loop comprises a duplex of 14 nucleotides in length.

[00265] In some embodiments, a stem-loop provides the oligonucleotide protection against degradation (*e.g.*, enzymatic degradation), facilitates or improves targeting and/or delivery to a target cell, tissue, or organ (*e.g.,* the liver), or both. For example, in some embodiments, the loop of a stem-loop is comprised of nucleotides comprising one or more modifications that facilitate, improve, or increase targeting to a target, inhibition of target gene expression, and/or delivery, uptake, and/or penetrance into a target cell, tissue, or organ *(e.g.,* the liver), or a combination thereof. In some embodiments, the stem-loop itself or modification(s) to the stem-loop do not affect or do not substantially affect the inherent gene expression inhibition activity of the oligonucleotide, but facilitates, improves, or increases stability (*e.g.,* provides protection against degradation) and/or delivery, uptake, and/or penetrance of the oligonucleotide to a target cell, tissue, or organ. In certain embodiments, an oligonucleotide herein comprises a sense strand comprising (*e.g.*, at its 3′ end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a single-stranded loop of linked nucleotides between S1 and S2 of up to about 10 nucleotides in length (*e.g.*, 3, 4, 5, 6, 7, 8, 9 or 10 nucleotides in length). In some embodiments, the loop (L) is 3 nucleotides in length (referred to herein as "triloop". In some embodiments, the loop (L) is 4 nucleotides in length (referred to herein as "tetraloop"). In some embodiments, the loop (L) is 5 nucleotides in length. In some embodiments, the loop (L) is 6 nucleotides in length. In some embodiments, the loop (L) is 7 nucleotides in length. In some embodiments, the loop (L) is 8 nucleotides in length. In some embodiments, the loop (L) is 9 nucleotides in length. In some embodiments, the loop (L) is 10 nucleotides in length.

[00266] In some embodiments, the tetraloop comprises the sequence 5'-GAAA-3'. In some embodiments, the stem loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO: 86).

[00267] In some embodiments, a sense strand comprises a stem-loop structure at its 3′ end. In some embodiments, a sense strand comprises a stem-loop structure at its 5′ end. In some embodiments, a stem is a duplex of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 bp in length. In some embodiments, a stem-loop provides the molecule protection against degradation (*e.g.*, enzymatic degradation) and facilitates targeting characteristics for delivery to a target cell. For example, in some embodiments, a loop provides added nucleotides on which modification can be made without substantially affecting the gene expression inhibition activity of an oligonucleotide. In certain embodiments, an oligonucleotide is herein in which the sense strand comprises (*e.g.*, at its 3′ end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a loop between S1 and S2 of up to about 10 nucleotides in length (*e.g.*, 3, 4, 5, 6, 7, 8, 9 or 10 nucleotides in length). **FIG. 1** depicts non-limiting examples of such an oligonucleotide.

[00268] In some embodiments, a loop (L) of a stem-loop having the structure S1-L-S2 as described herein is a triloop. In some embodiments, the triloop comprises ribonucleotides, deoxyribonucleotides, modified nucleotides, ligands (e.g., delivery ligands), and combinations thereof.

[00269] In some embodiments, a loop of a stem-loop is a tetraloop (*e.g.*, within a nicked tetraloop structure). A tetraloop may contain ribonucleotides, deoxyribonucleotides, modified nucleotides and combinations thereof. Typically, a tetraloop has 4 to 5 nucleotides.

Duplex Length

[00270] In some embodiments, a duplex formed between a sense and antisense strand is at least 12 (*e.g.,* at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 21) nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is in the range of 12-30 nucleotides in length (*e.g.,* 12 to 30, 12 to 27, 12 to 22, 15 to 25, 18 to 30, 18 to 22, 18 to 25, 18 to 27, 18 to 30, 19 to 30 or 21 to 30 nucleotides in length). In some embodiments, a duplex formed between a sense and antisense strand is 12, 13, 14, 15, 16, 17, 18, 19, 29, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 12 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 13 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 14

nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 15 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 16 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 17 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 18 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 19 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 20 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 21 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 22 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 23 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 24 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 25 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 26 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 27 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 28 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 29 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand is 30 nucleotides in length. In some embodiments, a duplex formed between a sense and antisense strand does not span the entire length of the sense strand and/or antisense strand. In some embodiments, a duplex between a sense and antisense strand spans the entire length of either the sense or antisense strands. In some embodiments, a duplex between a sense and antisense strand spans the entire length of both the sense strand and the antisense strand.

Oligonucleotide Termini

[00271] In some embodiments, an oligonucleotide disclosed herein (*e.g.,* an RNAi oligonucleotide) comprises a sense strand and an antisense strand, wherein the termini of either or both strands comprise a blunt end. In some embodiments, an oligonucleotide herein comprises sense and antisense strands that are separate strands which form an asymmetric duplex region having an overhang at the 3' terminus of the antisense strand. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the termini of

either or both strands comprise an overhang comprising one or more nucleotides. In some embodiments, the one or more nucleotides comprising the overhang are unpaired nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the 3' termini of the sense strand and the 5' termini of the antisense strand comprise a blunt end. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the 5' termini of the sense strand and the 3' termini of the antisense strand comprise a blunt end.

[00272] In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the 3' terminus of either or both strands comprise a 3'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the sense strand comprises a 3'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the antisense strand comprises a 3'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein both the sense strand and the antisense strand comprises a 3'-overhang comprising one or more nucleotides.

[00273] In some embodiments, the 3'-overhang is about one (1) to twenty (20) nucleotides in length (*e.g.,* about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or about 20 nucleotides in length). In some embodiments, the 3' overhang is about one (1) to nineteen (19), one (1) to eighteen (18), one (1) to seventeen (17), one (1) to sixteen (16), one (1) to fifteen (15), one (1) to fourteen (14), one (1) to thirteen (13), one (1) to twelve (12), one (1) to eleven (11), one (1) to ten (10), one (1) to nine (9), one (1) to eight (8), one (1) to seven (7), one (1) to six (6), one (1) to five (5), one (1) to four (4), one (1) to three (3), or about one (1) to two (2) nucleotides in length. In some embodiments, the 3'-overhang is (1) nucleotide in length. In some embodiments, the 3'-overhang is two (2) nucleotides in length. In some embodiments, the 3'-overhang is three (3) nucleotides in length. In some embodiments, the 3'-overhang is four (4) nucleotides in length. In some embodiments, the 3'-overhang is five (5) nucleotides in length. In some embodiments, the 3'-overhang is six (6) nucleotides in length. In some embodiments, the 3'-overhang is seven (7) nucleotides in length. In some embodiments, the 3'-overhang is eight (8) nucleotides in length. In some embodiments, the 3'-overhang is nine (9) nucleotides in length. In some embodiments, the 3'-overhang is ten (10) nucleotides in length. In some

embodiments, the 3'-overhang is eleven (11) nucleotides in length. In some embodiments, the 3'-overhang is twelve (12) nucleotides in length. In some embodiments, the 3'-overhang is thirteen (13) nucleotides in length. In some embodiments, the 3'-overhang is fourteen (14) nucleotides in length. In some embodiments, the 3'-overhang is fifteen (15) nucleotides in length. In some embodiments, the 3'-overhang is sixteen (16) nucleotides in length. In some embodiments, the 3'-overhang is seventeen (17) nucleotides in length. In some embodiments, the 3'-overhang is eighteen (18) nucleotides in length. In some embodiments, the 3'-overhang is nineteen (19) nucleotides in length. In some embodiments, the 3'-overhang is twenty (20) nucleotides in length.

[00274] In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the 5' terminus of either or both strands comprise a 5'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the sense strand comprises a 5'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein the antisense strand comprises a 5'-overhang comprising one or more nucleotides. In some embodiments, an oligonucleotide herein comprises a sense strand and an antisense strand, wherein both the sense strand and the antisense strand comprises a 5'-overhang comprising one or more nucleotides.

[00275] In some embodiments, the 5'-overhang is about one (1) to twenty (20) nucleotides in length (*e.g.,* about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or about 20 nucleotides in length). In some embodiments, the 5' overhang is about one (1) to nineteen (19), one (1) to eighteen (18), one (1) to seventeen (17), one (1) to sixteen (16), one (1) to fifteen (15), one (1) to fourteen (14), one (1) to thirteen (13), one (1) to twelve (12), one (1) to eleven (11), one (1) to ten (10), one (1) to nine (9), one (1) to eight (8), one (1) to seven (7), one (1) to six (6), one (1) to five (5), one (1) to four (4), one (1) to three (3), or about one (1) to two (2) nucleotides in length. In some embodiments, the 5'-overhang is (1) nucleotide in length. In some embodiments, the 5'-overhang is two (2) nucleotides in length. In some embodiments, the 5'-overhang is three (3) nucleotides in length. In some embodiments, the 5'-overhang is four (4) nucleotides in length. In some embodiments, the 5'-overhang is five (5) nucleotides in length. In some embodiments, the 5'-overhang is six (6) nucleotides in length. In some embodiments, the 5'-overhang is seven (7) nucleotides in length. In some embodiments, the 5'-overhang is eight

(8) nucleotides in length. In some embodiments, the 5'-overhang is nine (9) nucleotides in length. In some embodiments, the 5'-overhang is ten (10) nucleotides in length. In some embodiments, the 5'-overhang is eleven (11) nucleotides in length. In some embodiments, the 5'-overhang is twelve (12) nucleotides in length. In some embodiments, the 5'-overhang is thirteen (13) nucleotides in length. In some embodiments, the 5'-overhang is fourteen (14) nucleotides in length. In some embodiments, the 5'-overhang is fifteen (15) nucleotides in length. In some embodiments, the 5'-overhang is sixteen (16) nucleotides in length. In some embodiments, the 5'-overhang is seventeen (17) nucleotides in length. In some embodiments, the 5'-overhang is eighteen (18) nucleotides in length. In some embodiments, the 5'-overhang is nineteen (19) nucleotides in length. In some embodiments, the 5'-overhang is twenty (20) nucleotides in length.

[00276] In some embodiments, one or more (*e.g.*, 2, 3, 4, 5, or more) nucleotides comprising the 3' terminus or 5' terminus of a sense and/or antisense strand are modified. For example, in some embodiments, one or two terminal nucleotides of the 3' terminus of the antisense strand are modified. In some embodiments, the last nucleotide at the 3' terminus of an antisense strand is modified, such that it comprises 2' modification, or it comprises, a 2'-O-methoxyethyl. In some embodiments, the last one or two terminal nucleotides at the 3' terminus of an antisense strand are complementary with the target. In some embodiments, the last one or two nucleotides at the 3' terminus of the antisense strand are not complementary with the target.

[00277] In some embodiments, an oligonucleotide disclosed herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand and an antisense strand, wherein the 3' terminus of the sense strand comprises a step-loop described herein and the 3' terminus of the antisense strand comprises a 3'-overhang described herein. In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) comprises a sense strand and an antisense strand that form a nicked tetraloop structure described herein, wherein the 3' terminus of the sense strand comprises a stem-loop, wherein the loop is a tetraloop described herein, and wherein the 3' terminus of the antisense strand comprises a 3'-overhang described herein. In some embodiments, the 3'-overhang is two (2) nucleotides in length. In some embodiments, the two (2) nucleotides comprising the 3'-overhang both comprise guanine (G) nucleobases. Typically, one or both of the nucleotides comprising the 3'-overhang of the antisense strand are not complementary with the target mRNA.

Oligonucleotide Modifications

a. Sugar Modifications

[00278] In some embodiments, a modified sugar (also referred herein to a sugar analog) includes a modified deoxyribose or ribose moiety in which, for example, one or more modifications occur at the 2′, 3′, 4′ and/or 5′ carbon position of the sugar. In some embodiments, a modified sugar may also include non-natural alternative carbon structures such as those present in locked nucleic acids ("LNA"; *see*, *e.g.*, Koshkin *et al.,* (1998) TETRAHEDON 54:3607-3630), unlocked nucleic acids ("UNA"; see, *e.g.*, Snead *et al.,* (2013) MOL. THER-NUCL. ACIDS 2:e103) and bridged nucleic acids ("BNA"; *see*, *e.g.*, Imanishi and Obika (2002) CHEM COMMUN. (CAMB) 21:1653-1659).

[00279] In some embodiments, a nucleotide modification in a sugar comprises a 2′-modification. In some embodiments, a 2′-modification may be 2′-O-propargyl, 2′-O-propylamin, 2′-amino, 2′-ethyl, 2′-fluoro (2′-F), 2′-aminoethyl (EA), 2′-O-methyl (2′-OMe), 2′-O-methoxyethyl (2′-MOE), 2′-O-[2-(methylamino)-2-oxoethyl] (2′-O-NMA) or 2′-deoxy-2′-fluoro-β-d-arabinonucleic acid (2′-FANA). In some embodiments, the modification is 2′-F, 2′-OMe or 2′-MOE. In some embodiments, a modification in a sugar comprises a modification of the sugar ring, which may comprise modification of one or more carbons of the sugar ring. For example, a modification of a sugar of a nucleotide may comprise a 2′-oxygen of a sugar is linked to a 1′-carbon or 4′-carbon of the sugar, or a 2′-oxygen is linked to the 1′-carbon or 4′-carbon *via* an ethylene or methylene bridge. In some embodiments, a modified nucleotide has an acyclic sugar that lacks a 2′-carbon to 3′-carbon bond. In some embodiments, a modified nucleotide has a thiol group, *e.g.*, in the 4′ position of the sugar.

[00280] In some embodiments, the oligonucleotide described herein comprises at least about 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, or more). In some embodiments, the sense strand of the oligonucleotide comprises at least about 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, or more). In some embodiments, the antisense strand of the oligonucleotide comprises at least about 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, or more).

[00281] In some embodiments, all the nucleotides of the sense strand of the oligonucleotide are modified. In some embodiments, all the nucleotides of the antisense strand of the oligonucleotide are modified. In some embodiments, all the nucleotides of the oligonucleotide (*i.e.*, both the sense strand and the antisense strand) are modified. In some embodiments, the modified nucleotide comprises a 2′-modification (*e.g.*, a 2′-F or 2′-OMe, 2′-MOE, and 2′-deoxy-2′-fluoro-β-d-arabinonucleic acid). In some embodiments, the modified nucleotide comprises a 2′-modification (*e.g.*, a 2′-F or 2′-OMe).

[00282] In some embodiments, the disclosure provides oligonucleotides having different modification patterns. In some embodiments, an oligonucleotide herein comprises a sense strand having a modification pattern as set forth in the Examples and Sequence Listing and an antisense strand having a modification pattern as set forth in the Examples and Sequence Listing.

[00283] In some embodiments, an oligonucleotide disclosed herein (*e.g.,* an RNAi oligonucleotide) comprises an antisense strand having nucleotides that are modified with 2′-F. In some embodiments, an oligonucleotide herein comprises an antisense strand comprising nucleotides that are modified with 2′-F and 2′-OMe. In some embodiments, an oligonucleotide disclosed herein comprises a sense strand having nucleotides that are modified with 2′-F. In some embodiments, an oligonucleotide disclosed herein comprises a sense strand comprises nucleotides that are modified with 2′-F and 2′-OMe.

[00284] In some embodiments, an oligonucleotide described herein comprises a sense strand with about 10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprising a 2’-fluoro modification. In some embodiments, about 11% of the nucleotides of the sense strand comprise a 2-fluoro modification. In some embodiments, an oligonucleotide described herein comprises an antisense strand with about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the antisense strand comprising a 2’-fluoro modification. In some embodiments, about 32% of the nucleotides of the antisense strand comprise a 2’-fluoro modification. In some embodiments, the oligonucleotide has about 15-25%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, or 25% of its nucleotides comprising a 2’-fluoro modification. In some embodiments, about 19% of the nucleotides in the dsRNAi oligonucleotide comprise a 2’-fluoro modification.

[00285] In some embodiments, the modified oligonucleotides comprise a sense strand sequence having a modification pattern as set forth in **FIG 1** or **Example 12** and an antisense

strand having a modification pattern as set forth in **FIG 1** or **Example 12.** In some embodiments, for these oligonucleotides, one or more of positions 8, 9, 10 or 11 of the sense strand is modified with a 2′-F group. In other embodiments, for these oligonucleotides, the sugar moiety at each of nucleotides at positions 1-7 and 12-20 in the sense strand is modified with a 2′-OMe.

[00286] In some embodiments, the antisense strand has 3 nucleotides that are modified at the 2′-position of the sugar moiety with a 2′-F. In some embodiments, the sugar moiety at positions 2, 5 and 14 and optionally up to 3 of the nucleotides at positions 1, 3, 7 and 10 of the antisense strand are modified with a 2′-F. In some embodiments, the sugar moiety at positions 2, 5 and 14 and optionally up to 3 of the nucleotides at positions 3, 4, 7 and 10 of the antisense strand are modified with a 2′-F. In other embodiments, the sugar moiety at each of the positions at positions 2, 5 and 14 of the antisense strand is modified with the 2′-F. In other embodiments, the sugar moiety at each of the positions at positions 1, 2, 5 and 14 of the antisense strand is modified with the 2′-F. In other embodiments, the sugar moiety at each of the positions at positions 2, 4, 5 and 14 of the antisense strand is modified with the 2′-F. In still other embodiments, the sugar moiety at each of the positions at positions 1, 2, 3, 5, 7 and 14 of the antisense strand is modified with the 2′-F. In other embodiments, the sugar moiety at each of the positions at positions 2, 3, 4, 5, 7 and 14 of the antisense strand is modified with the 2′-F. In yet another embodiment, the sugar moiety at each of the positions at positions 1, 2, 3, 5, 10 and 14 of the antisense strand is modified with the 2′-F. In other embodiments, the sugar moiety at each of the positions at positions 2, 3, 4, 5, 10 and 14 of the antisense strand is modified with the 2′-F. In another embodiment, the sugar moiety at each of the positions at positions 2, 3, 5, 7, 10 and 14 of the antisense strand is modified with the 2′-F. In yet another embodiment, the sugar moiety at each of the positions at positions 2, 3, 4, 5, 7, 10 and 14 of the antisense strand is modified with the 2′-F.

[00287] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, or position 22 modified with 2′-F.

[00288] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5,

position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, or position 22 modified with 2′-OMe.

[00289] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, or position 22 modified with a modification selected from the group consisting of 2′-O-propargyl, 2′-O-propylamin, 2′-amino, 2′-ethyl, 2’-aminoethyl (EA), 2′-O-methyl (2′-OMe), 2′-O-methoxyethyl (2′-MOE), 2′-O-[2-(methylamino)-2-oxoethyl] (2′-O-NMA), and 2′-deoxy-2′-fluoro-β-d-arabinonucleic acid (2′-FANA).

[00290] In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 8-11 modified with 2′-F. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 3, 8, 9, 10, 12, 13 and 17 modified with 2′-F. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 1-7 and 12-17 or 12-20 modified with 2’OMe. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 1-7, 12-27 and 31-36 modified with 2’OMe. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety of each of the nucleotides at positions 1-7 and 12-17 or 12-20 of the sense strand modified with a modification selected from the group consisting of 2′-O-propargyl, 2′-O-propylamin, 2′-amino, 2′-ethyl, 2’-aminoethyl (EA), 2′-O-methyl (2′-OMe), 2′-O-methoxyethyl (2′-MOE), 2′-O-[2-(methylamino)-2-oxoethyl] (2′-O-NMA), and 2′-deoxy-2′-fluoro-β-d-arabinonucleic acid (2′-FANA). In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 1-2, 4-7, 11, 14-16 and 18-20 modified with 2’OMe. In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety of each of the nucleotides at positions 1-2, 4-7, 11, 14-16 and 18-20 of the sense strand modified with a modification selected from the group consisting of 2′-O-propargyl, 2′-O-propylamin, 2′-amino, 2′-ethyl, 2’-aminoethyl (EA), 2′-O-methyl (2′-OMe), 2′-O-methoxyethyl (2′-MOE), 2′-O-[2-(methylamino)-2-oxoethyl] (2′-O-NMA), and 2′-deoxy-2′-fluoro-β-d-arabinonucleic acid (2′-FANA).

[00291] In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, position 22, position 23, position 24, position 25, position 26, position 27, position 28, position 29, position 30, position 31, position 32, position 33, position 34, position 35, or position 36 modified with 2′-F.

[00292] In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, position 22, position 23, position 24, position 25, position 26, position 27, position 28, position 29, position 30, position 31, position 32, position 33, position 34, position 35, or position 36 modified with 2′-OMe.

[00293] In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at position 1, position 2, position 3, position 4, position 5, position 6, position 7, position 8, position 9, position 10, position 11, position 12, position 13, position 14, position 15, position 16, position 17, position 18, position 19, position 20, position 21, position 22, position 23, position 24, position 25, position 26, position 27, position 28, position 29, position 30, position 31, position 32, position 33, position 34, position 35, or position 36 modified with a modification selected from the group consisting of 2′-O-propargyl, 2′-O-propylamin, 2′-amino, 2′-ethyl, 2’-aminoethyl (EA), 2′-O-methyl (2′-OMe), 2′-O-methoxyethyl (2′-MOE), 2′-O-[2-(methylamino)-2-oxoethyl] (2′-O-NMA), and 2′-deoxy-2′-fluoro-β-d-arabinonucleic acid (2′-FANA).

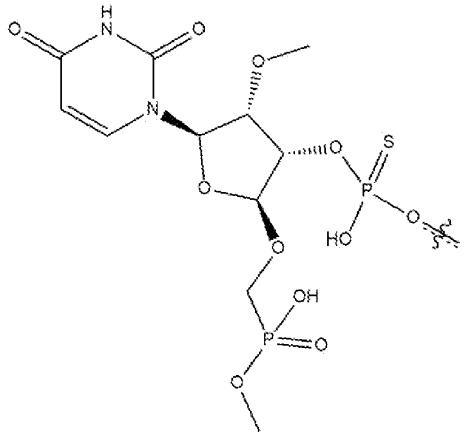
b. 5′ Terminal Phosphates

[00294] In some embodiments, 5′-terminal phosphate groups of oligonucleotides enhance the interaction with Ago2. However, oligonucleotides comprising a 5′-phosphate group may be susceptible to degradation *via* phosphatases or other enzymes, which can limit their bioavailability *in vivo*. In some embodiments, oligonucleotides include analogs of 5′ phosphates that are resistant to such degradation. In some embodiments, a phosphate analog may be oxymethylphosphonate, vinylphosphonate or malonyl phosphonate. In certain embodiments, the

1′ end of an oligonucleotide strand is attached to chemical moiety that mimics the electrostatic and steric properties of a natural 5′-phosphate group ("phosphate mimic").

[00295] In some embodiments, an oligonucleotide has a phosphate analog at a 4′-carbon position of the sugar (referred to as a "4′-phosphate analog"). *See*, *e.g.*, Intl. Patent Application Publication No. WO 2018/045317. In some embodiments, an oligonucleotide herein comprises a 4′-phosphate analog at a 5′-terminal nucleotide. In some embodiments, a phosphate analog is an oxymethylphosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (*e.g.*, at its 4′-carbon) or analog thereof. In other embodiments, a 4′-phosphate analog is a thiomethyl phosphonate or an amino methyl phosphonate, in which the sulfur atom of the thiomethyl group or the nitrogen atom of the amino methyl group is bound to the 4′-carbon of the sugar moiety or analog thereof. In certain embodiments, a 4′-phosphate analog is an oxymethyl phosphonate. In some embodiments, an oxymethyl phosphonate is represented by the formula $–O–CH_2–PO(OH)_2$ or $–O–CH_2–PO(OR)_2$, in which R is independently selected from H, CH_3, an alkyl group, CH_2CH_2CN, $CH_2OCOC(CH_3)_3$, $CH_2OCH_2CH_2Si(CH_3)_3$ or a protecting group. In certain embodiments, the alkyl group is CH_2CH_3. More typically, R is independently selected from H, CH_3 or CH_2CH_3.

[00296] In some embodiments, an oligonucleotide provided herein comprises an antisense strand comprising a 4′-phosphate analog at the 5′-terminal nucleotide, wherein 5'-terminal nucleotide comprises the following structure:



4'-O-monomethylphosphonate-2'-O-methyluridine phosphorothioate [MePhosphonate-4O-mUs].

Chem 1

c. Modified Internucleotide Linkages

[00297] In some embodiments, an oligonucleotide may comprise a modified internucleoside linkage. In some embodiments, phosphate modifications or substitutions may result in an oligonucleotide that comprises at least about 1 (*e.g.*, at least 1, at least 2, at least 3 or at least 5) modified internucleotide linkage. In some embodiments, any one of the oligonucleotides disclosed herein comprises about 1 to about 10 (*e.g.*, 1 to 10, 2 to 8, 4 to 6, 3 to 10, 5 to 10, 1 to 5, 1 to 3 or 1 to 2) modified internucleotide linkages. In some embodiments, any one of the oligonucleotides disclosed herein comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 modified internucleotide linkages.

[00298] A modified internucleotide linkage may be a phosphorodithioate linkage, 4′-O-methylene phosphonate linkage, a phosphorothioate linkage, a phosphotriester linkage, a thionoalkylphosphonate linkage, a thionalkylphosphotriester linkage, a phosphoramidite linkage, a phosphonate linkage or a boranophosphate linkage. In some embodiments, at least one modified internucleotide linkage of any one of the oligonucleotides as disclosed herein is a phosphorothioate linkage. In some embodiments, at least one modified internucleotide linkage of any one of the oligonucleotides as disclosed herein is a 4′-O-methylene phosphonate linkage.

[00299] In some embodiments, the oligonucleotide described herein has a phosphorothioate linkage between one or more of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand. In some embodiments, the oligonucleotide described herein has a phosphorothioate linkage between each of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

d. Base Modifications

[00300] In some embodiments, oligonucleotides herein have one or more modified nucleobases. In some embodiments, modified nucleobases (also referred to herein as base analogs) are linked at the 1′ position of a nucleotide sugar moiety. In certain embodiments, a modified nucleobase is a nitrogenous base. In certain embodiments, a modified nucleobase does

not contain nitrogen atom. *See*, *e.g.*, US Patent Application Publication No. 2008/0274462. In some embodiments, a modified nucleotide comprises a universal base. However, in certain embodiments, a modified nucleotide does not contain a nucleobase (abasic).

[00301] In some embodiments, a universal base is a heterocyclic moiety located at the 1′ position of a nucleotide sugar moiety in a modified nucleotide, or the equivalent position in a nucleotide sugar moiety substitution, that, when present in a duplex, can be positioned opposite more than one type of base without substantially altering structure of the duplex. In some embodiments, compared to a reference single-stranded nucleic acid (*e.g.*, oligonucleotide) that is fully complementary to a target nucleic acid, a single-stranded nucleic acid containing a universal base forms a duplex with the target nucleic acid that has a lower T_m than a duplex formed with the complementary nucleic acid. However, in some embodiments, when compared to a reference single-stranded nucleic acid in which the universal base has been replaced with a base to generate a single mismatch, the single-stranded nucleic acid containing the universal base forms a duplex with the target nucleic acid that has a higher T_m than a duplex formed with the nucleic acid comprising the mismatched base.

[00302] Non-limiting examples of universal-binding nucleotides include, but are not limited to, inosine, 1-β-D-ribofuranosyl-5-nitroindole and/or 1-β-D-ribofuranosyl-3-nitropyrrole (*see*, US Patent Application Publication No. 2007/0254362; Van Aerschot *et al.*, (1995) NUCLEIC ACIDS RES. 23:4363-4370; Loakes *et al.*, (1995) NUCLEIC ACIDS RES. 23:2361-66; and Loakes and Brown (1994) NUCLEIC ACIDS RES. 22:4039-43).

e. Reversible Modifications

[00303] While certain modifications to protect an oligonucleotide from the *in vivo* environment before reaching target cells can be made, they can reduce the potency or activity of the oligonucleotide once it reaches the cytosol of the target cell. Reversible modifications can be made such that the molecule retains desirable properties outside of the cell, which are then removed upon entering the cytosolic environment of the cell. Reversible modification can be removed, for example, by the action of an intracellular enzyme or by the chemical conditions inside of a cell (*e.g.*, through reduction by intracellular glutathione).

[00304] In some embodiments, a reversibly modified nucleotide comprises a glutathione-sensitive moiety. Typically, nucleic acid molecules have been chemically modified with cyclic disulfide moieties to mask the negative charge created by the internucleotide diphosphate

linkages and improve cellular uptake and nuclease resistance. *See* US Patent Application Publication No. 2011/0294869, Intl. Patent Application Publication Nos. WO 2014/088920 and WO 2015/188197, and Meade *et al.,* (2014) NAT. BIOTECHNOL. 32:1256-63. This reversible modification of the internucleotide diphosphate linkages is designed to be cleaved intracellularly by the reducing environment of the cytosol (*e.g.,* glutathione). Earlier examples include neutralizing phosphotriester modifications that were reported to be cleavable inside cells (*see*, Dellinger *et al.,* (2003) J. AM. CHEM. SOC. 125:940-50).

[00305] In some embodiments, such a reversible modification allows protection during *in vivo* administration (*e.g.*, transit through the blood and/or lysosomal/endosomal compartments of a cell) where the oligonucleotide will be exposed to nucleases and other harsh environmental conditions (*e.g.*, pH). When released into the cytosol of a cell where the levels of glutathione are higher compared to extracellular space, the modification is reversed, and the result is a cleaved oligonucleotide. Using reversible, glutathione-sensitive moieties, it is possible to introduce sterically larger chemical groups into the oligonucleotide of interest when compared to the options available using irreversible chemical modifications. This is because these larger chemical groups will be removed in the cytosol and, therefore, should not interfere with the biological activity of the oligonucleotides inside the cytosol of a cell. As a result, these larger chemical groups can be engineered to confer various advantages to the nucleotide or oligonucleotide, such as nuclease resistance, lipophilicity, charge, thermal stability, specificity, and reduced immunogenicity. In some embodiments, the structure of the glutathione-sensitive moiety can be engineered to modify the kinetics of its release.

[00306] In some embodiments, a glutathione-sensitive moiety is attached to the sugar of the nucleotide. In some embodiments, a glutathione-sensitive moiety is attached to the 2′-carbon of the sugar of a modified nucleotide. In some embodiments, the glutathione-sensitive moiety is located at the 5′-carbon of a sugar, particularly when the modified nucleotide is the 5′-terminal nucleotide of the oligonucleotide. In some embodiments, the glutathione-sensitive moiety is located at the 3′-carbon of sugar, particularly when the modified nucleotide is the 3′-terminal nucleotide of the oligonucleotide. In some embodiments, the glutathione-sensitive moiety comprises a sulfonyl group. *See*, *e.g.*, US Provisional Patent Application No. 62/378,635, entitled *Compositions Comprising Reversibly Modified Oligonucleotides and Uses Thereof*, which was filed on August 23, 2016.

Oligonucleotide Inhibitors of STAT3

[00307] In some aspects, the disclosure provides, *inter alia*, oligonucleotides that reduce or inhibit STAT3 expression. In some embodiments, an oligonucleotide that inhibits STAT3 expression herein is targeted to a *STAT3* mRNA. The sequence of human *STAT3* mRNA (NM_001369512.1) is set forth as SEQ ID NO: 85 or NM_139276.3 (SEQ ID NO: 1217). STAT3 is a known target for conventional cancer therapies.

[00308] The tolerogenic activities of MDSCs are controlled by an oncogenic transcription factor, signal transducer and activator of transcription 3 (STAT3) (Su *et al.*,, INT J. MOL SCI (2018) 19(6): 1803). STAT3 is also known to be highly expressed across a range of cancer types and in *in vitro* and *in vivo* preclinical models (Huynh *et al.*, NAT. REV. CANCER (2019) 19: 82-96). The inhibition of STAT3 leads to the selective apoptosis of tumor cells and tumor growth inhibition through modulation of downstream target genes (Wang *et al.*, INTERNATIONAL JOURNAL OF BIOLOGICAL SCIENCES, 15(3): 668–79 (2019)). STAT3 is of particular interest in immuno-oncology due to its well documented contributions to an immunosuppressive tumor microenvironment. STAT3 contributes to an immunosuppressive tumor microenvironment by upregulating the inhibitory receptor expressed by T-cells, and *via* expression of its ligand (PD-1/PD-L1), through increased secretion of IFNɣ ((Bu *et al.*, JOURNAL OF DENTAL RESEARCH, 96(9): 1027–34 (2017)). It has long been known that inhibition of STAT3 signaling in antigen presenting cells (APCs) results in priming of antigen-specific CD4+ T cells in response to otherwise tolerogenic stimuli (Cheng *et al.*, IMMUNITY, 19: 425–36 (2003)). In addition, phosphorylated STAT3 on MDSCs directly contributes to the modulation of the suppressive tumor microenvironment by regulating suppressive components such as the amino acid arginine, through transcriptional control (Vasques-Dunndel *et al.*, J. CLIN. INVEST., 15(3): 668–79 (2013)). Over the years several methodologies have been explored to therapeutically target STAT3. While direct targeting of the protein is attractive, the true target is a protein-protein interaction that has been held up as an example of an ‘undruggable’ target due historical data showing that multiple classes of compounds have failed to effectively inhibit its activity (Lau *et al.*, CANCERS (2019) 11(11): 1681, Zou *et al.*, MOL CANCER (2020) 19: 145). In addition, ubiquitous expression of STAT3 across several tissues have led to concerns about severe on-target toxicities

(Wong *et al.*, EXPERT OPINION ON INVESTIGATIONAL DRUGS, 26 (8):883-87 (2017), (Kortylewski *et al.*, CANCER IMMUNOL IMMUNOTHER (2017) 66(8): 979-88).

STAT3 Target Sequences

[00309] In some embodiments, the oligonucleotide is targeted to a target sequence comprising a STAT3 mRNA. In some embodiments, the oligonucleotide, or a portion, fragment, or strand thereof (*e.g.*, an antisense strand or a guide strand of a dsRNA) binds or anneals to a target sequence comprising a *STAT3* mRNA, thereby inhibiting *STAT3* expression. In some embodiments, the oligonucleotide is targeted to a *STAT3* target sequence for the purpose of inhibiting *STAT3* expression *in vivo*. In some embodiments, the amount or extent of inhibition of *STAT3* expression by an oligonucleotide targeted to a *STAT3* target sequence correlates with the potency of the oligonucleotide. In some embodiments, the amount or extent of inhibition of *STAT3* expression by an oligonucleotide targeted to a *STAT3* target sequence correlates with the amount or extent of therapeutic benefit in a subject or patient having a disease, disorder or condition associated with the expression of STAT3 treated with the oligonucleotide.

[00310] Through examination of the nucleotide sequence of mRNAs encoding STAT3, including mRNAs of multiple different species (*e.g.*, human, cynomolgus monkey, mouse, and rat; *see*, *e.g.*, Example 11) and as a result of *in vitro* and *in vivo* testing (*see*, *e.g.*, Example 12 and Example 13), it has been discovered that certain nucleotide sequences of *STAT3* mRNA are more amenable than others to oligonucleotide-based inhibition and are thus useful as target sequences for the oligonucleotides herein. In some embodiments, a sense strand of an oligonucleotide (e.g., a dsRNA) described herein comprises a STAT3 target sequence. In some embodiments, a portion or region of the sense strand of a dsRNA described herein comprises a *STAT3* target sequence. In some embodiments, a *STAT3* mRNA target sequence comprises, or consists of, a sequence of SEQ ID NO 85. In some embodiments, a *STAT3* mRNA target sequence comprises, or consists of, a sequence of SEQ ID NO: 1217. In some embodiments, a *STAT3* mRNA target sequence comprises, or consists of, a sequence of any one of SEQ ID NOs: 89-280. In some embodiments, a *STAT3* mRNA target sequence comprises, or consists of, the sequence set forth in SEQ ID NO: 108. In some embodiments, a *STAT3* mRNA target sequence comprises, or consists of, the sequence set forth in SEQ ID NO: 140. In some embodiments, a *STAT3* mRNA target sequence comprises, or consists of, the sequence set forth in SEQ ID NO: 141. In some embodiments, a

STAT3 mRNA target sequence comprises, or consists of, the sequence set forth in SEQ ID NO: 147.

STAT3 Targeting Sequences

[00311] In some embodiments, the oligonucleotides herein have regions of complementarity to *STAT3* mRNA (*e.g.*, within a target sequence of STAT3 mRNA) for purposes of targeting the mRNA in cells and reducing or inhibiting its expression. In some embodiments, the oligonucleotides herein comprise a STAT3 targeting sequence (*e.g.*, an antisense strand or a guide strand of a dsRNA) having a region of complementarity that binds or anneals to a *STAT3* target sequence by complementary (Watson-Crick) base pairing. The targeting sequence or region of complementarity is generally of a suitable length and base content to enable binding or annealing of the oligonucleotide (or a strand thereof) to a *STAT3* mRNA for purposes of inhibiting its expression. In some embodiments, the targeting sequence or region of complementarity is at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 26, at least about 27, at least about 28, at least about 29 or at least about 30 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is about 12 to about 30 (*e.g.*, 12 to 30, 12 to 22, 15 to 25, 17 to 21, 18 to 27, 19 to 27, or 15 to 30) nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 18 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 19 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 20 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 21 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 22 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 23 nucleotides in length. In some embodiments, the targeting sequence or region of complementarity is 24 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 89-280 ,

and the targeting sequence or region of complementarity is 18 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 89-280, and the targeting sequence or region of complementarity is 19 nucleotides in length. In some embodiments, an oligonucleotide comprises a target sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 473-664, and the targeting sequence or region of complementarity is 20 nucleotides in length. In some embodiments, an oligonucleotide comprises a targeting sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 473-664, and the targeting sequence or region of complementarity is 21 nucleotides in length. In some embodiments, an oligonucleotide comprises a targeting sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 473-664, and the targeting sequence or region of complementarity is 22 nucleotides in length. In some embodiments, an oligonucleotide comprises a targeting sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 473-664, and the targeting sequence or region of complementarity is 23 nucleotides in length. In some embodiments, an oligonucleotide comprises a targeting sequence or region of complementarity complementary to a sequence of any one of SEQ ID NOs: 473-664 and the targeting sequence or region of complementarity is 24 nucleotides in length.

[00312] In some embodiments, an oligonucleotide herein comprises a targeting sequence or a region of complementarity (*e.g.*, an antisense strand or a guide strand of a double-stranded oligonucleotide) that is fully complementary to a *STAT3* target sequence. In some embodiments, the targeting sequence or region of complementarity is partially complementary to a *STAT3* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to a sequence of *STAT3* or *STAT3*. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to a sequence of *STAT3* or *STAT3*.

[00313] In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to a sequence of any one of SEQ ID NOs: 89-280. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to the sequence set forth in SEQ ID NOs: 108, 140, 141, and 147. In some embodiments, the oligonucleotide comprises a targeting sequence or

region of complementarity that is partially complementary to a sequence of any one of SEQ ID NOs: 89-280. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to the sequence set forth in SEQ ID NOs: 108, 140, 141, and 147.

[00314] In some embodiments, the oligonucleotide herein comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising a *STAT3* mRNA, wherein the contiguous sequence of nucleotides is about 12 to about 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 28, 12 to 26, 12 to 24, 12 to 20, 12 to 18, 12 to 16, 14 to 22, 16 to 20, 18 to 20 or 18 to 19 nucleotides in length). In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising a *STAT3* mRNA, wherein the contiguous sequence of nucleotides is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising a *STAT3* mRNA, wherein the contiguous sequence of nucleotides is 19 nucleotides in length.

[00315] In some embodiments, an oligonucleotide herein (*e.g.*, an RNAi oligonucleotide) comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 89-280, optionally wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 108, 140, 141, and 147, wherein the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 473-664, wherein the contiguous sequence of nucleotides is 20 nucleotides in length. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 492, 524, 525, and 531, wherein the contiguous sequence of nucleotides is 20 nucleotides in length.

[00316] In some embodiments, a targeting sequence or region of complementarity of an oligonucleotide that is complementary to contiguous nucleotides of *STAT3* or *STAT3* target

sequence spans the entire length of an antisense strand. In some embodiments, a region of complementarity of an oligonucleotide that is complementary to contiguous nucleotides of *STAT3* or *STAT3* target sequence spans a portion of the entire length of an antisense strand. In some embodiments, an oligonucleotide herein comprises a region of complementarity (*e.g.*, on an antisense strand of a dsRNA) that is at least partially (*e.g.*, fully) complementary to a contiguous stretch of nucleotides spanning nucleotides 1-20 of a target sequence of *STAT3* or *STAT3*.

[00317] In some embodiments, a targeting sequence or region of complementarity of an oligonucleotide herein (*e.g.,* an RNAi oligonucleotide) is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 89-280 and spans the entire length of an antisense strand. In some embodiments, a targeting sequence or region of complementarity of the oligonucleotide is complementary to a contiguous sequence of nucleotides of SEQ ID NOs: 89-280 and spans a portion of the entire length of an antisense strand. In some embodiments, an oligonucleotide herein (*e.g.,* an RNAi oligonucleotide) comprises a region of complementarity (*e.g.*, on an antisense strand of a dsRNA) that is at least partially (*e.g.*, fully) complementary to a contiguous stretch of nucleotides spanning nucleotides 1-19 or 1-20 of a sequence as set forth in any one of SEQ ID NOs: 473-664.

[00318] In some embodiments, an oligonucleotide herein comprises a targeting sequence or region of complementarity having one or more bp mismatches with the corresponding *STAT3* target sequence. In some embodiments, the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *STAT3* target sequence provided that the ability of the targeting sequence or region of complementarity to bind or anneal to the *STAT3* mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotide to inhibit STAT3 expression is maintained. Alternatively, the targeting sequence or region of complementarity may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *STAT3* target sequence provided that the ability of the targeting sequence or region of complementarity to bind or anneal to the *STAT3* mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotide to inhibit STAT3 expression is maintained. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 1 mismatch with the corresponding target

sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 2 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 3 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 4 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity having 5 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity more than one mismatch (*e.g.*, 2, 3, 4, 5 or more mismatches) with the corresponding target sequence, wherein at least 2 (*e.g.*, all) of the mismatches are positioned consecutively (*e.g.*, 2, 3, 4, 5 or more mismatches in a row), or where in the mismatches are interspersed throughout the targeting sequence or region of complementarity. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 89-280, wherein the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *STAT3* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 89-280, wherein the targeting sequence or region of complementarity may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *STAT3* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 108, 140, 141, and 147, wherein the targeting sequence or region of complementarity may have up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding *STAT3* target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 108, 140, 141, and 147, wherein the targeting sequence or region of complementarity may have no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding *STAT3* target sequence.

Targeting Ligands

[00319] In some embodiments, it is desirable to target the STAT3 targeting oligonucleotides of the disclosure to one or more cells or one or more organs. Such a strategy can help to avoid undesirable effects in other organs or avoid undue loss of the oligonucleotide to cells, tissue or organs that would not benefit from the oligonucleotide. Targeting of oligonucleotides to one or more cells or one or more organs can be achieved through a variety of approaches. Conjugation of oligonucleotides to tissue or cell specific antibodies, small molecules or targeting ligands can facilitate delivery to and modify accumulation of the oligonucleotide in one or more target cells or tissues (Chernolovskaya *et al.,* (2019) FRONT PHARMACOL. 10:444). For example, conjugation of an oligonucleotide to a saturated fatty acid (*e.g., C22)* may facilitate delivery to cells or tissues like adipose tissue or immune cells which uptake such ligands more readily than conventional oligonucleotide ligands. Accordingly, in some embodiments, oligonucleotides disclosed herein are modified to facilitate targeting and/or delivery of a tissue, cell, or organ (*e.g.*, to facilitate delivery of the oligonucleotide to the liver). In certain embodiments, oligonucleotides disclosed herein are modified to facilitate delivery of the oligonucleotide to cells of the immune system. In certain embodiments, oligonucleotides disclosed herein are modified to facilitate delivery of the oligonucleotide to myeloid derived suppressor cells. In some embodiments, an oligonucleotide comprises at least one nucleotide (*e.g.*, 1, 2, 3, 4, 5, 6 or more nucleotides) conjugated to one or more targeting ligand(s).

[00320] In some embodiments, the targeting ligand comprises a carbohydrate, amino sugar, cholesterol, peptide, polypeptide, protein, or part of a protein (*e.g.*, an antibody or antibody fragment), or lipid. In some embodiments, the targeting ligand is an aptamer. For example, a targeting ligand may be an RGD peptide that is used to target tumor vasculature or glioma cells, CREKA peptide to target tumor vasculature or stoma, transferring, lactoferrin, or an aptamer to target transferrin receptors expressed on CNS vasculature, or an anti-EGFR antibody to target EGFR on glioma cells. In certain embodiments, the targeting ligand is one or more GalNAc moieties.

[00321] In some embodiments, 1 or more (*e.g.*, 1, 2, 3, 4, 5 or 6) nucleotides of an oligonucleotide are each conjugated to a separate targeting ligand. In some embodiments, 2 to 4 nucleotides of an oligonucleotide are each conjugated to a separate targeting ligand. In some

embodiments, targeting ligands are conjugated to 2 to 4 nucleotides at either ends of the sense or antisense strand (*e.g.*, targeting ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5′ or 3′ end of the sense or antisense strand) such that the targeting ligands resemble bristles of a toothbrush and the oligonucleotide resembles a toothbrush. For example, an oligonucleotide may comprise a stem-loop at either the 5′ or 3′ end of the sense strand and 1, 2, 3 or 4 nucleotides of the loop of the stem may be individually conjugated to a targeting ligand. In some embodiments, an oligonucleotide (*e.g.*, a dsRNA) provided by the disclosure comprises a stem-loop at the 3′ end of the sense strand, wherein the loop of the stem-loop comprises a triloop or a tetraloop, and wherein the 3 or 4 nucleotides comprising the triloop or tetraloop, respectfully, are individually conjugated to a targeting ligand. In some embodiments, an oligonucleotide provided by the disclosure (*e.g.,* a RNAi oligonucleotide) comprises a stem-loop at the 3′ terminus of the sense strand, wherein the loop of the stem-loop comprises a tetraloop, and wherein 3 nucleotides of the tetraloop are individually conjugated to a targeting ligand.

[00322] GalNAc is a high affinity ligand for the ASGPR, which is primarily expressed on the sinusoidal surface of hepatocyte cells and has a major role in binding, internalizing and subsequent clearing circulating glycoproteins that contain terminal galactose or GalNAc residues (asialoglycoproteins). Conjugation (either indirect or direct) of GalNAc moieties to oligonucleotides of the instant disclosure can be used to target these oligonucleotides to the ASGPR expressed on cells. In some embodiments, an oligonucleotide of the instant disclosure is conjugated to at least one or more GalNAc moieties, wherein the GalNAc moieties target the oligonucleotide to an ASGPR expressed on human liver cells (e.g., human hepatocytes). In some embodiments, the GalNAc moiety target the oligonucleotide to the liver.

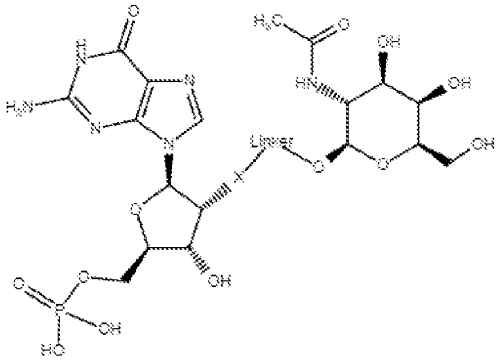
[00323] In some embodiments, an oligonucleotide of the instant disclosure is conjugated directly or indirectly to a monovalent GalNAc. In some embodiments, the oligonucleotide is conjugated directly or indirectly to more than one monovalent GalNAc (*i.e.*, is conjugated to 2, 3 or 4 monovalent GalNAc moieties, and is typically conjugated to 3 or 4 monovalent GalNAc moieties). In some embodiments, an oligonucleotide is conjugated to one or more bivalent GalNAc, trivalent GalNAc or tetravalent GalNAc moieties.

[00324] In some embodiments, 1 or more (*e.g.*, 1, 2, 3, 4, 5 or 6) nucleotides of an oligonucleotide are each conjugated to a GalNAc moiety. In some embodiments, 2 to 4 nucleotides of a tetraloop are each conjugated to a separate GalNAc. In some embodiments, 1 to

3 nucleotides of a triloop are each conjugated to a separate GalNAc. In some embodiments, targeting ligands are conjugated to 2 to 4 nucleotides at either ends of the sense or antisense strand (*e.g.*, ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5′ or 3′ end of the sense or antisense strand) such that the GalNAc moieties resemble bristles of a toothbrush and the oligonucleotide resembles a toothbrush. In some embodiments, GalNAc moieties are conjugated to a nucleotide of the sense strand. For example, 4 GalNAc moieties can be conjugated to nucleotides in the tetraloop of the sense strand where each GalNAc moiety is conjugated to 1 nucleotide.

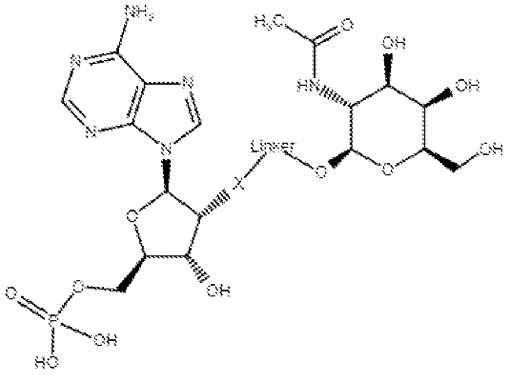
[00325] In some embodiments, the tetraloop is any combination of adenine and guanine nucleotides.

[00326] In some embodiments, the tetraloop (tetraL) has a monovalent GalNAc moiety attached to any one or more guanine nucleotides of the tetraloop *via* any linker described herein, as depicted below in Chem 2 (X=heteroatom):



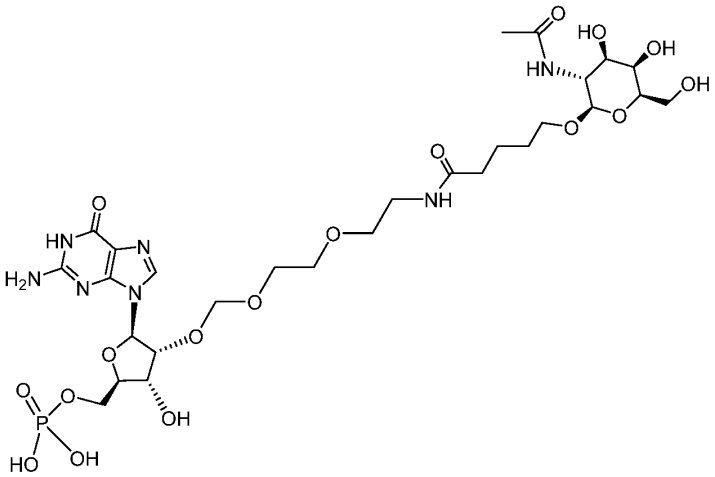
Chem 2

[00327] In some embodiments, the tetraloop (tetraL) has a monovalent GalNAc attached to any one or more adenine nucleotides of the tetraloop *via* any linker described herein, as depicted below in Chem 3 (X=heteroatom):



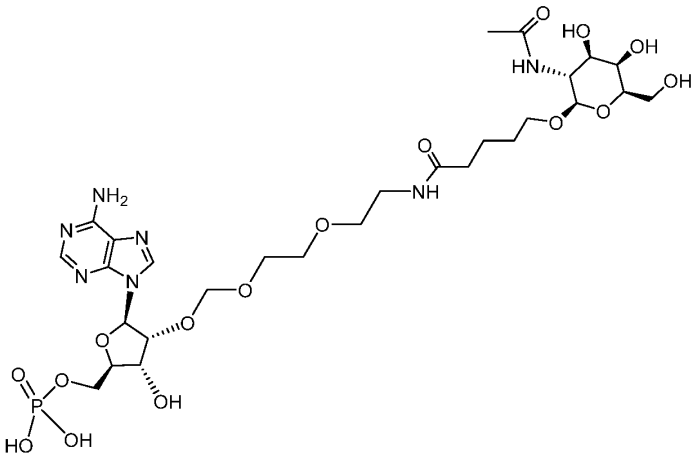
Chem 3

[00328] In some embodiments, an oligonucleotide herein comprises a monovalent GalNAc attached to a guanine nucleotide referred to as [ademG-GalNAc] or 2′-aminodiethoxymethanol-Guanine-GalNAc, as depicted below in Chem 4:



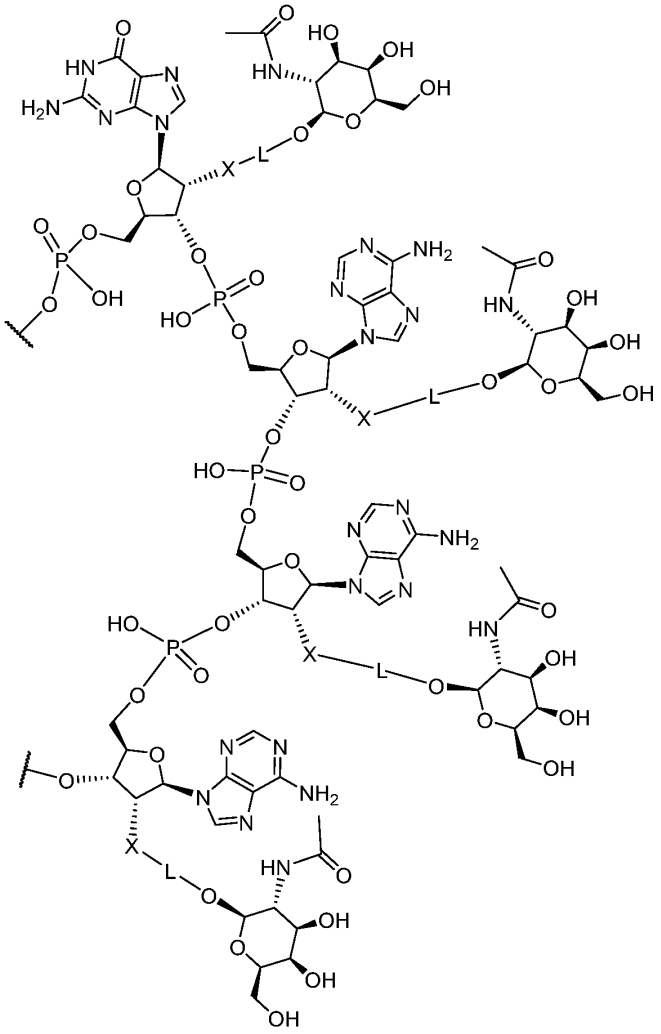
Chem 4

[00329] In some embodiments, an oligonucleotide herein comprises a monovalent GalNAc attached to an adenine nucleotide, referred to as [ademA-GalNAc] or 2′-aminodiethoxymethanol-Adenine-GalNAc, as depicted below in Chem 5:



Chem 5

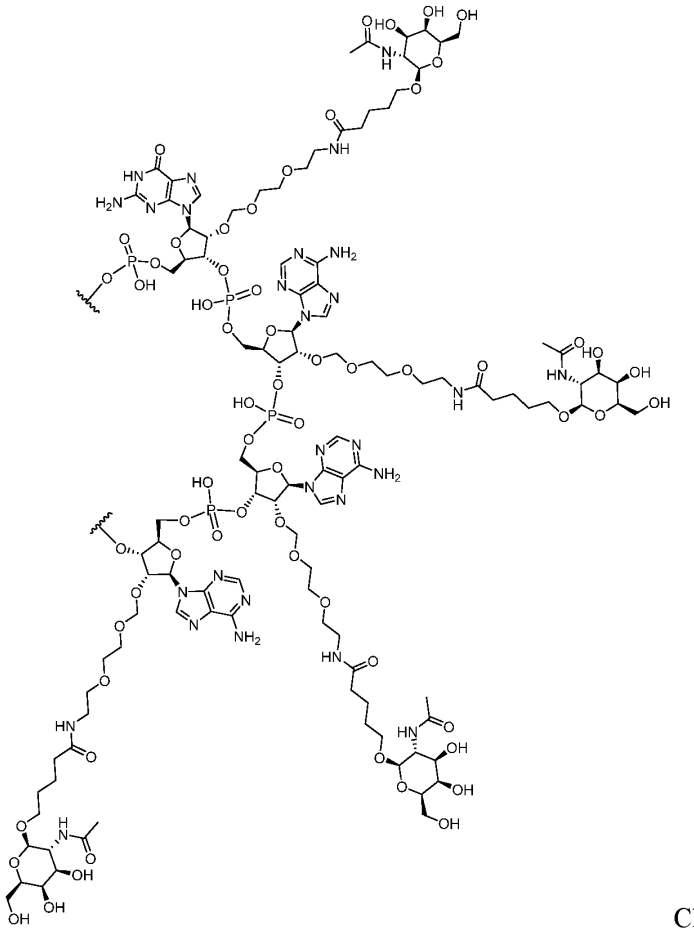
[00330] An example of such conjugation is shown below (Chem 6) for a loop comprising from 5′ to 3′ the nucleotide sequence GAAA (L = linker, X = heteroatom) stem attachment points are shown. Such a loop may be present, for example, at positions 27-30 of the sense strand as shown in **FIG. 1.** In the chemical formula, ≈ is used to describe an attachment point to the oligonucleotide strand (Chem 6).



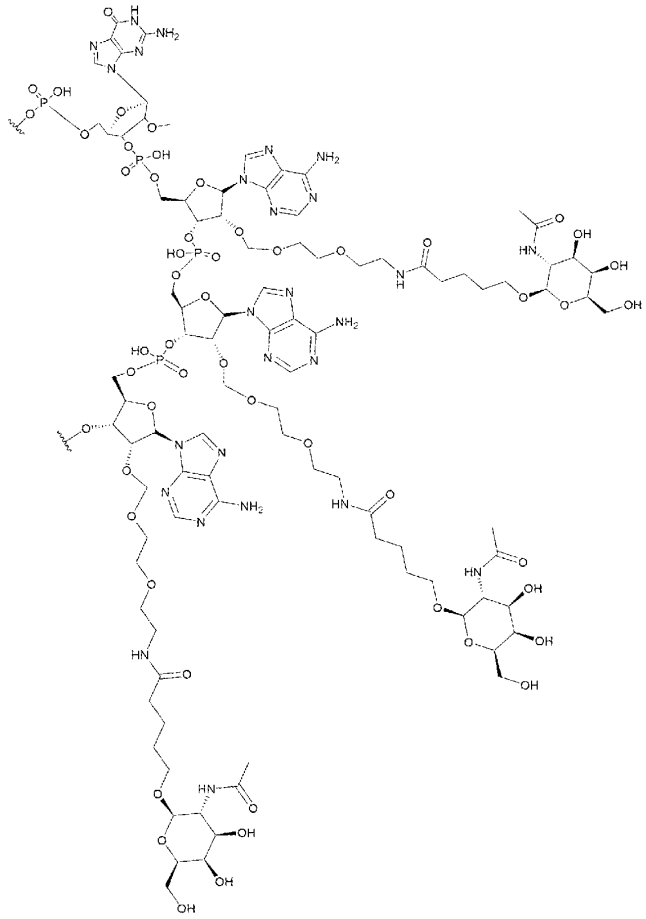
Chem 6

[00331] Appropriate methods or chemistry (*e.g.*, click chemistry) can be used to link a targeting ligand to a nucleotide. In some embodiments, a targeting ligand is conjugated to a nucleotide using a click linker. In some embodiments, an acetal-based linker is used to conjugate a targeting ligand to a nucleotide of any one of the oligonucleotides described herein. Acetal-based linkers are disclosed, for example, in Intl. Patent Application Publication No. WO 2016/100401. In some embodiments, the linker is a labile linker. However, in other embodiments, the linker is stable. Examples are shown below for a loop comprising from 5′ to 3′ the nucleotides GAAA, in which GalNAc moieties are attached to nucleotides of the loop using an acetal linker (Chem 7 and Chem 8). Such a loop may be present, for example, at positions 27-

30 of the any one of the sense strand as shown in **FIG. 1**. In the chemical formula,  is an attachment point to the oligonucleotide strand (Chem 7 and Chem 8).



Chem 6, or



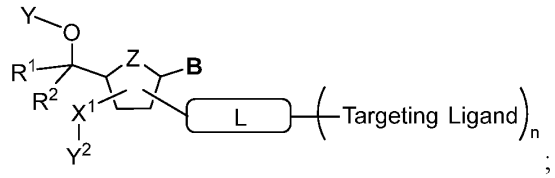
Chem 7.

[00332] As mentioned, various appropriate methods or chemistry synthetic techniques (*e.g.*, click chemistry) can be used to link a targeting ligand to a nucleotide. In some embodiments, a targeting ligand is conjugated to a nucleotide using a click linker. In some embodiments, an acetal-based linker is used to conjugate a targeting ligand to a nucleotide of any one of the oligonucleotides described herein. Acetal-based linkers are disclosed, for example, in Intl. Patent Application Publication No. WO 2016/100401. In some embodiments, the linker is a labile linker. However, in other embodiments, the linker is a stable linker.

[00333] In some embodiments, a duplex extension (*e.g.*, of up to 3, 4, 5 or 6 bp in length) is provided between a targeting ligand (*e.g.*, a GalNAc moiety) and a dsRNA. In some embodiments, the oligonucleotides herein do not have a GalNAc conjugated thereto.

Structure of Conjugated STAT3 Targeting Oligonucleotides

[00334] In some embodiments, a STAT3 targeting oligonucleotide described herein comprises a nucleotide sequence having a region of complementarity to a *STAT3* mRNA target sequence and one or more targeting ligands, wherein the nucleotide sequence comprises one or more nucleosides (nucleic acids) conjugated with one or more targeting ligands represented by formula **I-a**:



;

I-a

or a pharmaceutically acceptable salt thereof,

wherein:

B is a nucleobase or hydrogen;

R^1 and R^2 are independently hydrogen, halogen, R^A, -CN, -S(O)R, -$S(O)_2$R, -$Si(OR)_2$R, -$Si(OR)R_2$, or -SiR_3; or

R^1 and R^2 on the same carbon are taken together with their intervening atoms to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

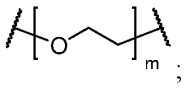
each R is independently hydrogen, a suitable protecting group, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same atom are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, silicon, and sulfur;

each targeting ligand is selected from lipid conjugate moiety (LC), carbohydrate, amino sugar or GalNAc; and wherein each LC is independently a lipid conjugate moiety comprising a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -Cy-, -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, -P(S)OR-;

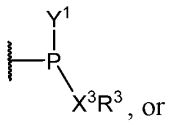
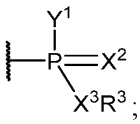
each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

n is 1-10;

L is a covalent bond or a bivalent saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -Cy-, -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, -P(S)OR-, -$V^1CR^2W^1$-, or  ;

m is 1-50;

X^1, V^1 and W^1 are independently -$C(R)_2$-, -OR, -O-, -S-, -Se-, or -NR-;

Y is hydrogen, a suitable hydroxyl protecting group,  , or  ;

R^3 is hydrogen, a suitable protecting group, a suitable prodrug, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen,

and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

X^2 is O, S, or NR;

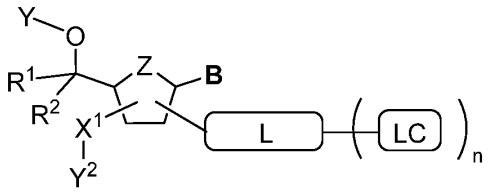
X^3 is -O-, -S-, -BH_2-, or a covalent bond;

Y^1 is a linking group attaching to the 2′- or 3′-terminal of a nucleoside, a nucleotide, or an oligonucleotide;

Y^2 is hydrogen, a suitable protecting group, a phosphoramidite analogue, an internucleotide linking group attaching to the 5′-terminal of a nucleoside, a nucleotide, or an oligonucleotide, or a linking group attaching to a solid support; and

Z is -O-, -S-, -NR-, or -CR_2-.

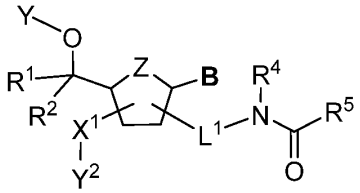
[00335] In some embodiments, the STAT3 targeting oligonucleotide comprises one or more nucleic acids conjugated with targeting ligands represented by formula **II-a**:



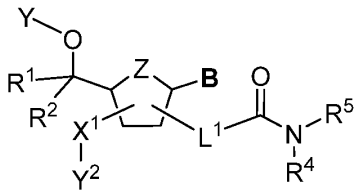
II-a.

or a pharmaceutically acceptable salt thereof.

[00336] In some embodiments, the STAT3 targeting oligonucleotide comprises one or more nucleic acids conjugated with targeting ligands represented by formula **II-b** or **II-c**:

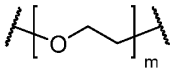


II-b



II-c

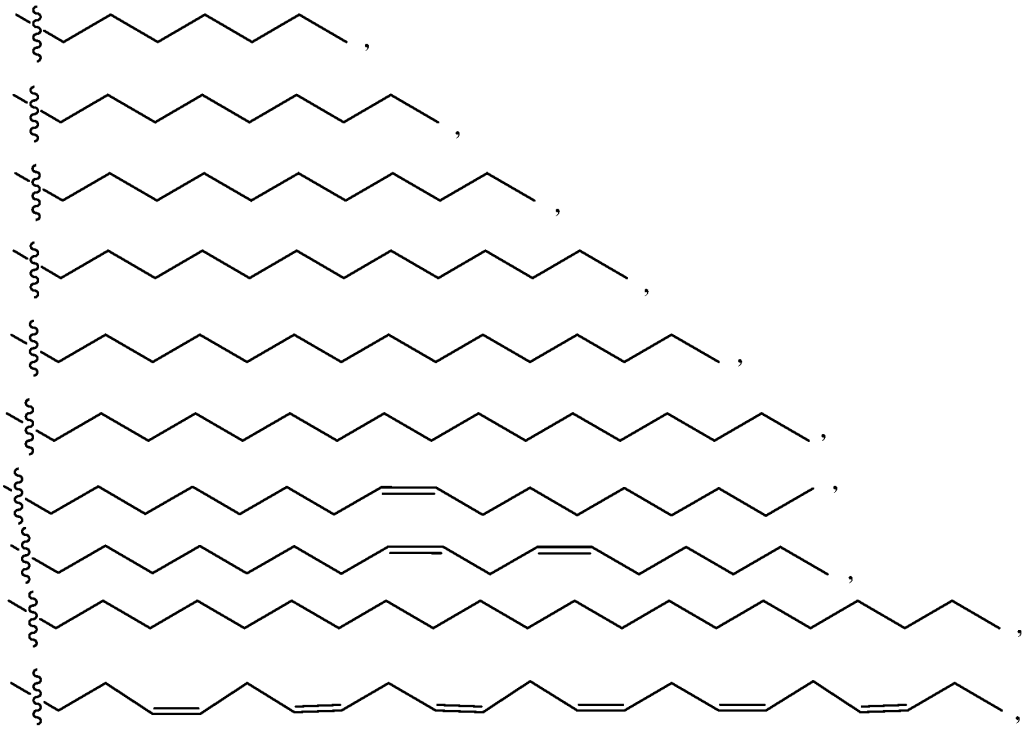
or a pharmaceutically acceptable salt thereof, wherein:

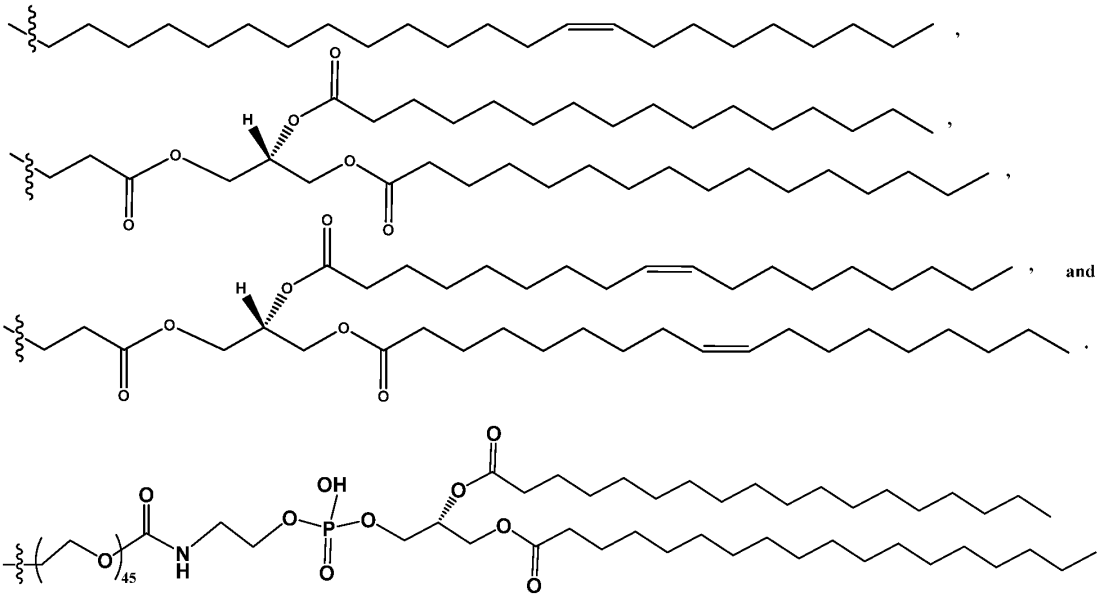
L^1 is a covalent bond, a monovalent or a bivalent saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -Cy-, -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, -P(S)OR-, or  ;

R^4 is hydrogen, R^A, or a suitable amine protection group; and

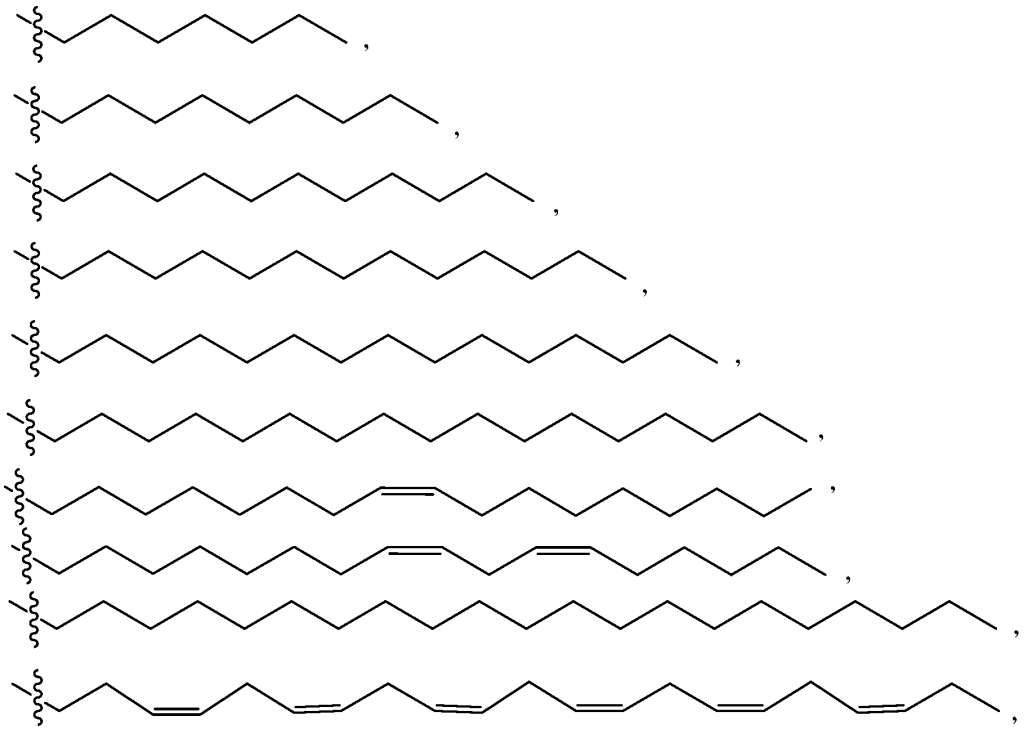
R^5 is adamantyl, or a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, or -P(S)OR.

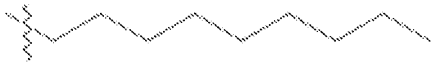
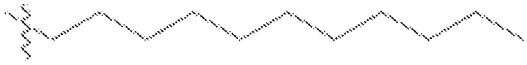
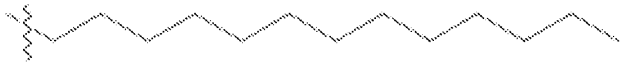
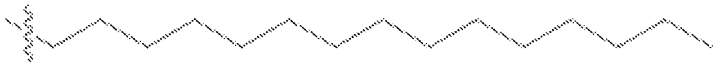
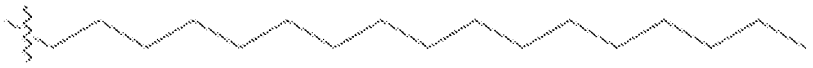
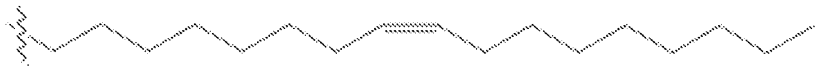
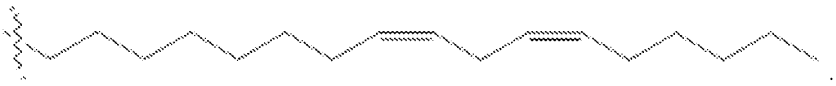
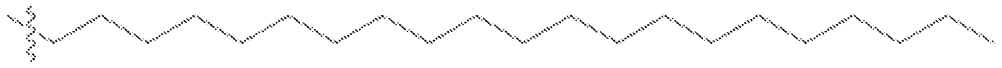
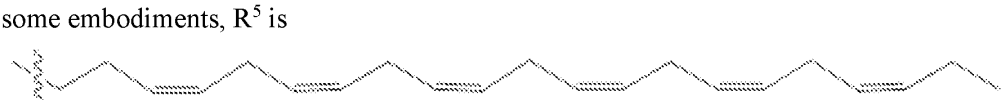
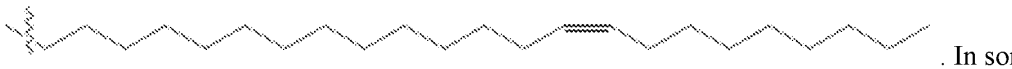
[00337] In some embodiments, R^5 is selected from

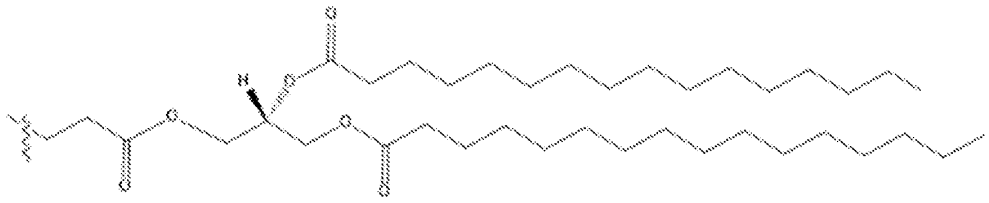




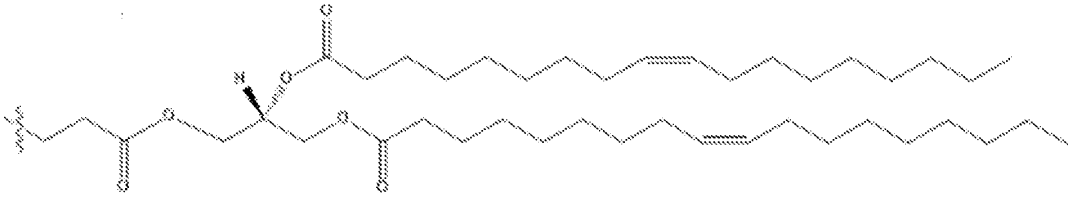
[00338] In some embodiments, R^5 is selected from:



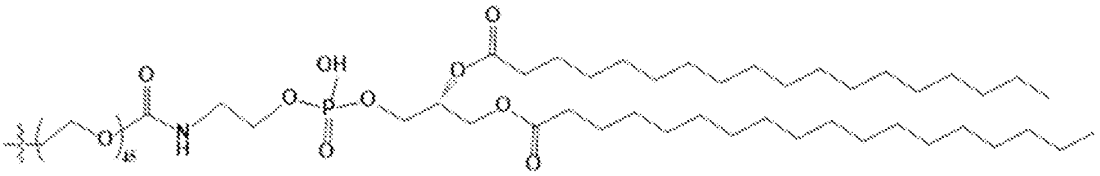
[00339] In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is



. In some embodiments, R^5 is

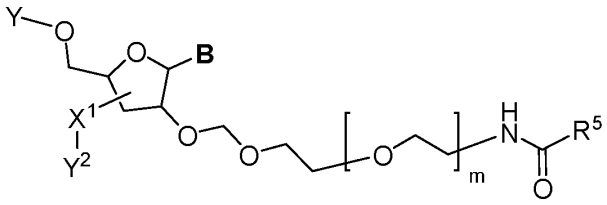


. In some embodiments, R^5 is

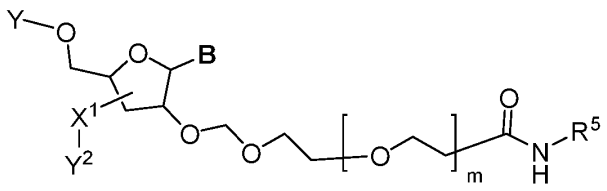


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[00340] In some embodiments, the STAT3 targeting oligonucleotide comprises one or more nucleic acids conjugated with targeting ligands represented by formula **II-Ib** or **II-Ic**:



II-Ib



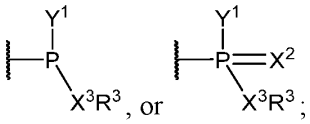
II-Ic

or a pharmaceutically acceptable salt thereof; wherein

B is a nucleobase or hydrogen;

m is 1-50;

X^1 is -O-, or -S-;

Y is hydrogen,  , or ;

R^3 is hydrogen, or a suitable protecting group;

X^2 is O, or S;

X^3 is -O-, -S-, or a covalent bond;

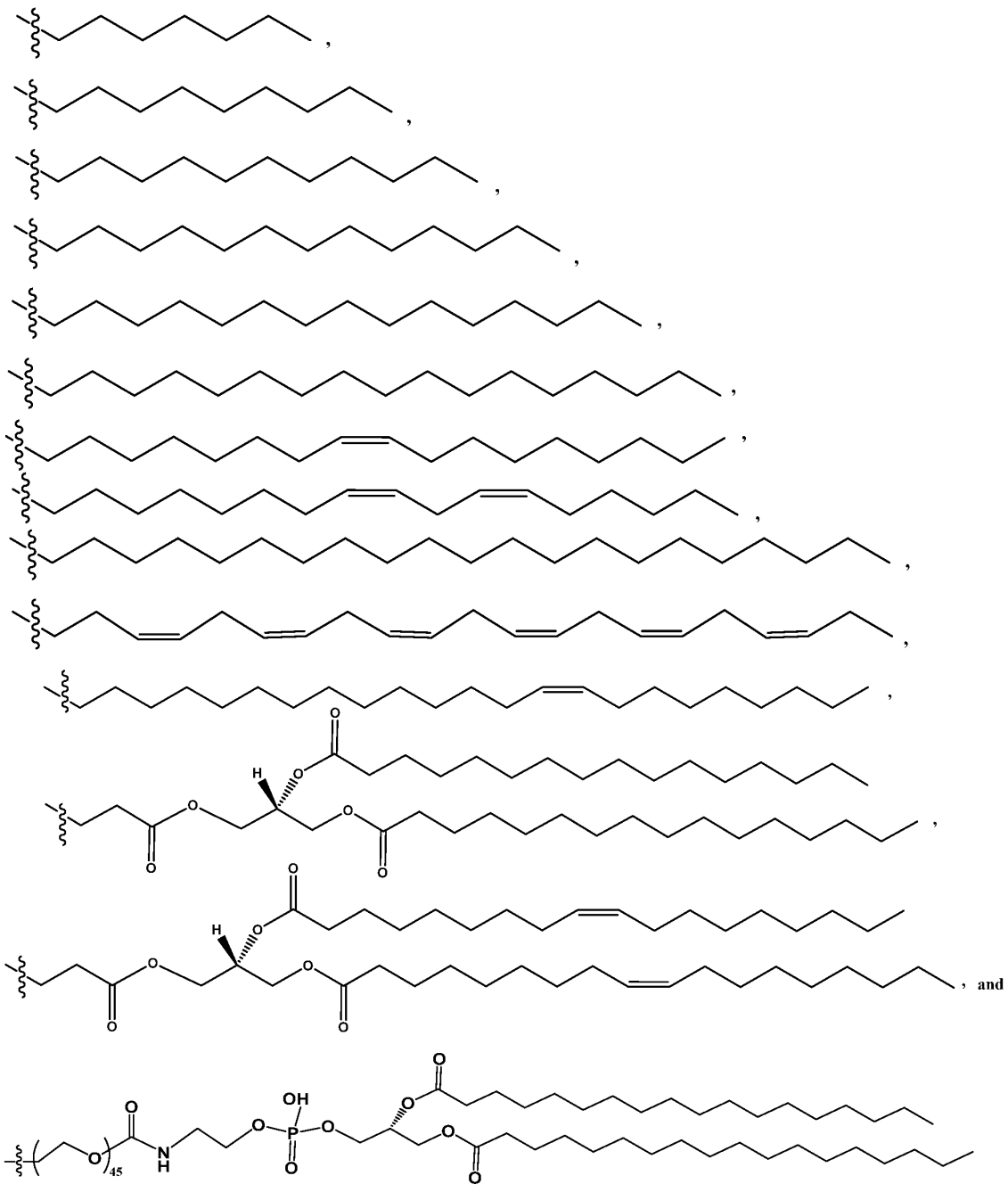
Y^1 is a linking group attaching to the 2′- or 3′-terminal of a nucleoside, a nucleotide, or an oligonucleotide;

Y^2 is hydrogen, a phosphoramidite analogue, an internucleotide linking group attaching to the 5′-terminal of a nucleoside, a nucleotide, or an oligonucleotide, or a linking group attaching to a solid support;

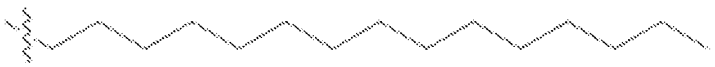
R^5 is adamantyl, or a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, or -P(S)OR-; and

R is hydrogen, a suitable protecting group, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

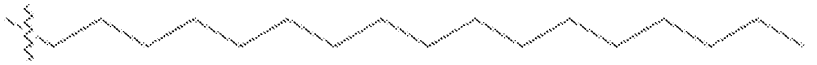
[00341] In some embodiments, R^5 is selected from



[00342] In some embodiments, R^5 is



[00343] In some embodiments, R^5 is



[00344] In some embodiments, the nucleotide sequence of the STAT3 targeting oligonucleotide comprises 1-10 targeting ligands. In some embodiments, the nucleotide sequence comprises 1, 2 or 3 targeting ligands.

[00345] In some embodiments, the STAT3 targeting oligonucleotide is a double-stranded molecule. In some embodiments, the STAT3 targeting oligonucleotide is an RNAi molecule. In some embodiments, the STAT3 targeting double stranded oligonucleotide comprises a stem loop. In some embodiments, the ligand is conjugated to any of the nucleotides in the stem loop. In some embodiments, the ligand is conjugated to the first nucleotide from 5' to 3', in the stem loop. In some embodiments, the ligand is conjugated to the second nucleotide from 5' to 3' in the stem loop. In some embodiments, the ligand is conjugated to the third nucleotide from 5' to 3' in the stem loop. In some embodiments, the ligand is conjugated to the fourth nucleotide from 5' to 3' in the stem loop. In some embodiments, the ligand is conjugated to one, two, three, or four of the nucleotides in the stem loop. In some embodiments, the ligand is conjugated to three of the nucleotides in the stem loop.

[00346] In some embodiments, the STAT3 targeting double stranded oligonucleotide comprises a stem loop, wherein one or more lipids are conjugated to one or more nucleotides of the stem loop. In some embodiments, the STAT3 targeting double stranded oligonucleotide comprises a stem loop, wherein one or more C16 lipids are conjugated to one or more nucleotides of the stem loop. In some embodiments, the STAT3 targeting double stranded oligonucleotide comprises a stem loop, wherein one or more C18 lipids are conjugated to one or more nucleotides of the stem loop.

[00347] In some embodiments, the STAT3 targeting oligonucleotide comprises a sense strand of 36 nucleotides with positions numbered 1-36 from 5' to 3'. In some embodiments, the STAT3 targeting oligonucleotide comprises a lipid conjugated to position 27 of a 36-nucleotide sense strand. In some embodiments, STAT3 targeting oligonucleotide comprises a lipid

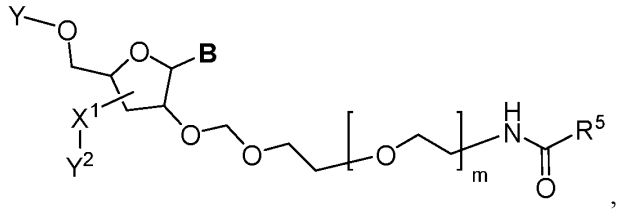
conjugated to position 28 of a 36-nucleotide sense strand. In some embodiments, the STAT3 targeting oligonucleotide comprises a lipid conjugated to position 29 of a 36-nucleotide sense strand. In some embodiments, the STAT3 targeting oligonucleotide comprises a lipid conjugated to position 30 of a 36-nucleotide sense strand. In some embodiments, a 36-nucleotide sense strand forms a stem loop having a loop with positions 27-30. In some embodiments, a lipid is conjugated to more than one position of the loop (e.g., positions 27 and 28 of a 36-nucleotide sense strand).

[00348] In some embodiments, the STAT3 targeting oligonucleotide comprises a C16 lipid conjugated to position 27 of a 36-nucleotide sense strand. In some embodiments, STAT3 targeting oligonucleotide comprises a C16 lipid conjugated to position 28 of a 36-nucleotide sense strand. In some embodiments, the STAT3 targeting oligonucleotide comprises a C16 lipid conjugated to position 29 of a 36-nucleotide sense strand. In some embodiments, the STAT3 targeting oligonucleotide comprises a C16 lipid conjugated to position 30 of a 36-nucleotide sense strand. In some embodiments, a 36-nucleotide sense strand forms a stem loop having a loop with positions 27-30. In some embodiments, a C16 lipid is conjugated to more than one position of the loop (e.g., positions 27 and 28 of a 36-nucleotide sense strand).

[00349] In some embodiments, the STAT3 targeting oligonucleotide comprises a C18 lipid conjugated to position 27 of a 36-nucleotide sense strand. In some embodiments, STAT3 targeting oligonucleotide comprises a C18 lipid conjugated to position 28 of a 36-nucleotide sense strand. In some embodiments, the STAT3 targeting oligonucleotide comprises a C18 lipid conjugated to position 29 of a 36-nucleotide sense strand. In some embodiments, the STAT3 targeting oligonucleotide comprises a C18 lipid conjugated to position 30 of a 36-nucleotide sense strand. In some embodiments, a 36-nucleotide sense strand forms a stem loop having a loop with positions 27-30. In some embodiments, a C18 lipid is conjugated to more than one position of the loop (e.g., positions 27 and 28 of a 36-nucleotide sense strand).

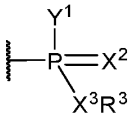
[00350] In some embodiments, a STAT3 targeting oligonucleotide comprises an antisense strand of 15 to 30 nucleotides and a sense strand of 15 to 40 nucleotide, wherein the sense and antisense strands form a duplex region, wherein the antisense strand comprises a region of complementarity to a *STAT3* mRNA target sequence expressed in an immune cell associated with a tumor microenvironment, wherein the sense strand comprises at its 3' end a stem-loop

comprising a tetraloop comprising 4 nucleosides, wherein one or more of the 4 nucleosides is represented by formula II-Ib:

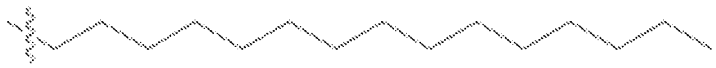


,

wherein B is selected from an adenine and a guanine nucleobase, and wherein R^5 is a hydrocarbon chain. In some embodiments, m is 1, X1 is O, Y2 is an internucleotide linking group attaching to the 5' terminal of a nucleoside,

Y is represented by  , Y1 is a linking group attaching to the 2' or 3' terminal of a nucleotide, X2 is O, X3 is O, and R3 is H.

[00351] In some embodiments, the hydrocarbon chain is a C8-C30 hydrocarbon chain. In some embodiments, the hydrocarbon chain is a C16 hydrocarbon chain. In some embodiments, the C16 hydrocarbon chain is represented by



. In some embodiments, the hydrocarbon chain is a C18 hydrocarbon chain. In some embodiments, the C18 hydrocarbon chain is represented by



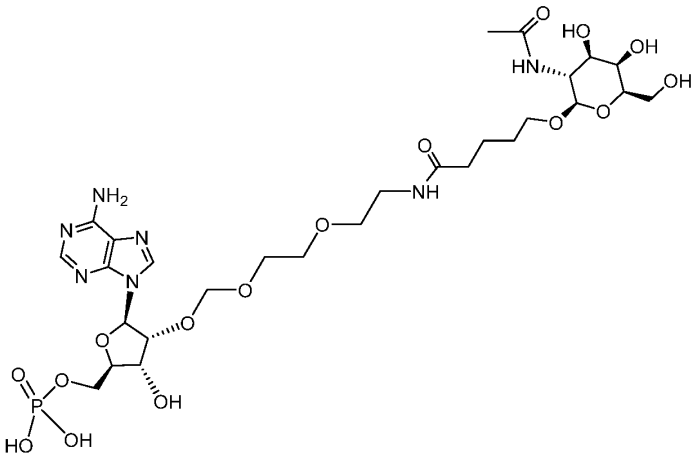
.

[00352] In some embodiments, the oligonucleotide comprises a sense strand comprising a sequence selected from SEQ ID NOs: 89-280, wherein the sense strand comprises a C18 lipid. In some embodiments, the 4 nucleosides of the tetraloop are numbered 1-4 from 5' to 3' and position 1 is represented by formula II-Ib. In some embodiments, position 2 is represented by formula II-Ib. In some embodiments, position 3 is represented by formula II-Ib. In some embodiments, position 4 is represented by formula II-Ib. In some embodiments, the sense strand is 36 nucleotides with positions numbered 1-36 from 5' to 3', wherein the stem-loop comprises

nucleotides at positions 21-36, and wherein one or more nucleosides at positions 27-30 are represented by formula II-Ib. In some embodiments, the antisense strand is 22 nucleotides.

Exemplary STAT3 Targeting Oligonucleotides

[00353] In some embodiments, an oligonucleotide targeting STAT3 comprises a sense strand and an antisense strand as set forth in **Tables 3, 4, 5, 10, 11, 12, 13, and 14**, wherein the oligonucleotide comprises a stem loop structure having a double-stranded stem of about 2-6 base pairs and a loop of 3-4 nucleotides, and wherein the sense and antisense strands comprise the modification pattern set forth in **FIG. 1** or **Example 12**. In some embodiments, an oligonucleotide targeting STAT3 comprises a sense strand and an antisense strand as set forth in **Tables 3, 4, 5, 10, 11, 12, 13, and 14**, wherein the oligonucleotide comprises a stem loop structure having a double-stranded stem of about 2-6 base pairs and a loop of 3-4 nucleotides, wherein the sense and antisense strands comprise the modification pattern set forth in **FIG. 1,** and wherein antisense strand is modified with an oxymethylphosphonate at the 4' carbon of the 5' terminal nucleotide. In some embodiments, the oligonucleotide comprises a stem loop comprising the nucleotide sequence of SEQ ID NO: 86. In some embodiments, the oligonucleotide comprises a double-stranded stem of 6 base pairs and a stem loop of 4 nucleotides comprising one, two, three or four GalNAc conjugated nucleotides. In some embodiments, the GalNAc conjugated nucleotide is a monovalent GalNAc conjugated to an adenine nucleotide, referred to as [ademA-GalNAc] or 2′-aminodiethoxymethanol-Adenine-GalNAc, as depicted below:



[00354] In some embodiments, the stem loop comprises a double-stranded stem of 6 base pairs and a loop comprising the nucleotide sequence GAAA, wherein each adenine nucleotide is ademA-GalNAc.

[00355] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 9 and 10, respectively;

(b) SEQ ID NOs: 37 and 38, respectively;

(c) SEQ ID NOs: 65 and 66, respectively; and

(d) SEQ ID NOs: 69 and 70, respectively.

[00356] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand and an antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 9 and 10, respectively;

(b) SEQ ID NOs: 37 and 38, respectively;

(c) SEQ ID NOs: 65 and 66, respectively; and

(d) SEQ ID NOs: 69 and 70, respectively,

wherein the sense and antisense strands are modified based on the pattern below

Sense Strand:

[mXs][mX][mX][mX][mX][mX][mX][fX][fX][fX][fX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademX-C#] [mX] [mX] [mX] [mX] [mX] [mX][mX][mX]

Hybridized to

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fX][fX][fX][mX][fX][mX][mX] [fX][mX][mX][mX][fX][mX][mX][mX][mX][mX][mXs][mXs][mX]

(key provided in **Table 1**). In some embodiments, C# is C16 or C18.

[00357] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand and an antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 862 and 952, respectively;

(b) SEQ ID NOs: 875 and 965, respectively;

(c) SEQ ID NOs: 876 and 966, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the sense and antisense strands are modified based on the pattern below

Sense Strand:

[mXs][mX][mX][mX][mX][mX][mX][fX][fX][fX][fX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademX-C#] [mX] [mX] [mX] [mX] [mX] [mX][mX][mX]

Hybridized to

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fX][fX][fX][mX][fX][mX][mX] [fX][mX][mX][mX][fX][mX][mX][mX][mX][mX][mXs][mXs][mX]

(key provided in **Table 1**). In some embodiments, C# is C16 or C18.

[00358] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand and an antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 862 and 952, respectively;

(b) SEQ ID NOs: 875 and 965, respectively;

(c) SEQ ID NOs: 876 and 966, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the sense and antisense strands are modified based on the pattern below

Sense Strand:

[mXs][mX][mX][mX][mX][mX][mX][fX][fX][fX][fX][mX][mX][mX][mX][mX][mX][mX

][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademX-C#] [mX] [mX] [mX] [mX] [mX] [mX][mX][mX]

Hybridized to

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fXs][fX][fX][mX][fX][mX][mX] [fX][mX][mX][mX][fX][mX][mX][mX][mX][mX][mXs][mXs][mX]

(key provided in **Table 1**). In some embodiments, C# is C16 or C18.

[00359] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 11 and 12, respectively;

(b) SEQ ID NOs: 39 and 40, respectively;

(c) SEQ ID NOs: 67 and 68, respectively; and

(d) SEQ ID NOs: 71 and 72, respectively.

[00360] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sequence set forth in SEQ ID NO: 81. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sequence set forth in SEQ ID NO: 82. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sequence set forth in SEQ ID NO: 83. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sequence set forth in SEQ ID NO: 84.

[00361] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand having nucleotide sequences set forth in SEQ ID NOs: 87 and 68, respectively. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand having nucleotide sequences set forth in SEQ ID NOs: 88 and 71, respectively.

[00362] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 89-280. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 857-946. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 857-888. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 889-912. In some

embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 913-934. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 935-946.

[00363] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence selected from SEQ ID NOs: 947-1036. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence selected from SEQ ID NOs: 947-978. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence selected from SEQ ID NOs: 979-1002. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence selected from SEQ ID NOs: 1003-1024. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence selected from SEQ ID NOs: 1025-1036.

[00364] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 857-946 and an antisense strand selected from SEQ ID NOs: 947-1036. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 857-888 and an antisense strand selected from SEQ ID NOs: 947-978. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 889-912 and an antisense strand selected from SEQ ID NOs: 979-1002. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 913-934 and an antisense strand selected from SEQ ID NOs:1003-1024. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 935-946 and an antisense strand selected from SEQ ID NOs:1025-1036.

[00365] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 1037-1126. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 1037-1068. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs:1069-1092. In some embodiments, an oligonucleotide for reducing

expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 1093-1114. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs:1115-1126.

[00366] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence selected from SEQ ID NOs: 1127-1216. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence selected from SEQ ID NOs: 1127-1158. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence selected from SEQ ID NOs: 1159-1182. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence selected from SEQ ID NOs:1183-1204. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence selected from SEQ ID NOs:1205-1216.

[00367] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 1037-1126 and an antisense strand selected from SEQ ID NOs: 1127-1216. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 1037-1068 and an antisense strand selected from SEQ ID NOs: 1127-1182. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 1069-1092 and an antisense strand selected from SEQ ID NOs: 1159-1182. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 1093-1114 and an antisense strand selected from SEQ ID NOs:1183-1204. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence selected from SEQ ID NOs: 1115-1126 and an antisense strand selected from SEQ ID NOs:1205-1216.

[00368] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 857 and 947, respectively;

(b) SEQ ID NOs: 858 and 948, respectively;

(c) SEQ ID NOs: 859 and 949, respectively;

(d) SEQ ID NOs: 860 and 950, respectively;

(e) SEQ ID NOs: 862 and 952, respectively;

(f) SEQ ID NOs: 867 and 957, respectively;

(g) SEQ ID NOs: 875 and 965, respectively; and

(h) SEQ ID NOs: 876 and 966, respectively.

[00369] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively.

[00370] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively.

[00371] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively.

[00372] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 862 and 952, respectively;

(b) SEQ ID NOs: 875 and 965, respectively;

(c) SEQ ID NOs: 876 and 966, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively.

[00373] In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 862 and the antisense strand comprises the sequence of SEQ ID NO: 952.

[00374] In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 875 and the antisense strand comprises the sequence of SEQ ID NO: 965.

[00375] In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 876 and the antisense strand comprises the sequence of SEQ ID NO: 966.

[00376] In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 920 and the antisense strand comprises the sequence of SEQ ID NO: 1010.

[00377] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 1037 and 1127, respectively;

(b) SEQ ID NOs: 1038 and 1128, respectively;

(c) SEQ ID NOs: 1039 and 1129, respectively;

(d) SEQ ID NOs: 1040 and 1130, respectively;

(e) SEQ ID NOs: 1042 and 1132, respectively;

(f) SEQ ID NOs: 1047 and 1137, respectively;

(g) SEQ ID NOs: 1055 and 1145, respectively; and

(h) SEQ ID NOs: 1056 and 1146, respectively.

[00378] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 1081 and 1171, respectively;

(b) SEQ ID NOs: 1090 and 1180, respectively;

(c) SEQ ID NOs: 1079 and 1169, respectively;

(d) SEQ ID NOs: 1076 and 1166, respectively;

(e) SEQ ID NOs: 1072 and 1162, respectively;

(f) SEQ ID NOs: 1070 and 1160, respectively; and

(g) SEQ ID NOs: 1069 and 1159, respectively.

[00379] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 1120 and 1210, respectively;

(b) SEQ ID NOs: 1117 and 1207, respectively; and

(c) SEQ ID NOs: 1119 and 1209, respectively.

[00380] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 1095 and 1185, respectively;

(b) SEQ ID NOs: 1104 and 1194, respectively;

(c) SEQ ID NOs: 1093 and 1183, respectively; and

(d) SEQ ID NOs: 1100 and 1190, respectively.

[00381] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 1042 and 1132, respectively;

(b) SEQ ID NOs: 1055 and 1145, respectively;

(c) SEQ ID NOs: 1056 and 1146, respectively; and

(d) SEQ ID NOs: 1100 and 1190, respectively.

[00382] In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 1042 and the antisense strand comprises the sequence of SEQ ID NO: 1132.

[00383] In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 1055 and the antisense strand comprises the sequence of SEQ ID NO: 1145.

[00384] In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 1056 and the antisense strand comprises the sequence of SEQ ID NO: 1146.

[00385] In some embodiments, the sense strand comprises the sequence of SEQ ID NO: 1100 and the antisense strand comprises the sequence of SEQ ID NO: 1190.

[00386] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising nucleotide sequences selected from:

(a) SEQ ID NOs: 1042 and 1225, respectively;

(b) SEQ ID NOs: 1055 and 1226, respectively;

(c) SEQ ID NOs: 1056 and 1227, respectively; and

(d) SEQ ID NOs: 1100 and 1228, respectively.

[00387] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA described herein comprises minimal off-target effects. For example, in some embodiments, an oligonucleotide described herein reduces STAT3 expression and does not reduce STAT1 expression or reduces STAT1 expression less than STAT3 expression. In some

embodiments, the oligonucleotide comprises a sense strand comprising the nucleotide sequence set forth in SEQ ID NO: 862 and an antisense strand comprising the nucleotide sequence set forth in SEQ ID NO: 952, wherein the oligonucleotide reduces STAT3 expression and does not reduce STAT1 expression or reduces STAT1 expression less than STAT3 expression. In some embodiments, the oligonucleotide comprises a sense strand comprising the nucleotide sequence set forth in SEQ ID NO: 1042 and an antisense strand comprising the nucleotide sequence set forth in SEQ ID NO: 1132, wherein the oligonucleotide reduces STAT3 expression and does not reduce STAT1 expression or reduces STAT1 expression less than STAT3 expression. In some embodiments, the oligonucleotide comprises a sense strand comprising the nucleotide sequence set forth in SEQ ID NO: 875 and an antisense strand comprising the nucleotide sequence set forth in SEQ ID NO: 965, wherein the oligonucleotide reduces STAT3 expression and does not reduce STAT1 expression or reduces STAT1 expression less than STAT3 expression. In some embodiments, the oligonucleotide comprises a sense strand comprising the nucleotide sequence set forth in SEQ ID NO: 1055 and an antisense strand comprising the nucleotide sequence set forth in SEQ ID NO: 1145, wherein the oligonucleotide reduces STAT3 expression and does not reduce STAT1 expression or reduces STAT1 expression less than STAT3 expression.

[00388] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA described herein is a species cross-reactive oligonucleotide. In some embodiments, an oligonucleotide described herein is capable of reducing expression of *STAT3* mRNA of at least two different species. In some embodiments, an oligonucleotide described herein is capable of reducing expression of *STAT3* mRNA of at least two different species but does not cross-react with non-*STAT3* mRNA (e.g., STAT1). In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA is cross-reactive between at least two species. In some embodiments, an oligonucleotide for reducing expression of STAT3 cross-reacts with human, non-human primate, and mouse *STAT3* mRNA. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA cross-reacts with human and mouse *STAT3* mRNA. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA cross-reacts with human and non-human primate *STAT3* mRNA.

[00389] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA reduces *STAT3* mRNA by at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%.

[00390] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA reduces *STAT3* mRNA by at least 50% to at least 75% in human, non-human primate, and mouse (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide). In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA reduces *STAT3* mRNA by at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, or at least 75% in human, non-human primate, and mouse (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide). In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA reduces *STAT3* mRNA by at least 80%, at least 85%, at least 90%, or at least 95% in human, non-human primate, and mouse (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00391] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA reduces *STAT3* mRNA by at least 50% to at least 75% in human and non-human primate (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide). In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA reduces *STAT3* mRNA by at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, or at least 75% in human and non-human primate (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide). In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA reduces *STAT3* mRNA by at least 80%, at least 85%, at least 90%, or at least 95% in human and non-human primate (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00392] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA reduces *STAT3* mRNA by at least 50% to at least 75% in human and mouse (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide). In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA reduces *STAT3* mRNA by at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, or at least 75% in human and mouse (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide). In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA reduces *STAT3* mRNA by at least 80%, at least 85%, at least 90%, or at least 95% in human and mouse (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide). In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively,

wherein the oligonucleotide reduces *STAT3* mRNA in humans, non-human primates, and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00393] In some embodiments, an oligonucleotide for reducing expression of STAT3 mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively,

wherein the oligonucleotide reduces *STAT3* mRNA in humans, non-human primates, and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00394] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide reduces *STAT3* mRNA in humans, non-human primates, and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00395] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 862 and the antisense strand sequence of SEQ ID NO: 952, wherein the oligonucleotide reduces *STAT3* mRNA in humans and non-human primates (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00396] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 875 and the antisense strand sequence of SEQ ID NO: 965, wherein the oligonucleotide reduces *STAT3* mRNA in humans.

[00397] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 876 and the antisense strand sequence of SEQ ID NO: 966, wherein the oligonucleotide reduces *STAT3* mRNA in humans.

[00398] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 920 and the antisense strand sequence of SEQ ID NO: 1010, wherein the oligonucleotide reduces *STAT3* mRNA in humans.

[00399] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 857 and 947, respectively;

(b) SEQ ID NOs: 858 and 948, respectively;

(c) SEQ ID NOs: 859 and 949, respectively;

(d) SEQ ID NOs: 860 and 950, respectively;

(e) SEQ ID NOs: 862 and 952, respectively;

(f) SEQ ID NOs: 867 and 957, respectively;

(g) SEQ ID NOs: 875 and 965, respectively; and

(h) SEQ ID NOs: 876 and 966, respectively,

wherein the oligonucleotide reduces *STAT3* mRNA by at least 75%.

[00400] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively,

wherein the oligonucleotide reduces *STAT3* mRNA by at least 75%.

[00401] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively,

wherein the oligonucleotide reduces *STAT3* mRNA by at least 75%.

[00402] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide reduces *STAT3* mRNA by at least 75%.

[00403] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 862 and 952, respectively;

(b) SEQ ID NOs: 875 and 965, respectively;

(c) SEQ ID NOs: 876 and 966, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide reduces *STAT3* mRNA by at least 75%.

[00404] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 862 and the antisense strand sequence of SEQ ID NO: 952, wherein the oligonucleotide reduces *STAT3* mRNA by at least 75%.

[00405] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 875 and the antisense strand sequence of SEQ ID NO: 965, wherein the oligonucleotide reduces *STAT3* mRNA by at least 75%.

[00406] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 876 and the antisense strand sequence of SEQ ID NO: 966, wherein the oligonucleotide reduces *STAT3* mRNA by at least 75%.

[00407] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 920 and the antisense strand

sequence of SEQ ID NO: 1010, wherein the oligonucleotide reduces *STAT3* mRNA by at least 75%.

[00408] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 857 and 947, respectively;

(b) SEQ ID NOs: 858 and 948, respectively;

(c) SEQ ID NOs: 859 and 949, respectively;

(d) SEQ ID NOs: 860 and 950, respectively;

(e) SEQ ID NOs: 862 and 952, respectively;

(f) SEQ ID NOs: 867 and 957, respectively;

(g) SEQ ID NOs: 875 and 965, respectively; and

(h) SEQ ID NOs: 876 and 966, respectively,

wherein the oligonucleotide is conjugated to a lipid.

[00409] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively,

wherein the oligonucleotide is conjugated to a lipid on the sense strand.

[00410] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively,

wherein the oligonucleotide is conjugated to a lipid on the sense strand.

[00411] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide is conjugated to a lipid on the sense strand.

[00412] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 862 and 952, respectively;

(b) SEQ ID NOs: 875 and 965, respectively;

(c) SEQ ID NOs: 876 and 966, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide is conjugated to a lipid on the sense strand.

[00413] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 862 and the antisense strand sequence of SEQ ID NO: 952, wherein the oligonucleotide is conjugated to a lipid on the sense strand.

[00414] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 875 and the antisense strand sequence of SEQ ID NO: 965, wherein the oligonucleotide is conjugated to a lipid on the sense strand.

[00415] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 876 and the antisense strand sequence of SEQ ID NO: 966, wherein the oligonucleotide is conjugated to a lipid on the sense strand.

[00416] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 920 and the antisense strand sequence of SEQ ID NO: 1010, wherein the oligonucleotide is conjugated to a lipid on the sense strand.

[00417] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 857 and 947, respectively;

(b) SEQ ID NOs: 858 and 948, respectively;

(c) SEQ ID NOs: 859 and 949, respectively;

(d) SEQ ID NOs: 860 and 950, respectively;

(e) SEQ ID NOs: 862 and 952, respectively;

(f) SEQ ID NOs: 867 and 957, respectively;

(g) SEQ ID NOs: 875 and 965, respectively; and

(h) SEQ ID NOs: 876 and 966, respectively,

wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand.

[00418] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively,

wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand.

[00419] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively,

wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand.

[00420] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand.

[00421] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 862 and 952, respectively;

(b) SEQ ID NOs: 875 and 965, respectively;

(c) SEQ ID NOs: 876 and 966, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand.

[00422] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 862 and the antisense strand sequence of SEQ ID NO: 952, wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand.

[00423] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 875 and the antisense strand sequence of SEQ ID NO: 965, wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand.

[00424] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 876 and the antisense strand sequence of SEQ ID NO: 966, wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand.

[00425] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 920 and the antisense strand sequence of SEQ ID NO: 1010, wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand.

[00426] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively,

wherein the oligonucleotide reduces *STAT3* mRNA in humans, non-human primates, and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide) by at least 75%.

[00427] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively,

wherein the oligonucleotide reduces *STAT3* mRNA in humans and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide) by at least 75%.

[00428] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide reduces *STAT3* mRNA in humans by at least 75%.

[00429] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 862 and the antisense strand sequence of SEQ ID NO: 952, wherein the oligonucleotide reduces *STAT3* mRNA in humans and non-human primates (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide) by at least 75%.

[00430] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 875 and the antisense strand sequence of SEQ ID NO: 965, wherein the oligonucleotide reduces *STAT3* mRNA in humans by at least 75%.

[00431] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 876 and the antisense strand sequence of SEQ ID NO: 966, wherein the oligonucleotide reduces *STAT3* mRNA in humans by at least 75%.

[00432] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 920 and the antisense strand sequence of SEQ ID NO: 1010, wherein the oligonucleotide reduces *STAT3* mRNA in humans by at least 75%.

[00433] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively,

wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces *STAT3* mRNA in humans, non-human primates, and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00434] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively,

wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces *STAT3* mRNA in humans and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00435] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces *STAT3* mRNA in humans.

[00436] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 862 and the antisense strand sequence of SEQ ID NO: 952, wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces *STAT3* mRNA in humans and non-human primates (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00437] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 875 and the antisense strand sequence of SEQ ID NO: 965, wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces *STAT3* mRNA in humans.

[00438] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 876 and the antisense strand sequence of SEQ ID NO: 966, wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces *STAT3* mRNA in humans.

[00439] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 920 and the antisense strand sequence of SEQ ID NO: 1010, wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces STAT3 mRNA in humans.

[00440] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively,

wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans, non-human primates, and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00441] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively,

wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00442] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans.

[00443] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 862 and the antisense strand sequence of SEQ ID NO: 952, wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans and non-human primates (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide).

[00444] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 875 and the antisense strand sequence of SEQ ID NO: 965, wherein the oligonucleotide is conjugated to a C18 on the sense strand lipid and reduces *STAT3* mRNA in humans.

[00445] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 876 and the antisense strand sequence of SEQ ID NO: 966, wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans.

[00446] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 920 and the antisense strand sequence of SEQ ID NO: 1010, wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans.

[00447] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively,

wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces *STAT3* mRNA in humans, non-human primates, and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide) by at least 75%.

[00448] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively,

wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces STAT3 mRNA in humans and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide) by at least 75%.

[00449] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces *STAT3* mRNA in humans by at least 75%.

[00450] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 862 and the antisense strand sequence of SEQ ID NO: 952, wherein the oligonucleotide is conjugated to a lipid on the sense

strand and reduces *STAT3* mRNA in humans and non-human primates (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide) by at least 75%.

[00451] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 875 and the antisense strand sequence of SEQ ID NO: 965, wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces *STAT3* mRNA in humans by at least 75%.

[00452] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 876 and the antisense strand sequence of SEQ ID NO: 966, wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces *STAT3* mRNA in humans by at least 75%.

[00453] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 920 and the antisense strand sequence of SEQ ID NO: 1010, wherein the oligonucleotide is conjugated to a lipid on the sense strand and reduces *STAT3* mRNA in humans by at least 75%.

[00454] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively,

wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans, non-human primates, and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide) by at least 75%.

[00455] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively,

wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans and mice (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide) by at least 75%.

[00456] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand selected from:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively,

wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans by at least 75%.

[00457] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 862 and the antisense strand sequence of SEQ ID NO: 952, wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans and non-human primates (*i.e.* the oligonucleotide is a species cross-reactive oligonucleotide) by at least 75%.

[00458] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 875 and the antisense strand sequence of SEQ ID NO: 965, wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans by at least 75%.

[00459] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 876 and the antisense strand sequence of SEQ ID NO: 966, wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans by at least 75%.

[00460] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 920 and the antisense strand sequence of SEQ ID NO: 1010, wherein the oligonucleotide is conjugated to a C18 lipid on the sense strand and reduces *STAT3* mRNA in humans by at least 75%.

Formulations

[00461] Various formulations have been developed to facilitate oligonucleotide use. For example, oligonucleotides can be delivered to a subject or a cellular environment using a formulation that minimizes degradation, facilitates delivery and/or uptake, or provides another beneficial property to the oligonucleotides in the formulation. In some embodiments, an oligonucleotide is formulated in buffer solutions such as phosphate buffered saline solutions, liposomes, micellar structures, and capsids.

[00462] Formulations of oligonucleotides with cationic lipids can be used to facilitate transfection of the oligonucleotides into cells. For example, cationic lipids, such as lipofectin, cationic glycerol derivatives, and polycationic molecules (*e.g.*, polylysine, can be used. Suitable lipids include Oligofectamine, Lipofectamine (Life Technologies), NC388 (Ribozyme Pharmaceuticals, Inc., Boulder, Colo.), or FuGene 6 (Roche) all of which can be used according to the manufacturer's instructions.

[00463] Accordingly, in some embodiments, a formulation comprises a lipid nanoparticle. In some embodiments, an excipient comprises a liposome, a lipid, a lipid complex, a microsphere, a microparticle, a nanosphere or a nanoparticle, or may be otherwise formulated for administration to the cells, tissues, organs, or body of a subject in need thereof (*see*, *e.g.*, Remington: **THE SCIENCE AND PRACTICE OF PHARMACY**, 22nd edition, Pharmaceutical Press, 2013).

[00464] In some embodiments, the formulations herein comprise an excipient. In some embodiments, an excipient confers to a composition improved stability, improved absorption, improved solubility and/or therapeutic enhancement of the active ingredient. In some embodiments, an excipient is a buffering agent (*e.g.*, sodium citrate, sodium phosphate, a tris base, or sodium hydroxide) or a vehicle (*e.g.*, a buffered solution, petrolatum, dimethyl sulfoxide, or mineral oil). In some embodiments, an oligonucleotide is lyophilized for extending its shelf-life and then made into a solution before use (*e.g.*, administration to a subject). Accordingly, an excipient in a composition comprising any one of the oligonucleotides described herein may be a lyoprotectant (*e.g.*, mannitol, lactose, polyethylene glycol or polyvinylpyrrolidone) or a collapse temperature modifier (*e.g.*, dextran, Ficoll™ or gelatin).

[00465] In some embodiments, a pharmaceutical composition is formulated to be compatible with its intended route of administration. Examples of routes of administration

include parenteral (*e.g.*, intravenous, intramuscular, intraperitoneal, intradermal, subcutaneous), oral (*e.g.*, inhalation), transdermal (*e.g.*, topical), transmucosal and rectal administration.

[00466] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohol's such as mannitol, sorbitol, sodium chloride in the composition. Sterile injectable solutions can be prepared by incorporating the oligonucleotides in a required amount in a selected solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization.

[00467] In some embodiments, a composition may contain at least about 0.1% of the therapeutic agent or more, although the percentage of the active ingredient(s) may be between about 1% to about 80% or more of the weight or volume of the total composition. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

[00468] Even though several embodiments are directed to liver-targeted delivery of any of the oligonucleotides herein, targeting of other tissues is also contemplated.

Methods of Use

Reducing STAT3 Expression in Cells

[00469] The disclosure provides methods for contacting or delivering to a cell or population of cells an effective amount any one of oligonucleotides herein for purposes of reducing STAT3 expression. The methods can include the steps described herein, and these maybe be, but not necessarily, carried out in the sequence as described. Other sequences, however, also are conceivable. Moreover, individual, or multiple steps bay be carried out either

in parallel and/or overlapping in time and/or individually or in multiply repeated steps. Furthermore, the methods may include additional, unspecified steps.

[00470] Methods herein are useful in any appropriate cell type. In some embodiments, a cell is any cell that expresses mRNA (*e.g.*, hepatocytes, macrophages, monocyte-derived cells, prostate cancer cells, cells of the brain, endocrine tissue, bone marrow, lymph nodes, lung, gall bladder, liver, duodenum, small intestine, pancreas, kidney, gastrointestinal tract, bladder, adipose and soft tissue, and skin). In some embodiments, the cell is a primary cell obtained from a subject. In some embodiments, the primary cell has undergone a limited number of passages such that the cell substantially maintains is natural phenotypic properties. In some embodiments, a cell to which the oligonucleotide is delivered is *ex vivo* or *in vitro* (*i.e.*, can be delivered to a cell in culture or to an organism in which the cell resides).

[00471] In some embodiments, the oligonucleotides herein are delivered using appropriate nucleic acid delivery methods including, but not limited to, injection of a solution containing the oligonucleotides, bombardment by particles covered by the oligonucleotides, exposing the cell or population of cells to a solution containing the oligonucleotides, or electroporation of cell membranes in the presence of the oligonucleotides. Other appropriate methods for delivering oligonucleotides to cells may be used, such as lipid-mediated carrier transport, chemical-mediated transport, and cationic liposome transfection such as calcium phosphate, and others.

[00472] In some embodiments, reduction of STAT3 expression can be determined by an appropriate assay or technique to evaluate one or more properties or characteristics of a cell or population of cells associated with STAT3 expression (*e.g.*, using an STAT3 expression biomarker) or by an assay or technique that evaluates molecules that are directly indicative of STAT3 expression (*e.g.*, *STAT3* mRNA or STAT3 protein). In some embodiments, the extent to which an oligonucleotide herein reduces STAT3 expression is evaluated by comparing STAT3 expression in a cell or population of cells contacted with the oligonucleotide to an appropriate control (*e.g.*, an appropriate cell or population of cells not contacted with the oligonucleotide or contacted with a control oligonucleotide). In some embodiments, an appropriate control level of mRNA expression into protein, after delivery of a RNAi molecule may be a predetermined level or value, such that a control level need not be measured every time. The predetermined level or value can take a variety of forms. In some embodiments, a predetermined level or value can be single cut-off value, such as a median or mean.

[00473] In some embodiments, administration of an oligonucleotide herein results in a reduction in STAT3 expression in a cell or population of cells. In some embodiments, the reduction in STAT3 or STAT3 expression is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower when compared with an appropriate control level of mRNA. The appropriate control level may be a level of mRNA expression and/or protein translation in a cell or population of cells that has not been contacted with an oligonucleotide herein. In some embodiments, the effect of delivery of an oligonucleotide to a cell according to a method herein is assessed after a finite period. For example, levels of mRNA may be analyzed in a cell at least about 8 hours, about 12 hours, about 18 hours, about 24 hours; or at least about 1, 2, 3, 4, 5, 6, 7 or even up to 14 days after introduction of the oligonucleotide into the cell.

[00474] In some embodiments, an oligonucleotide is delivered in the form of a transgene that is engineered to express in a cell the oligonucleotide or strands comprising the oligonucleotide (*e.g.*, its sense and antisense strands). In some embodiments, an oligonucleotide is delivered using a transgene engineered to express any oligonucleotide disclosed herein. Transgenes may be delivered using viral vectors (*e.g.*, adenovirus, retrovirus, vaccinia virus, poxvirus, adeno-associated virus, or herpes simplex virus) or non-viral vectors (*e.g.*, plasmids or synthetic mRNAs). In some embodiments, transgenes can be injected directly to a subject.

Medical Use

[00475] The disclosure also provides oligonucleotides for use, or adaptable for use, to treat a subject (*e.g.*, a human having a disease, disorder or condition associated with STAT3 expression) that would benefit from reducing STAT3 expression. In some respects, the disclosure provides oligonucleotides for use, or adapted for use, to treat a subject having a disease, disorder or condition associated with expression of STAT3. The disclosure also provides oligonucleotides for use, or adaptable for use, in the manufacture of a medicament or pharmaceutical composition for treating a disease, disorder or condition associated with STAT3 expression. In some embodiments, the oligonucleotides for use, or adaptable for use, target *STAT3* mRNA and reduce STAT3 expression (*e.g.*, *via* the RNAi pathway). In some

embodiments, the oligonucleotides for use, or adaptable for use, target STAT3 mRNA and reduce the amount or level of *STAT3* mRNA or STAT3 mRNA, STAT3 protein and/or STAT3 activity.

[00476] In addition, the methods below can include selecting a subject having a disease, disorder or condition associated with STAT3 expression or is predisposed to the same. In some instances, the methods can include selecting an individual having a marker for a disease associated with STAT3 expression such as cancer or other chronic lymphoproliferative disorders.

[00477] Likewise, and as detailed below, the methods also may include steps such as measuring or obtaining a baseline value for a marker of STAT3 expression, and then comparing such obtained value to one or more other baseline values or values obtained after being administered the oligonucleotide to assess the effectiveness of treatment.

Methods of Treatment

[00478] The disclosure also provides methods of treating a subject having, suspected of having, or at risk of developing a disease, disorder, or condition with an oligonucleotide herein. In some aspects, the disclosure provides methods of treating or attenuating the onset or progression of a disease, disorder or condition associated with STAT3 expression using the oligonucleotides herein. In other aspects, the disclosure provides methods to achieve one or more therapeutic benefits in a subject having a disease, disorder or condition associated with STAT3 expression using the oligonucleotides herein. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of any one or more of the oligonucleotides herein. In some embodiments, treatment comprises reducing STAT3 expression. In some embodiments, the subject is treated therapeutically. In some embodiments, the subject is treated prophylactically.

[00479] In some embodiments of the methods herein, one or more oligonucleotides herein, or a pharmaceutical composition comprising one or more oligonucleotides, is administered to a subject having a disease, disorder or condition associated with STAT3 expression such that STAT3 expression is reduced in the subject, thereby treating the subject. In some embodiments, an amount or level of *STAT3* mRNA is reduced in the subject. In some embodiments, an amount or level of STAT3 and/or protein is reduced in the subject

[00480] In some embodiments of the methods herein, an oligonucleotide herein, or a pharmaceutical composition comprising the oligonucleotide, is administered to a subject having a disease, disorder or condition associated with STAT3 such that STAT3 expression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to STAT3 expression prior to administration of one or more oligonucleotides or pharmaceutical composition. In some embodiments, STAT3 expression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to STAT3 expression in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or oligonucleotides or pharmaceutical composition or receiving a control oligonucleotide or oligonucleotides, pharmaceutical composition or treatment.

[00481] In some embodiments of the methods herein, an oligonucleotide or oligonucleotides herein, or a pharmaceutical composition comprising the oligonucleotide or oligonucleotides, is administered to a subject having a disease, disorder or condition associated with STAT3 expression such that an amount or level of *STAT3* mRNA is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of *STAT3* mRNA prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of *STAT3* mRNA is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of *STAT3* mRNA in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or oligonucleotides or pharmaceutical composition or receiving a control oligonucleotide or oligonucleotides, pharmaceutical composition or treatment.

[00482] In some embodiments of the methods herein, an oligonucleotide or oligonucleotides herein, or a pharmaceutical composition comprising the oligonucleotide or oligonucleotides, is administered to a subject having a disease, disorder or condition associated with STAT3 expression such that an amount or level of STAT3 protein is reduced in the subject

by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of STAT3 protein prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of STAT3 protein is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of STAT3 protein in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or oligonucleotides or pharmaceutical composition or receiving a control oligonucleotide, oligonucleotides or pharmaceutical composition or treatment.

[00483] In some embodiments of the methods herein, an oligonucleotide or oligonucleotides herein, or a pharmaceutical composition comprising the oligonucleotide or oligonucleotides, is administered to a subject having a disease, disorder or condition associated with STAT3 such that an amount or level of STAT3 activity/expression is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to the amount or level of STAT3 activity prior to administration of the oligonucleotide or pharmaceutical composition. In some embodiments, an amount or level of STAT3 activity is reduced in the subject by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or greater than 99% when compared to an amount or level of STAT3 activity in a subject (*e.g.*, a reference or control subject) not receiving the oligonucleotide or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[00484] Because of their high specificity, the oligonucleotides herein specifically target mRNAs of target genes of diseased cells and tissues. In preventing disease, the target gene may be one which is required for initiation or maintenance of the disease or which has been identified as being associated with a higher risk of contracting the disease. In treating disease, the oligonucleotide can be brought into contact with the cells or tissue exhibiting the disease. For example, an oligonucleotide substantially identical to all or part of a wild-type (*i.e.*, native) or mutated gene associated with a disorder or condition associated with STAT3 expression may be

brought into contact with or introduced into a cell or tissue type of interest such as a hepatocyte or other liver cell.

[00485] In some embodiments, the target gene may be a target gene from any mammal, such as a human target. Any gene may be silenced according to the method described herein.

[00486] Methods described herein are typically involve administering to a subject in an effective amount of an oligonucleotide or oligonucleotides, that is, an amount capable of producing a desirable therapeutic result. A therapeutically acceptable amount may be an amount that can therapeutically treat a disease or disorder. The appropriate dosage for any one subject will depend on certain factors, including the subject's size, body surface area, age, the particular composition to be administered, the active ingredient(s) in the composition, time and route of administration, general health, and other drugs being administered concurrently.

[00487] In some embodiments, a subject is administered any one of the compositions herein either enterally (*e.g.*, orally, by gastric feeding tube, by duodenal feeding tube, *via* gastrostomy or rectally), parenterally (*e.g.*, subcutaneous injection, intravenous injection or infusion, intra-arterial injection or infusion, intraosseous infusion, intramuscular injection, intracerebral injection, intracerebroventricular injection, intrathecal), topically (*e.g.*, epicutaneous, inhalational, *via* eye drops, or through a mucous membrane), or by direct injection into a target organ (*e.g.*, the liver of a subject). Typically, oligonucleotides herein are administered intravenously or subcutaneously.

[00488] As a non-limiting set of examples, the oligonucleotides herein would typically be administered quarterly (once every three months), bi-monthly (once every two months), monthly or weekly. For example, the oligonucleotides may be administered every week or at intervals of two, or three weeks. Alternatively, the oligonucleotides may be administered daily. In some embodiments, a subject is administered one or more loading doses of the oligonucleotide followed by one or more maintenance doses of the oligonucleotide.

[00489] In some embodiments the oligonucleotides herein are administered alone or in combination. In some embodiments the oligonucleotides herein are administered in combination concurrently, sequentially (in any order), or intermittently. For example, two oligonucleotides may be co-administered concurrently. Alternatively, one oligonucleotide may be administered and followed any amount of time later (e.g., one hour, one day, one week or one month) by the administration of a second oligonucleotide.

[00490] In some embodiments, the subject to be treated is a human or non-human primate or other mammalian subject. Other exemplary subjects include domesticated animals such as dogs and cats; livestock such as horses, cattle, pigs, sheep, goats, and chickens; and animals such as mice, rats, guinea pigs, and hamsters.

Combination Treatment

[00491] In some embodiments, the oligonucleotides described herein are used in combination with at least one additional composition or therapeutic agent. In some aspects, the composition or therapeutic agent is selected from the group consisting of: a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy, or a combination thereof. In some embodiments, the composition or therapeutic agent targets TGFB, CXCR2, CCR2, ARG1, PTGS2, SOCS1 or PD-L1. In some embodiments, the composition or therapeutic agent targets TGFB. In some embodiments, the composition or therapeutic agent targets CXCR2. In some embodiments, the composition or therapeutic agent targets CCR2. In some embodiments, the composition or therapeutic agent targets ARG1. In some embodiments, the composition or therapeutic agent targets PTGS2. In some embodiments, the composition or therapeutic agent targets SOCS1. In some embodiments, the composition or therapeutic agent targets PD-L1. In some embodiments, the composition or therapeutic agent that targets any of the above targets, is an oligonucleotide (e.g., dsRNAi). In some embodiments, the composition or therapeutic agent that targets any of the above targets, is an antibody or antigen-binding fragment thereof.

Kits

[00492] In some embodiments, the disclosure provides a kit comprising an oligonucleotide herein, and instructions for use. In some embodiments, the kit comprises an oligonucleotide herein, and a package insert containing instructions for use of the kit and/or any component thereof. In some embodiments, the kit comprises, in a suitable container, an oligonucleotide herein, one or more controls, and various buffers, reagents, enzymes and other standard ingredients well known in the art. In some embodiments, the container comprises at least one

vial, well, test tube, flask, bottle, syringe, or other container means, into which the oligonucleotide is placed, and in some instances, suitably aliquoted. In some embodiments where an additional component is provided, the kit contains additional containers into which this component is placed. The kits can also include a means for containing the oligonucleotide and any other reagent in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which the desired vials are retained. Containers and/or kits can include labeling with instructions for use and/or warnings.

In some embodiments, a kit comprises an oligonucleotide herein, and a pharmaceutically acceptable carrier, or a pharmaceutical composition comprising the oligonucleotide and instructions for treating or delaying progression of a disease, disorder or condition associated with STAT3 expression in a subject in need thereof. In some embodiments, a kit comprises an oligonucleotide herein, and a pharmaceutically acceptable carrier, or a pharmaceutical composition comprising the oligonucleotide and instructions for treating or delaying progression of a cancer in a subject in need thereof.

EXAMPLES

[00493] While the disclosure has been described with reference to the specific embodiments set forth in the following Examples, it should be understood by those skilled in the art that various changes may be made, and equivalents may be substituted without departing from the true spirit and scope of the disclosure. Further, the following Examples are offered by way of illustration and are not intended to limit the scope of the disclosure in any manner. In addition, modifications may be made to adapt to a situation, material, composition of matter, process, process step or steps, to the objective, spirit, and scope of the disclosure. All such modifications are intended to be within the scope of the disclosure. Standard techniques well known in the art or the techniques specifically described below were utilized.

[00494] The following examples describe the development of lipid conjugate siRNA delivery mechanism to deliver an RNAi payload to myeloid-derived suppressor cells (MDSCs) to silence genes that mediate immune suppression. Initially a surrogate ALDH2-GalXC lipid conjugate was used to deliver payload to both subtypes of MDSCs in the tumor microenvironment (TME), as well as the MDSCs found in tumor draining lymph nodes (TdLN) to silence ALDH2. Later, a STAT3-GalXC lipid conjugate was constructed to target and silence

the STAT3 gene in MDSCs. Targeting STAT3 is considered a promising approach since it is a main transcription factor associated with immunosuppressive activity in myeloid cells. STAT3 activation is known to play an important role in promoting tolerogenic effects in TME. Although STAT3 is expressed by tumor cells, the approach to target the STAT3 signaling in tumor associated myeloid cells in TME and TdLN, without affecting STAT3 signaling in cancer cells, was previously demonstrated to be sufficient to inhibit the tolerogenic effects and induce anti-tumor immunity and inhibit tumor growth of various solid tumors. (Kortylewski et al, NAT MED 2005). As a proof-of-concept target, we demonstrated STAT3 knockdown in both MDSCs in the TME and TdLN. These data suggest that a GalXC-STAT3-lipid conjugate or another target-conjugate combination tailored to an MDSC or TdLN specific target has a potential to sensitize treatment-refractory tumors to immune checkpoint blockade.

[00495] In order that the disclosure provided herein may be more fully understood, the following examples are set forth. The examples described in this application are offered to illustrate the methods, compositions, and systems provided herein and are not to be construed in any way as limiting their scope.

Abbreviations

Ac: acetyl

AcOH: acetic acid

ACN: acetonitrile

Ad: adamantyl

AIBN: 2,2'-azo bisisobutyronitrile

Anhyd: anhydrous

Aq: aqueous

B_2Pin_2: bis (pinacolato)diboron -4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane)

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

BH_3: Borane

Bn: benzyl

Boc: *tert*-butoxycarbonyl

Boc_2O: di-tert-butyl dicarbonate

BPO: benzoyl peroxide

BuOH: n-butanol

CDI: carbonyldiimidazole

COD: cyclooctadiene

d: days

DABCO: 1,4-diazobicyclo[2.2.2]octane

DAST: diethylaminosulfur trifluoride

dba: dibenzylideneacetone

DBU: 1,8-diazobicyclo[5.4.0]undec-7-ene

DCE: 1,2-dichloroethane

DCM: dichloromethane

DEA: diethylamine

DHP: dihydropyran

DIBAL-H: diisobutylaluminum hydride

DIPA: diisopropylamine

DIPEA or DIEA: N,N-diisopropylethylamine

DMA: N,N-dimethylacetamide

DME: 1,2-dimethoxyethane

DMAP: 4-dimethylaminopyridine

DMF: N,N-dimethylformamide

DMP: Dess-Martin periodinane

DMSO-dimethyl sulfoxide

DMTr: 4,4'-dimethyoxytrityl

DPPA: diphenylphosphoryl azide

dppf: 1,1'-bis(diphenylphosphino)ferrocene

EDC or EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

ee: enantiomeric excess

ESI: electrospray ionization

EA: ethyl acetate

EtOAc: ethyl acetate

EtOH: ethanol

FA: formic acid

h or hrs: hours

HATU: N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate

HCl: hydrochloric acid

HPLC: high performance liquid chromatography

HOAc: acetic acid

IBX: 2-iodoxybenzoic acid

IPA: isopropyl alcohol

KHMDS: potassium hexamethyldisilazide

K_2CO_3: potassium carbonate

LAH: lithium aluminum hydride

LDA: lithium diisopropylamide

L-DBTA: dibenzoyl-L-tartaric acid

m-CPBA: meta-chloroperbenzoic acid

M: molar

MeCN: acetonitrile

MeOH: methanol

Me_2S: dimethyl sulfide

MeONa: sodium methylate

MeI: iodomethane

min: minutes

mL: milliliters

mM: millimolar

mmol: millimoles

MPa: mega pascal

MOMCl: methyl chloromethyl ether

MsCl: methanesulfonyl chloride

MTBE: methyl *tert*-butyl ether

nBuLi: n-butyllithium

$NaNO_2$: sodium nitrite

NaOH: sodium hydroxide

Na_2SO_4: sodium sulfate

NBS: N-bromosuccinimide

NCS: N-chlorosuccinimide

NFSI: N-Fluorobenzenesulfonimide

NMO: N-methylmorpholine N-oxide

NMP: N-methylpyrrolidine

NMR: Nuclear Magnetic Resonance

^oC: degrees Celsius

Pd/C: Palladium on Carbon

$Pd(OAc)_2$: Palladium Acetate

PBS: phosphate buffered saline

PE: petroleum ether

$POCl_3$: phosphorus oxychloride

PPh_3: triphenylphosphine

PyBOP: (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

Rel: relative

R.T. or rt: room temperature

s or sec: second

sat: saturated

SEMCl: chloromethyl-2-trimethylsilylethyl ether

SFC: supercritical fluid chromatography

$SOCl_2$: sulfur dichloride

tBuOK: potassium *tert*-butoxide

TBAB: tetrabutylammonium bromide

TBAF: tetrabutylammmonium fluoride

TBAI: tetrabutylammonium iodide

TEA: triethylamine

Tf: trifluoromethanesulfonate

TfAA, TFMSA or Tf_2O: trifluoromethanesulfonic anhydride

TFA: trifluoroacetic acid

TIBSCl: 2,4,6-triisopropylbenzenesulfonyl chloride

TIPS: triisopropylsilyl

THF: tetrahydrofuran

THP: tetrahydropyran

TLC: thin layer chromatography

TMEDA: tetramethylethylenediamine

pTSA: para-toluenesulfonic acid

UPLC: Ultra Performance Liquid Chromatography

wt: weight

Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Example 1: Preparation of Double-Stranded RNAi Oligonucleotides

General Synthetic Methods

[00496] The following examples are intended to illustrate the disclosure and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade (C). If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials was confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, NMR. Abbreviations used are those conventional in the art.

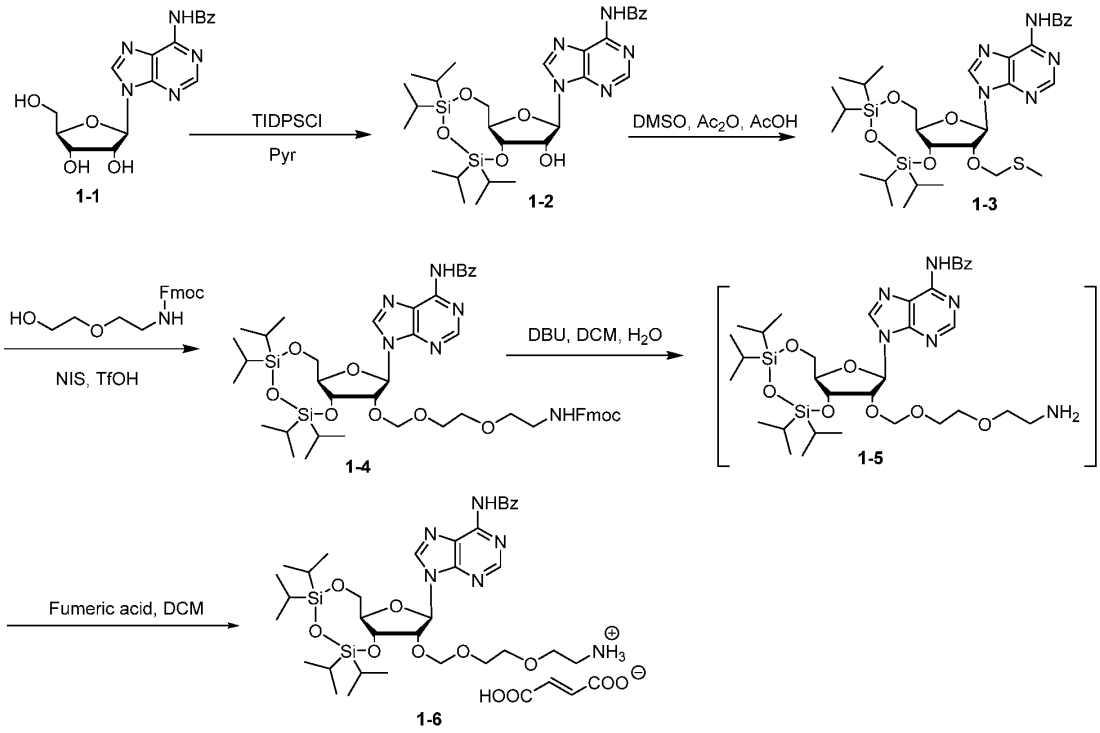
[00497] All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the nucleic acid or analogues thereof of the present disclosure are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (**METHODS OF ORGANIC SYNTHESIS,** Thieme, Volume 21 (Houben-Weyl 4th Ed. 1952)). Further, the nucleic acid or analogues thereof of the present disclosure can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

[00498] All reactions are carried out under nitrogen or argon unless otherwise stated.

[00499] Proton NMR (^{1}H NMR) was conducted in deuterated solvent. In certain nucleic acid or analogues thereof disclosed herein, one or more ^{1}H shifts overlap with residual proteo solvent signals; these signals have not been reported in the experimental provided hereinafter.

[00500] As depicted in the **Examples** below, in certain exemplary embodiments, the nucleic acid or analogues thereof were prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain nucleic acid or analogues thereof of the present disclosure, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all nucleic acid or analogues thereof and subclasses and species of each of these nucleic acid or analogues thereof, as described herein.

Example 1a: Synthesis of 2-(2-((((6aR,8R,9R,9aR)-8-(6-benzamido-9H-purin-9-yl)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl)oxy)methoxy)ethoxy) ethan-1-ammonium formate (1-6)



[00501] A solution of compound **1-1** (25.00 g, 67.38 mmol) in 20 mL of DMF was treated with pyridine (11 mL, 134.67 mmol) and tetraisopropyldisiloxane dichloride (22.63 mL, 70.75 mmol) at 10 °C. The resulting mixture was stirred at 25 °C for 3 h and quenched with 20% citric

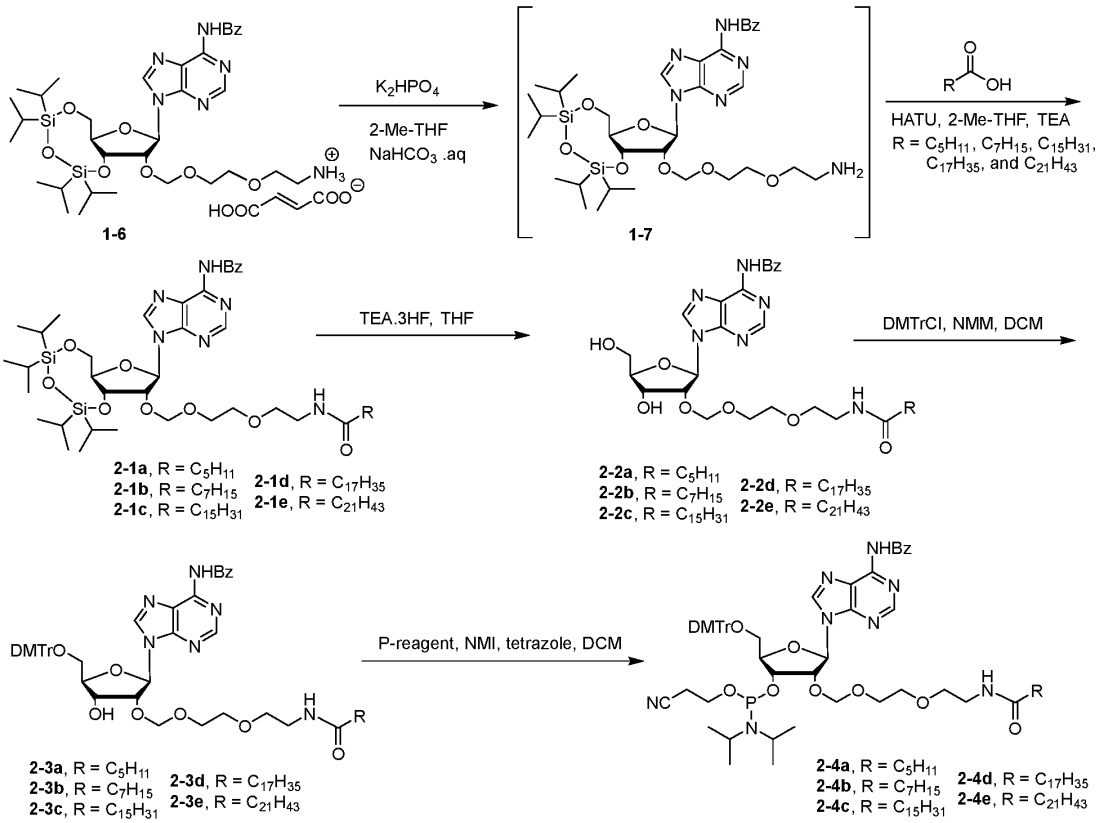
acid (50 mL). The aqueous layer was extracted with EtOAc (3X50 mL) and the combined organic layers were concentrated *in vacuo*. The crude residue was recrystallized from a mixture of MTBE and n-heptane (1:15, 320 mL) to afford compound **1-2** (37.20 g, 90%) as a white oily solid.

[00502] A solution of compound **1-2** (37.00 g, 60.33 mmol) in 20 mL of DMSO was treated with AcOH (20 mL, 317.20 mmol) and Ac_2O (15 mL, 156.68 mmol). The mixture was stirred at 25 °C for 15 h. The reaction was diluted with EtOAc (100 mL) and quenched with sat. K_2CO_3 (50 mL). The aqueous layer was extracted with EtOAc (3X50 mL). The combined organic layers were concentrated and recrystallized with ACN (30 mL) to afford compound **1-3** (15.65 g, 38.4%) as a white solid.

[00503] A solution of compound **1-3** (20.00 g, 29.72 mmol) in 120 mL of DCM was treated with Fmoc-amino-ethoxy ethanol (11.67 g, 35.66 mmol) at 25 °C. The mixture was stirred to afford a clear solution and then treated with 4Å molecular sieves (20.0 g), *N*-iodosuccinimide (8.02 g, 35.66 mmol), and TfOH (5.25 mL, 59.44 mmol). The mixture was stirred at 30 °C until the HPLC analysis indicated >95% consumption of compound **1-3**. The reaction was quenched with TEA (6 mL) and filtered. The filtrate was diluted with EtOAc, washed with sat. $NaHCO_3$ (2X100 mL), sat. Na_2SO_3 (2X100 mL), and water (2X100 mL) and concentrated *in vacuo* to afford crude compound **1-4** (26.34 g, 93.9%) as a yellow solid, which was used directly for the next step without further purification.

[00504] A solution of compound **1-4** (26.34 g, 27.62 mmol) in a mixture of DCM/water (10:7, 170 mL) was treated with DBU (7.00 mL, 45.08 mmol) at 5 °C. The mixture was stirred at 5-25 °C for 1 h. The organic layer was then separated, washed with water (100 mL), and diluted with DCM (130 mL). The solution was treated with fumaric acid (7.05 g, 60.76 mmol) and 4Å molecular sieves (26.34 g) in four portions. The mixture was stirred for 1 h, concentrated, and recrystallized from a mixture of MTBE and DCM (5:1) to afford compound **1-6** (14.74 g, 62.9%) as a white solid: ^{1}H NMR (400 MHz, d_6-DMSO) 8.73 (s, 1H), 8.58 (s, 1H), 8.15-8.02 (m, 2H), 7.65-7.60 (m, 1H), 7.59-7.51 (m, 2H), 6.52 (s, 2H), 6.15(s, 1H), 5.08-4.90 (m, 3H), 4.83-4.78 (m, 1H), 4.15-3.90 (m, 3H), 3.79-3.65 (m, 2H), 2.98-2.85 (m, 6H), 1.20-0.95 (m, 28H).

Example 1b: Synthesis of (2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((2-(2-[lipid]-amidoethoxy)ethoxy)methoxy) tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (2-4a to 2-4e)



[00505] A solution of compound **1-6** (50.00 g, 59.01 mmol) in 150 mL of 2-methyltetrahydrofuran was washed with ice cold aqueous K_2HPO_4 (6%, 100 mL) and brine (20%, 2X100 mL). The organic layer was separated and treated with hexanoic acid (10.33 mL, 82.61 mmol), HATU (33.66 g, 88.52 mmol), and DMAP (10.81 g, 147.52 mmol) at 0 °C. The resulting mixture was warmed to 25 °C and stirred for 1 h. The solution was washed with water (2X100 mL), brine (100 mL), and concentrated *in vacuo* to afford a crude residue. Flash chromatography on silica gel (1:1 hexanes/acetone) gave compound **2-1a** (34.95 g, 71.5%) as a white solid.

[00506] A mixture of compound **2-1a** (34.95 g, 42.19 mmol) and TEA (9.28 mL, 126.58 mmol) in 80 mL of THF was treated with triethylamine trihydrofluoride (20.61 mL, 126.58 mmol) dropwise at 10 °C. The mixture was warmed to 25 °C and stirred for 2 h. The reaction was concentrated, dissolved in DCM (100 mL), and washed with sat. $NaHCO_3$ (5X20 mL) and brine (50 mL). The organic layer was concentrated *in vacuo* to afford crude compound **2-2a** (24.72 g, 99%), which was used directly for the next step without further purification.

[00507] A solution of compound **2-2a** (24.72 g, 42.18 mmol) in 50 mL of DCM was treated with *N*-methylmorpholine (18.54 mL, 168.67 mmol) and DMTr-Cl (15.69 g, 46.38 mmol). The mixture was stirred at 25 °C for 2 h and quenched with sat. $NaHCO_3$ (50 mL). The organic layer was separated, washed with water, concentrated to afford a slurry crude. Flash chromatography on silica gel (1:1 hexanes/acetone) gave compound **2-3a** (30.05 g, 33.8 mmol, 79.9%) as a white solid.

[00508] A solution of compound **2-3a** (25.00 g, 28.17 mmol) in 50 mL of DCM was treated with *N*-methylmorpholine (3.10 mL, 28.17 mmol) and tetrazole (0.67 mL, 14.09 mmol) under nitrogen atmosphere. Bis(diisopropylamino) chlorophosphine (9.02 g, 33.80 mmol) was added to the solution dropwise and the resulting mixture was stirred at 25 °C for 4 h. The reaction was quenched with water (15 mL), and the aqueous layer was extracted with DCM (3X50 mL). The combined organic layers were washed with sat. $NaHCO_3$ (50 mL), concentrated to afford a crude solid that was recrystallized from a mixture of DCM/MTBE/n-hexane (1:4:40) to afford compound **2-4a** (25.52 g, 83.4%) as a white solid: ^{1}H NMR (400 MHz, d_6-DMSO) 11.25 (s, 1H), 8.65-8.60 (m, 2 H), 8.09-8.02 (m, 2H), 7.71 (s, 1H), 7.67-7.60 (m, 1H), 7.59-7.51 (m, 2H), 7.38-7.34 (m, 2H), 7.30-7.25 (m, 7H), 6.85-6.79 (m, 4H), 6.23-6.20 (m, 1H), 5.23-5.14 (m, 1H), 4. 80-4.69 (m, 3H), 4.33-4.23 (m, 2H), 3.90-3.78 (m, 1H), 3.75 (s, 6H), 3.74-3.52 (m, 3H), 3.50-3.20 (m, 6H), 3.14-3.09 (m, 2H), 3.09 (s, 1H), 2.82-2.80 (m, 1H), 2.65-2.60 (m, 1H), 2.05-1.96 (m, 2H), 1.50-1.39 (m, 2H), 1.31-1.10 (m, 14H), 1.08-1.05 (m, 2 H), 0.85-0.79 (m, 3H); ^{31}P NMR (162 MHz, d_6-DMSO) 149.43, 149.18.

[00509] Compound **2-4b, 2-4c, 2-4d,** and **2-4e** were prepared using similar procedures described above for compound **2-4a**. Compound **2-4b** was obtained (25.50 g, 85.4%) as a white solid: ^{1}H NMR (400 MHz, d_6-DMSO) 11.23 (s, 1H), 8.65-8.60 (m, 2 H), 8.05-8.02 (m, 2H), 7.73-7.70 (m, 1H), 7.67-7.60 (m, 1H), 7.59-7.51 (m, 2H), 7.38-7.34 (m, 2H), 7.30-7.25 (m, 7H), 6.89-6.80 (m, 4H), 6.21-6.15 (m, 1H), 5.23-5.17 (m, 1H), 4. 80-4.69 (m, 3H), 4.40-4.21 (m, 2H),

3.91-3.80 (m, 1H), 3.74 (s, 6H), 3.74-3.52 (m, 3H), 3.50-3.20 (m, 6H), 3.14-3.09 (m, 2H), 3.09 (s, 1H), 2.83-2.79 (m, 1H), 2.68-2.62 (m, 1H), 2.05-1.97 (m, 2H), 1.50-1.38 (m, 2H), 1.31-1.10 (m, 18H), 1.08-1.05 (m, 2H), 0.85-0.78 (m, 3H); ^{31}P NMR (162 MHz, *d*$_6$-DMSO) 149.43, 149.19.

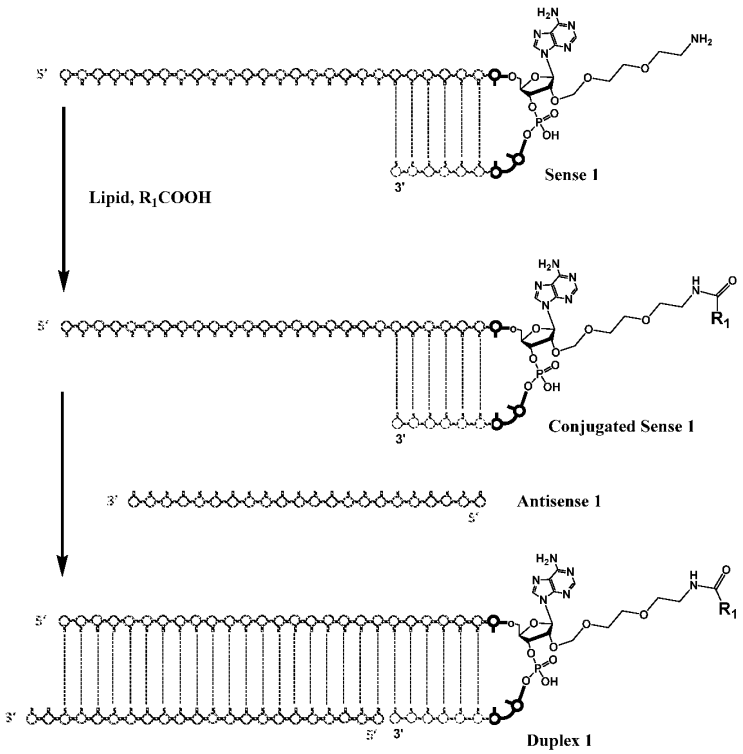
[00510] Compound **2-4c** was obtained (36.60 g, 66.3%) as an off-white solid: ^{1}H NMR (400 MHz, *d*$_6$-DMSO) 11.22 (s, 1H), 8.64-8.59 (m, 2H), 8.05-8.00 (m, 2H), 7.73-7.70 (m, 1H), 7.67-7.60 (m, 1H), 7.59-7.51 (m, 2H), 7.38-7.34 (m, 2H), 7.30-7.25 (m, 7H), 6.89-6.80 (m, 4H), 6.21-6.15 (m, 1H), 5.25-5.17 (m, 1H), 4.80-4.69 (m, 3H), 4.40-4.21 (m, 2H), 3.91-3.80 (m, 1H), 3.74 (s, 6H), 3.74-3.50 (m, 3H), 3.50-3.20 (m, 6H), 3.14-3.09 (m, 2H), 3.09 (s, 1H), 2.83-2.79 (m, 1H), 2.68-2.62 (m, 1H), 2.05-1.99 (m, 2H), 1.50-1.38 (m, 2H), 1.33-1.12 (m, 38H), 1.08-1.05 (m, 2 H), 0.86-0.80 (m, 3H); ^{31}P NMR (162 MHz, *d*$_6$-DMSO) 149.42, 149.17.

[00511] Compound **2-4d** was obtained (26.60 g, 72.9%) as an off-white solid: ^{1}H NMR (400 MHz, *d*$_6$-DMSO) 11.22 (s, 1H), 8.64-8.59 (m, 2H), 8.05-8.00 (m, 2H), 7.73-7.70 (m, 1H), 7.67-7.60 (m, 1H), 7.59-7.51 (m, 2H), 7.38-7.33 (m, 2H), 7.30-7.25 (m, 7H), 6.89-6.80 (m, 4H), 6.21-6.15 (m, 1H), 5.22-5.17 (m, 1H), 4.80-4.69 (m, 3H), 4.40-4.21 (m, 2H), 3.91-3.80 (m, 1H), 3.74 (s, 6H), 3.74-3.52 (m, 3H), 3.50-3.20 (m, 6H), 3.14-3.09 (m, 2H), 3.09 (s, 1H), 2.83-2.79 (m, 1H), 2.68-2.62 (m, 1H), 2.05-1.99 (m, 2H), 1.50-1.38 (m, 2H), 1.35-1.08 (m, 38H), 1.08-1.05 (m, 2 H), 0.85-0.79 (m, 3H); ^{31}P NMR (162 MHz, *d*$_6$-DMSO) 149.47, 149.22.

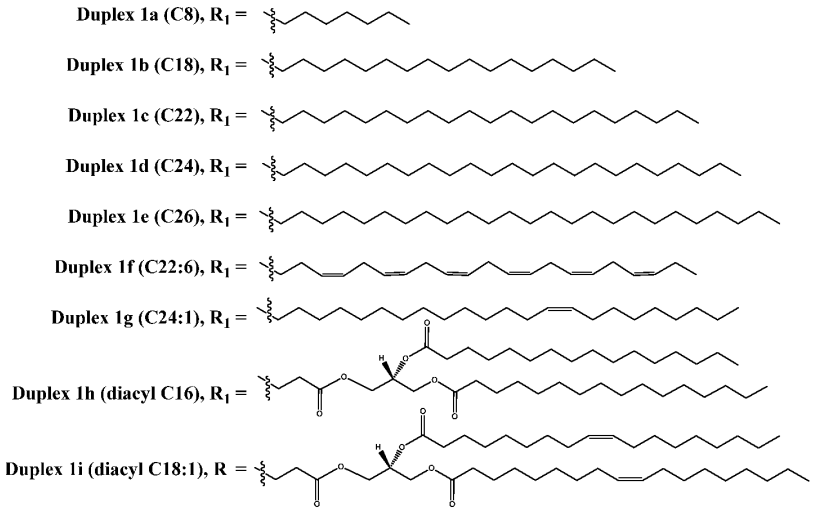
[00512] Compound **2-4e** was obtained (38.10 g, 54.0%) as a white solid: ^{1}H NMR (400 MHz, *d*$_6$-DMSO) 11.21 (s, 1H), 8.64-8.59 (m, 2H), 8.05-8.00 (m, 2H), 7.73-7.70 (m, 1H), 7.67-7.60 (m, 1H), 7.59-7.51 (m, 2H), 7.38-7.34 (m, 2H), 7.30-7.25 (m, 7H), 6.89-6.80 (m, 4H), 6.21-6.15 (m, 1H), 5.23-5.17 (m, 1H), 4.80-4.69 (m, 3H), 4.40-4.21 (m, 2H), 3.91-3.80 (m, 1H), 3.73 (s, 6H), 3.74-3.52 (m, 3H), 3.47-3.22 (m, 6H), 3.14-3.09 (m, 2H), 3.09 (s, 1H), 2.83-2.79 (m, 1H), 2.68-2.62 (m, 1H), 2.05-1.99 (m, 2H), 1.50-1.38 (m, 2H), 1.35-1.06 (m, 46H), 1.08-1.06 (m, 2 H), 0.85-0.77 (m, 3H); ^{31}P NMR (162 MHz, *d*$_6$-DMSO) 149.41, 149.15.

Example 2. Synthesis of GalXC RNAi Oligonucleotide-Lipid Conjugates

Scheme 1. Synthesis of GalXC RNAi oligonucleotide-lipid conjugates with mono-lipid (linear and branched) conjugated to the tetraloop. Post-synthetic conjugation was realized through amide coupling reactions.



R_1COOH group represents fatty acid C8:0, C10:0, C11:0, C12:0, C14:0, C16:0, C17:0, C18:0, C18:1, C18:2, C22:5, C22:0, C24:0, C26:0, C22:6, C24:1, diacyl C16:0 or diacyl C18:1



[00513] Synthesis **Sense 1** and **Antisense 1** were prepared by solid-phase synthesis.

Synthesis of **Conjugated Sense 1a-1i**.

[00514] **Conjugated Sense 1a** was synthesized through post-syntenic conjugation approach**.** In Eppendorf tube 1, a solution of octanoic acid (0.58 mg, 4 umol) in DMA (0.75 mL) was treated with HATU (1.52 mg, 4 umol) at rt. In Eppendorf tube 2, a solution of oligo **Sense 1** (10.00 mg, 0.8 umol) in H_2O (0.25 mL) was treated with DIPEA (1.39 uL, 8 umol). The solution in Eppendorf tube 1 was added to the Eppendorf tube 2 and mixed using Thermomixer at rt. After the reaction was completed indicated by LC-MS analysis, the reaction mixture was diluted with 5 mL of water and purified by revers phase XBridge C18 column using a 5-95% gradient of 100 mM TEAA in ACN and H_2O. The product fractions were concentrated under reduced pressure using Genevac. The combined residual solvent was dialyzed against water (1 X), saline (1 X), and water (3 X) using Amicon® Ultra-15 Centrifugal (3K). The Amicon membrane was washed with water (3 X 2 mL) and the combined solvents were then lyophilized to afford an amorphous white solid of **Conjugated Sense 1a** (6.43 mg, 64% yield).

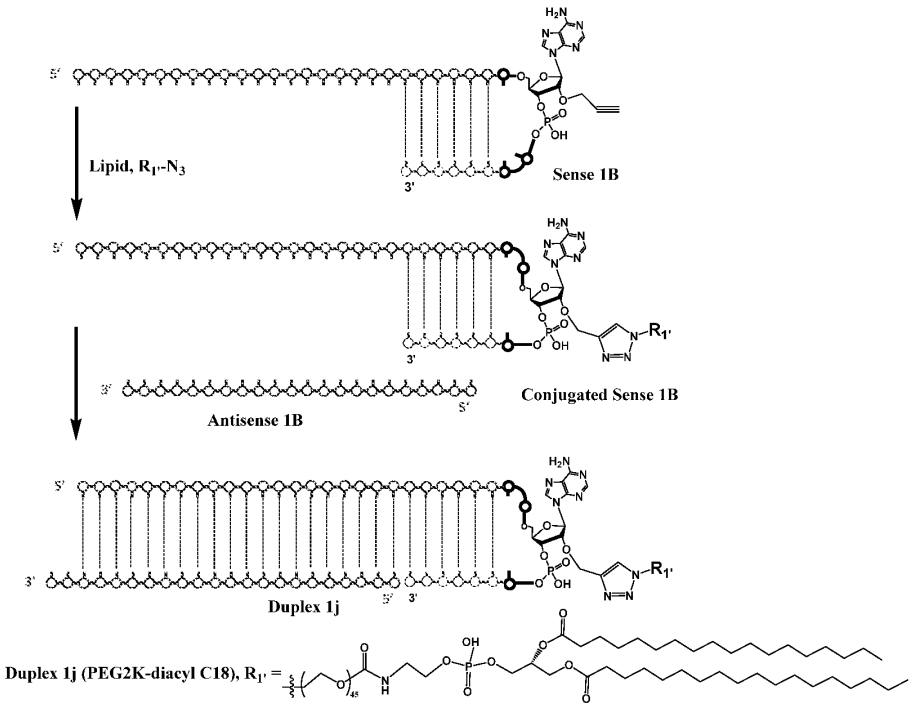
[00515] **Conjugated Sense 1b-1i** were prepared using similar procedures as described for the synthesis of **Conjugated Sense 1a** and obtained in 42%-69% yields.

Annealing of **Duplex 1a-1j.**

[00516] **Conjugated Sense 1a** (10 mg, measured by weight) was dissolved in 0.5 mL deionized water to prepare a 20 mg/mL solution. **Antisense 1** (10 mg, measured by OD) was dissolved in 0.5 mL deionized water to prepare a 20 mg/mL solution, which was used for the titration of the conjugated sense and quantification of the duplex amount. Based on the calculation of molar amounts of both conjugated sense and antisense, a proportion of required **Antisense 1** was added to the **Conjugated Sense 1a** solution. The resulting mixture was stirred at 95 °C for 5 min and allowed to cool down to rt. The annealing progress was monitored by ion-exchange HPLC. Based on the annealing progress, several proportions of **Antisense 1** were further added to complete the annealing with >95% purity. The solution was lyophilized to afford **Duplex 1a (C8)** and its amount was calculated based on the molar amount of the antisense consumed in the annealing.

[00517] **Duplex 1b-1i** were prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00518] The following Scheme 1-2 depicts the synthesis of Nicked tetraloop GalXC conjugates with mono-lipid on the loop. Post-synthetic conjugation was realized through Cu-catalyzed alkyne-azide cycloaddition reaction.



Scheme1-2

[00519] **Sense 1B** and **Antisense 1B** were prepared by solid-phase synthesis.

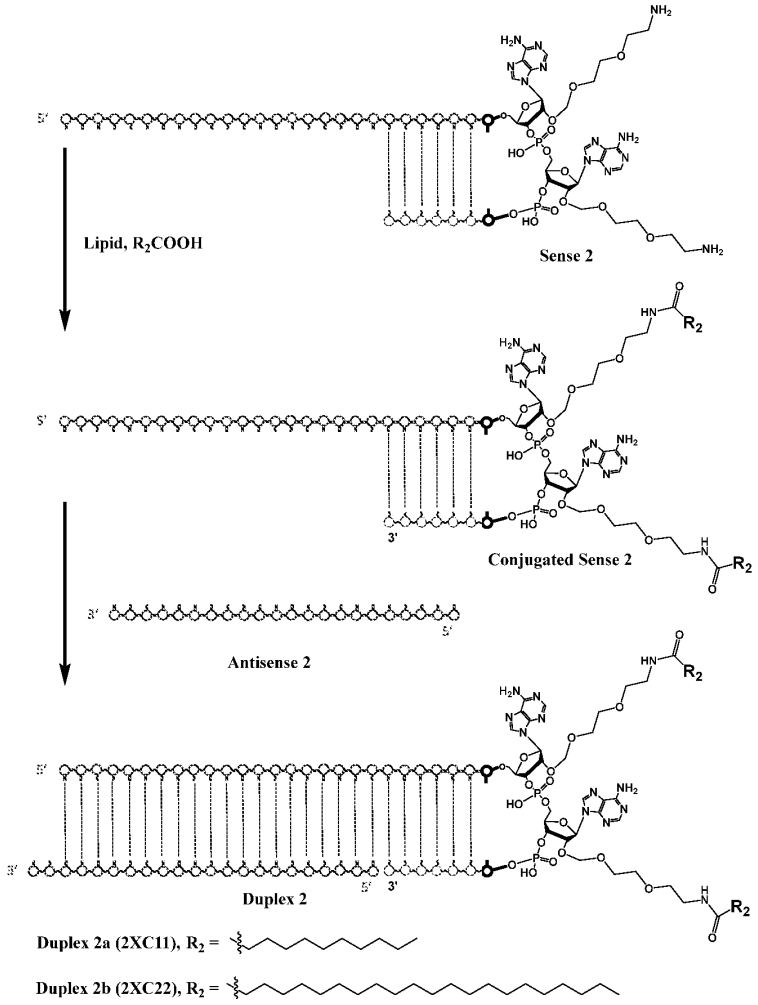
Synthesis of **Conjugated Sense 1j**.

[00520] In Eppendorf tube 1, a solution of oligo (10.00 mg, 0.8 umol) in a 3:1 mixture of DMA/ H_2O (0.5 mL) was treated with the lipid linker azide (11.26 mg, 4 umol). In Eppendorf tube 2, CuBr dimethyl sulfide (1.64 mg, 8 umol) was dissolved in ACN (0.5 mL). Both solutions were degassed for 10 min by bubbling N_2 through them. The ACN solution of $CuBrSMe_2$ was then added into tube 1 and the resulting mixture was stirred at 40 °C. After the reaction was completed indicated by LC-MS analysis, the reaction mixture was diluted with 0.5 M EDTA (2 mL) and dialyzed against water (2 X) using a Amicon® Ultra-15 Centrifugal (3K). The reaction crude was purified by revers phase XBridge C18 column using a 5-95% gradient of 100 mM TEAA in ACN (with 30% IPA spiked in) and H_2O. The product fractions were concentrated

under reduced pressure using Genevac. The combined residual solvent was dialyzed against water (1 X), saline (1 X), and water (3 X) using Amicon® Ultra-15 Centrifugal (3K). The Amicon membrane was washed with water (3 X 2 mL) and the combined solvents were lyophilized to afford an amorphous white solid of **Conjugated Sense 1j** (6.90 mg, 57% yield).

[00521] **Duplex 1j (PEG2K-diacyl C18)** was prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00522] The following Scheme 1-3 depicts the synthesis of Nicked tetraloop GalXC conjugates with di-lipid on the loop using post-synthetic conjugation approach.



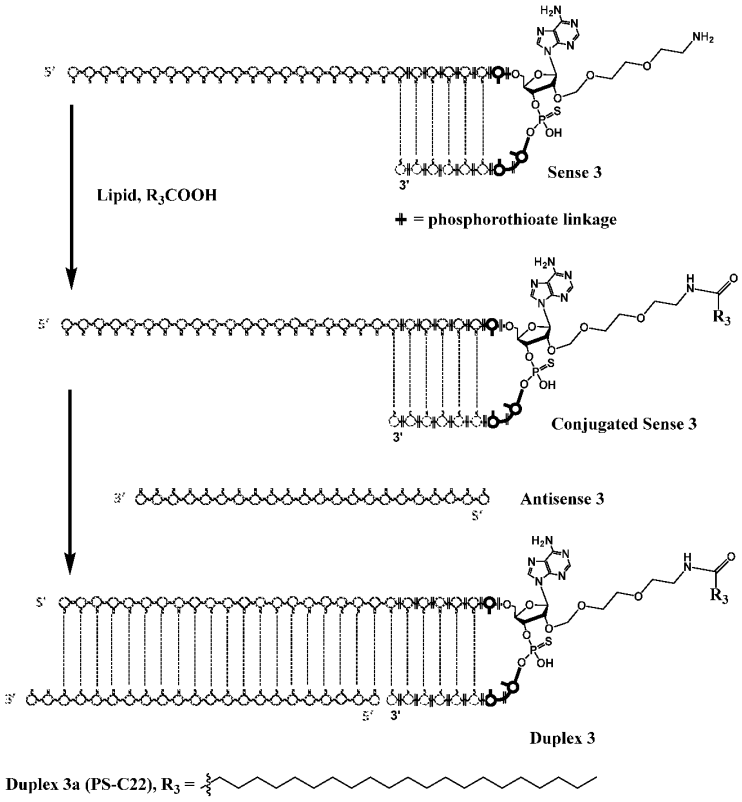
Scheme1-3

Sense 2 and **Antisense 2** were prepared by solid-phase synthesis.

[00523] **Conjugated Sense 2a** and **2b** were prepared using similar procedures as described for the synthesis of **Conjugated Sense 1a** but with 10 eq of lipid, 10 eq of HATU, and 20 eq of DIPEA.

[00524] **Duplex 2a (2XC11)** and **2b (2XC22)** were prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00525] The following Scheme 1-4 depicts the synthesis of GalXC of fully phosphorothioated stem-loop conjugated with mono-lipid using post-synthetic conjugation approach.



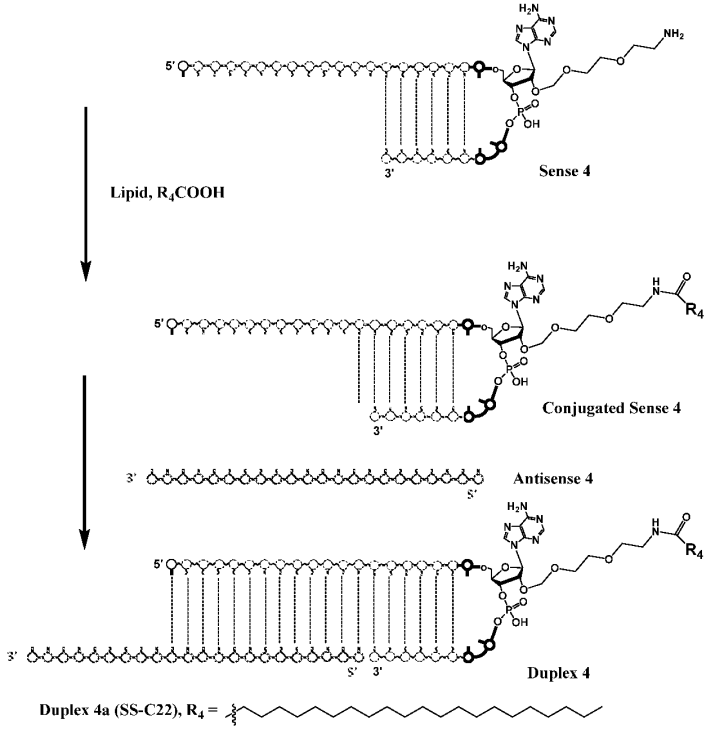
Scheme1-4

Sense 3 and **Antisense 3** were prepared by solid-phase synthesis.

[00526] **Conjugated Sense 3a** was prepared using similar procedures as described for the synthesis of **Conjugated Sense 1a** and obtained in a 65% yield.

[00527] **Duplex 3a (PS-C22)** was prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00528] The following Scheme1-5 depicts the synthesis of GalXC of short sense conjugated with mono-lipid using post-synthetic conjugation approach.



[00529]

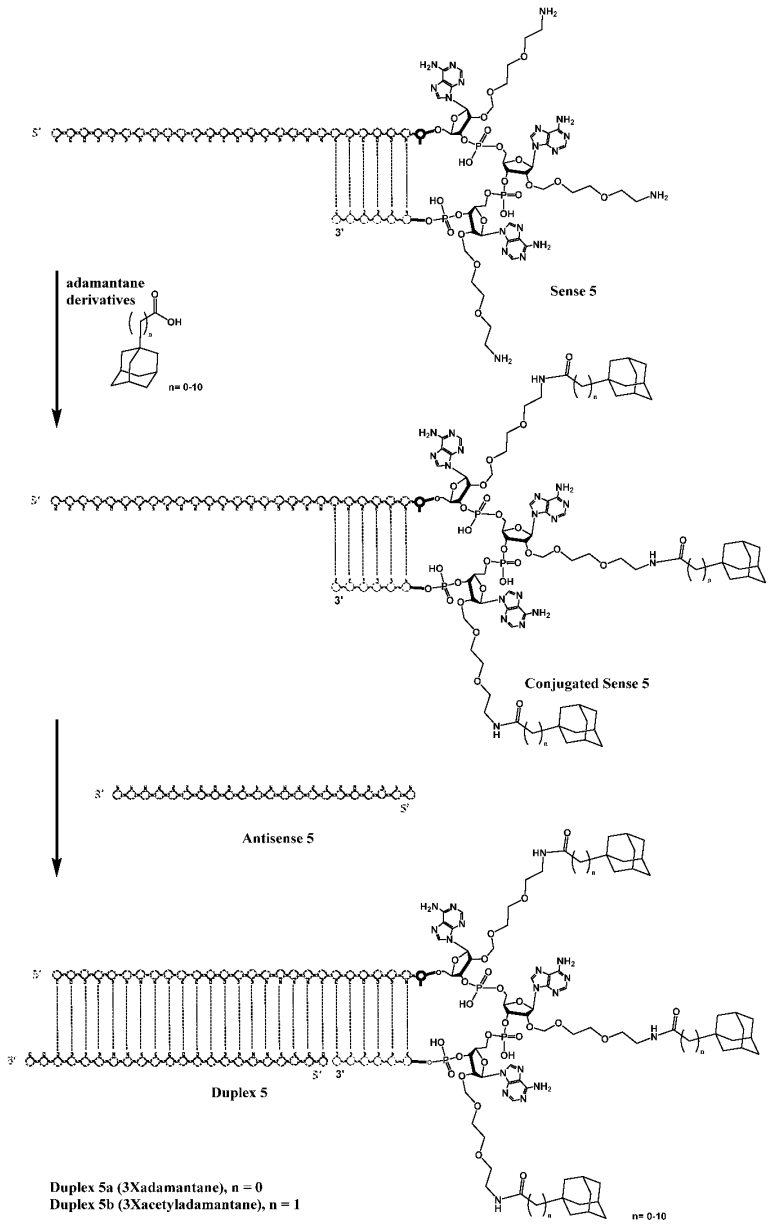
[00530] Scheme 1-5

[00531] **Sense 4** and **Antisense 4** were prepared by solid-phase synthesis.

[00532] **Conjugated Sense 4a** was prepared using similar procedures as described for the synthesis of **Conjugated Sense 1a** and obtained in a 74% yield.

[00533] **Duplex 4a (SS-C22)** was prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00534] The following Scheme 1-6 depicts the synthesis of Nicked tetraloop GalXC conjugated with tri-adamantane moiety on the loop using post-synthetic conjugation approach.



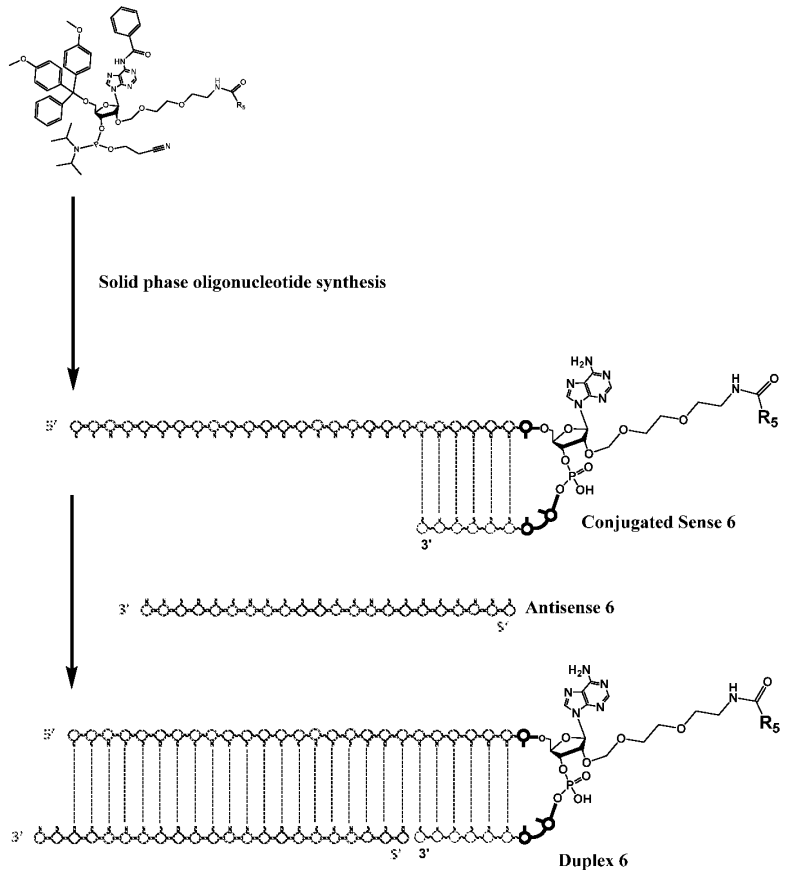
Scheme1-6

Sense 5 and **Antisense 5** were prepared by solid-phase synthesis.

[00535] **Conjugated Sense 5a** and **5b** were prepared using similar procedures as described for the synthesis of **Conjugated Sense 1a** and obtained in 42%-73% yields.

[00536] **Duplex 5a (3Xadamantane)** and **Duplex 5b (3Xacetyladamantane)** were prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00537] The following scheme 1-7 depicts an example of solid phase synthesis of Nicked tetraloop GalXC conjugated with lipid(s) on the loop.



Scheme 1-7

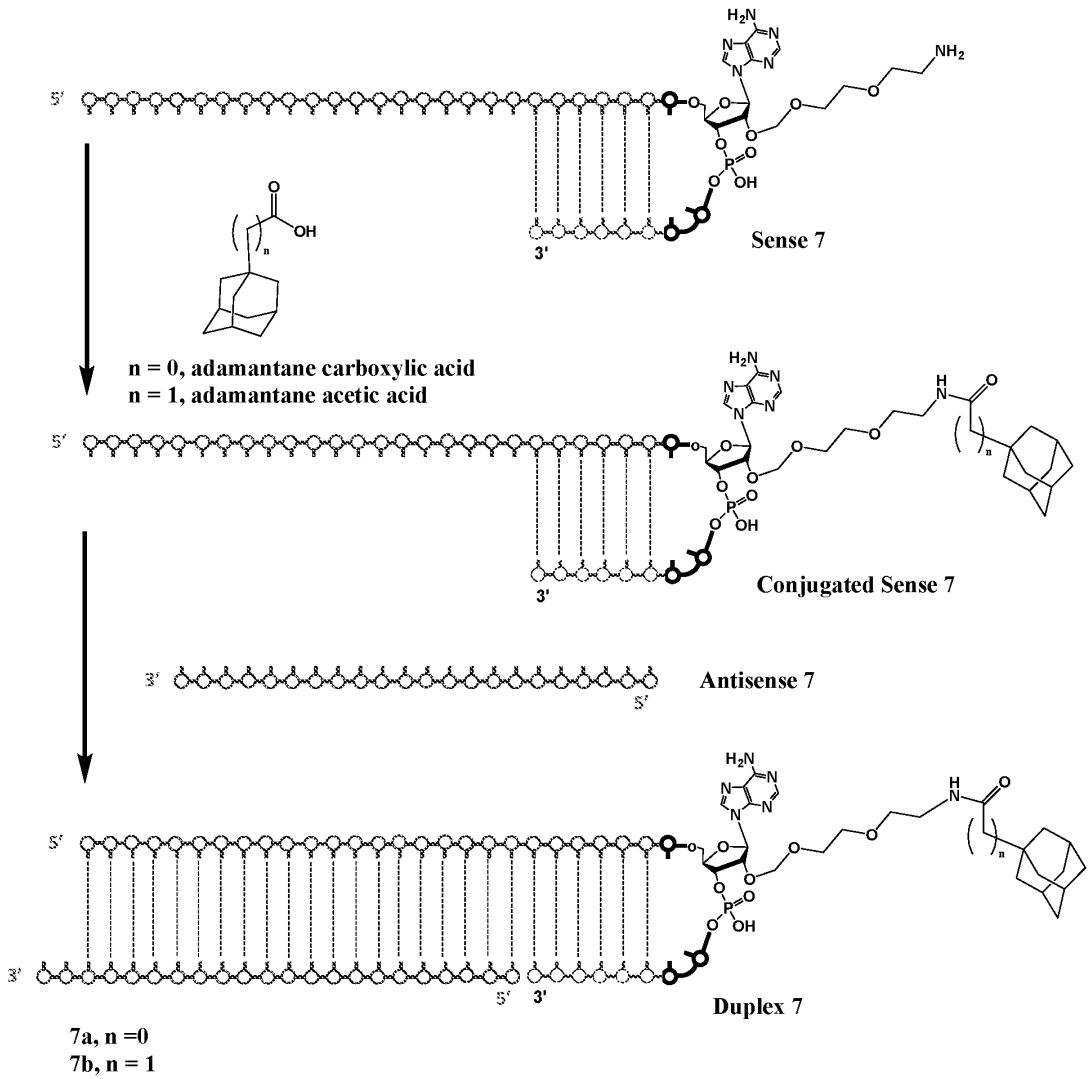
Synthesis of Conjugated Sense 6.

[00538] **Conjugated Sense 6** was prepared by solid-phase synthesis using a commercial oligo synthesizer. The oligonucleotides were synthesized using 2'-modified nucleoside phosphoramidites, such as 2'-F or 2'-OMe, and 2'-diethoxymethanol linked fatty acid amide nucleoside phosphoramidites. Oligonucleotide synthesis was conducted on a solid support in the 3' to 5'direction using a standard oligonucleotide synthesis protocol. In these efforts, 5-ethylthio-

1H-tetrazole (ETT) was used as an activator for the coupling reaction. Iodine solution was used for phosphite triester oxidation. 3-(Dimethylaminomethylidene)amino-3H-1,2,4-dithiazole-3-thione (DDTT) was used for the formation of phosphorothioate linkages. Synthesized oligonucleotides were treated with concentrated aqueous ammonium for 10 h. The ammonia was removed from the suspension and the solid support residues were removed by filtration. The crude oligonucleotide was treated with TEAA, analyzed, and purified by strong anion exchange high performance liquid chromatography (SAX-HPLC). The fractions were combined and dialyzed against water (3 X), saline (1 X), and water (3 X) using Amicon® Ultra-15 Centrifugal (3K). The remaining solvent was then lyophilized to afford the desired **Conjugated Sense 6.**

[00539] **Duplex 6** was prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

Scheme 8. Synthesis of Nicked tetraloop GalXC conjugated with one adamantane unit on the loop *via* a post-synthetic conjugation approach.



N = 0: Adamantane Carboxylic Acid; n = 1: Adamantane Acetic Acid

Scheme 1-8

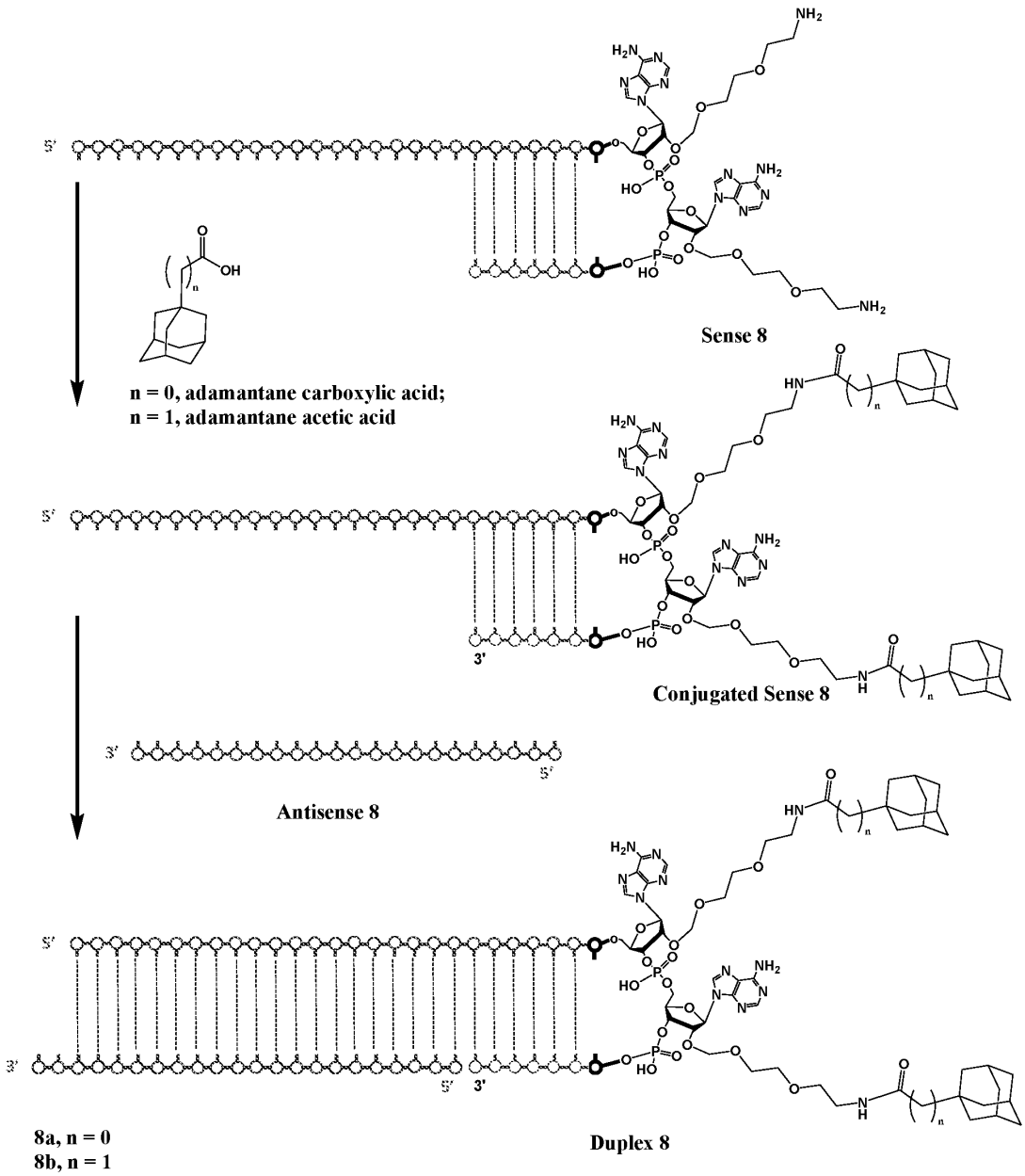
Synthesis of **Conjugated Sense 7a and 7b**

[00540] **Conjugated Sense 7a** and **Sense 7b** were obtained using the same method or a substantially similar method to the synthesis of **Conjugated Sense 5**.

Synthesis example of **Duplex 7a** and **7b**

[00541] **Duplex 7a** and **Duplex 7b** were obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00542] **Scheme 9.** Synthesis of nicked tetraloop GalXC conjugated with two adamantane units on the loop *via* a post-synthetic conjugation approach.



Scheme 1-9

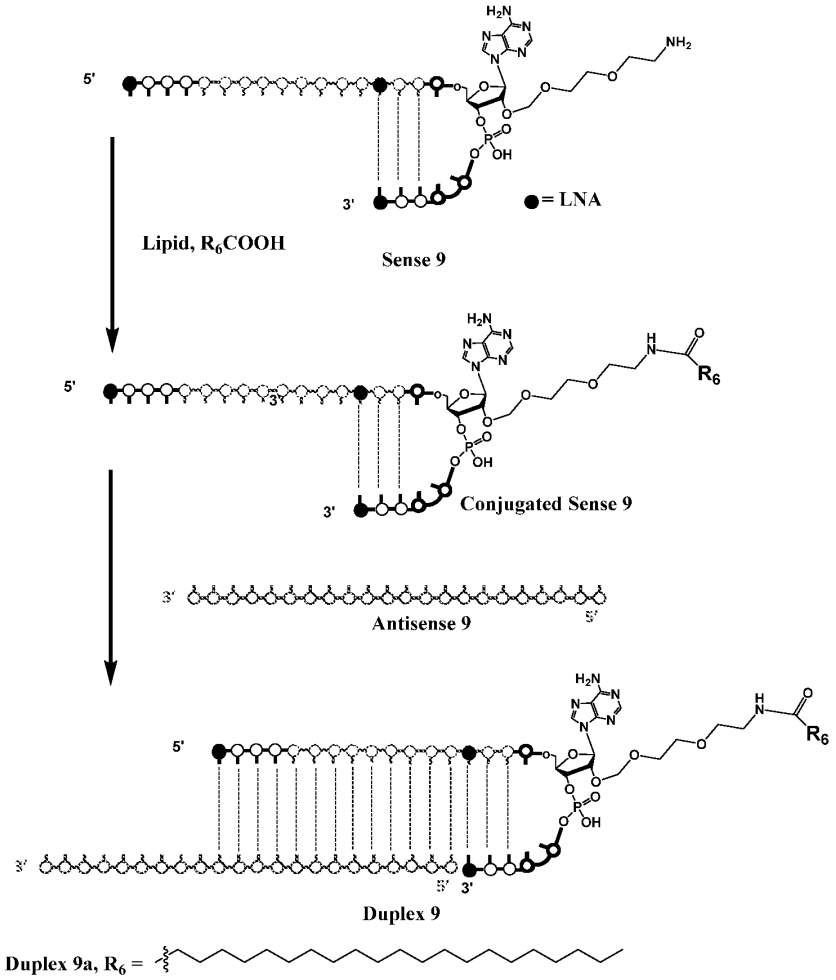
Synthesis of **Conjugated Sense 8a and 8b**

[00543] **Conjugated Sense 8a** and **Sense 8b** were obtained using the same method or a substantially similar method to the synthesis of **Conjugated Sense 5**.

Synthesis example of **Duplex 8a** and **8b**

[00544] **Duplex 8a** and **Duplex 8b** were obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00545] The following Scheme1-10 depicts the synthesis of GalXC of short sense and short stem loop conjugated with mono-lipid using post-synthetic conjugation approach.



Scheme 1-10

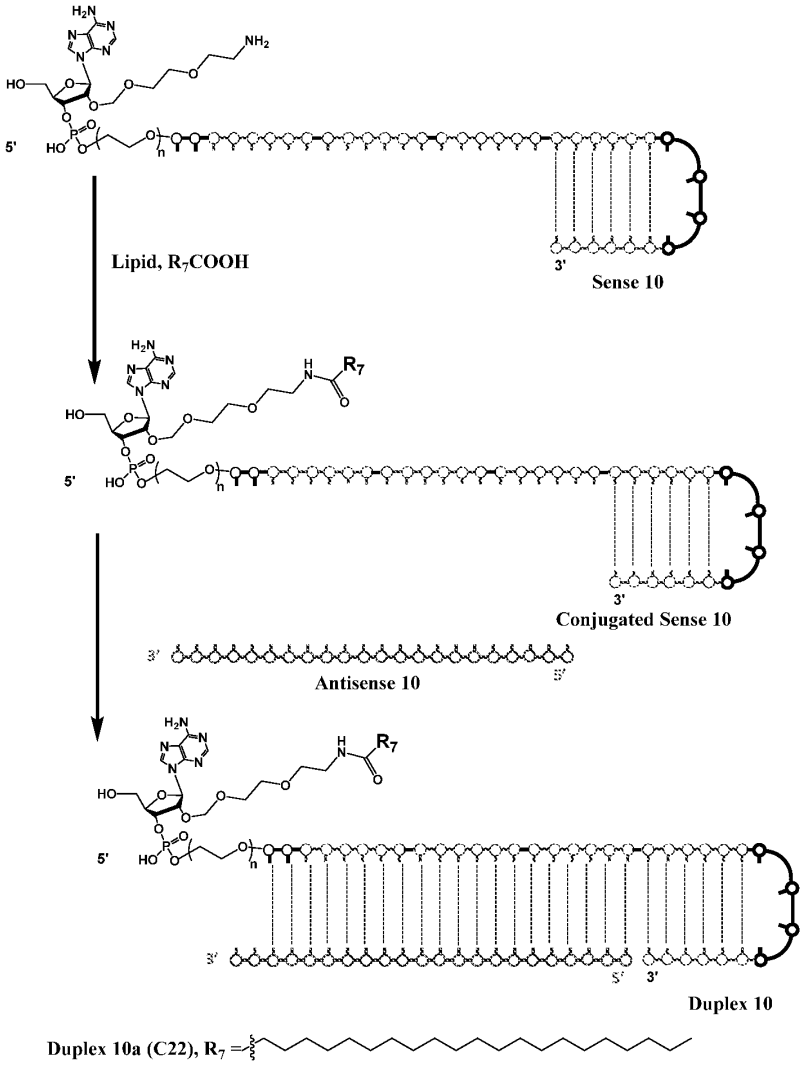
Synthesis of **Sense 9a**

[00546] **Conjugated Sense 9a** was obtained using the same method or a substantially similar method to the synthesis of **Conjugated Sense 5**.

Synthesis example of **Duplex 9a**

[00547] **Duplex 9a** was obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00548] The following **Scheme1-11** depicts the synthesis of GalXC conjugated with mono-lipid at 5'-end using post-synthetic conjugation approach.



Scheme 1-11

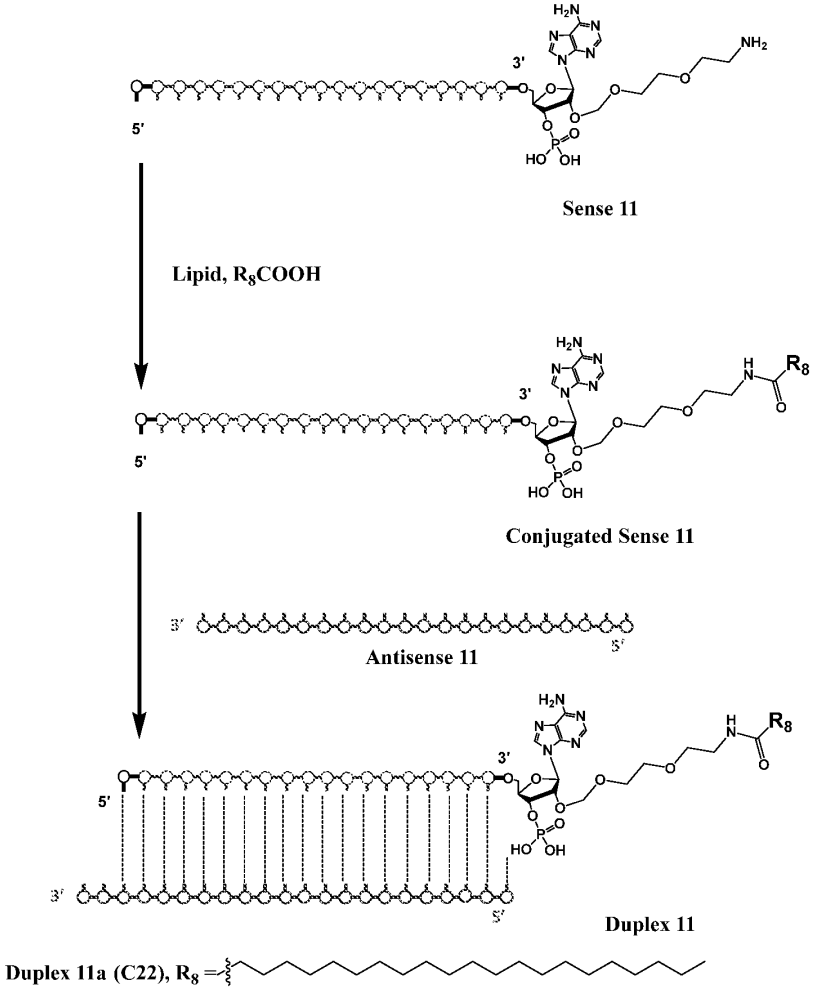
Synthesis of **Conjugated Sense 10a**

[00549] **Conjugated Sense 10a** was obtained using the same method or a substantially similar method to the synthesis of **Conjugated Sense 5**.

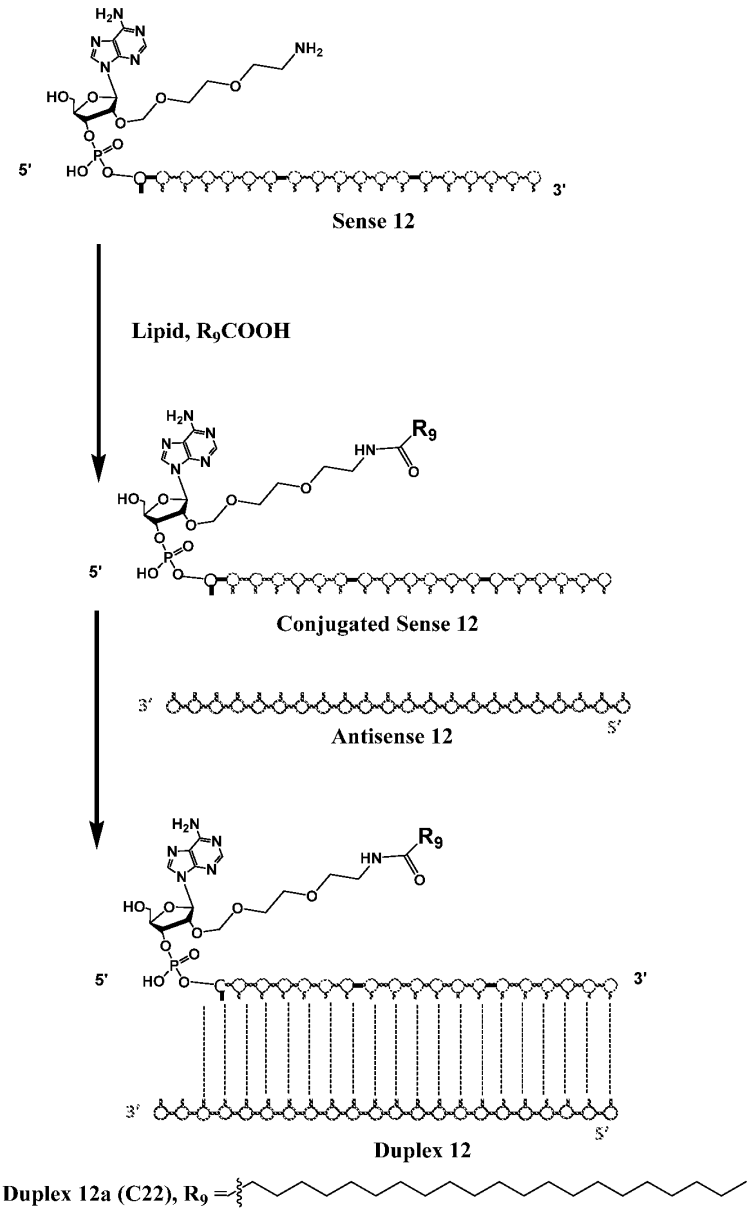
Synthesis example of **Duplex 10a**

[00550] **Duplex 10a** was obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00551] The following **Scheme1-12a** and **1-12b** depict the synthesis of GalXC with blunt end conjugated with mono-lipid at 3'-end or 5'-end using post-synthetic conjugation approach.



Scheme 1-12a



Scheme 1-12b

Synthesis of **Conjugated Sense 11a** and **12a**

[00552] **Conjugated Sense 11a** and **12a** were obtained using the same method or a substantially similar method to the synthesis of **Conjugated Sense 5**.

Synthesis example of **Duplex 11a** and **12a**

[00553] **Duplex 11a** and **12a** were obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00554] Conjugates **Duplex 8D** and **Duplex 9D** were obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00555] Later, acyl chains were conjugated to a nucleic acid inhibitor molecule that targets the STAT3 gene, a gene that is expressed in the tissues of interest. A passenger strand with 2'-amine linkers [ademA] was used for post solid phase conjugation. Different types of lipids were conjugated using the same chemistry to generate a series of conjugates (**FIG. 1A and 1B**). SAR studies were performed to identify a lipid conjugate that could be used to deliver payloads to the tissues of interest in order to mediate target knockdown.

Example 3: *In Vivo* Tumor Models

[00556] Briefly, 6-8-week-old immunocompromised (Nude)/ Immunocompetent (C57BL/6) mice were injected subcutaneously with $2x10^6$ Pan02 cells (mouse pancreatic cancer cell line), $2x10^6$ B16F10 cells (mouse melanoma cell line) or $5x10^6$ LS411N cells (human colorectal cancer cell line) under the right shoulder. When the tumors reached a volume of 300-500 mm^3, they were randomized into different cohorts and subjected to dosing with GalXC lipid conjugates. Each GalXC lipid conjugate was dosed subcutaneously at a total volume of 10 mL/kg. Mouse pancreatic cell line Pan02 was obtained from NCI and mouse melanoma cell line B16F10 and human colorectal cell line LS411N were obtained from ATCC (Manassas, VA). All cells were grown in RPMI/DMEM medium supplemented with 10% FBS. Pan02, B16F10 and LS411N tumors are known to maintain very suppressive, or cold, tumor microenvironments.

Example 4: Differential Delivery of GalXC lipid Conjugates to Different Components of the Tumor Microenvironment

[00557] To elucidate differential delivery of GalXC lipid conjugates, human xenograft tumors (LS411N cells) were implanted in nude mice, as described in Example 3. At about two

weeks post implant, when tumor volume reached ~300-400 mm^3, mice were randomized into 6 groups (n=3) and treated with a single dose of either Phosphate Buffered Saline (PBS) or an GalXC-ALDH2-lipid conjugate as outlined in Scheme 1 of **Example 2** (GalXC-C8, GalXC-C18, GalXC-C18-1, GalXC-C18-2 or GalXC-C22) at 10 mg/kg. Three days post subcutaneous injection, tumors were collected and analyzed by qPCR to determine mRNA levels of human *ALDH2* and mouse *Aldh2*. In bulk tumor tissue, mRNA expression levels of the human *ALDH2* gene remained at baseline across all groups, however mouse *Aldh2* mRNA levels were decreased by ~40-50% across all groups treated with GalXC-ALDH2-lipid conjugates, including C18, C18-1, C18-2 and C22, except C8 as compared to the PBS control (**FIGs. 2A and 2B**). These data suggest that the GalXC-ALDH2-lipid conjugates did not mediate siRNA delivery and target knockdown in human tumor epithelium, but mediated siRNA delivery to components in tumor microenvironment in order to facilitate target knockdown. To further confirm this observation, a follow-up study was run in the same tumor type. LS411N human xenograft tumors were implanted in nude mice, as described above. After randomization into 12 groups, GalXC-ALDH2-C22 conjugate at 10, 25 and 50 mg/kg and PBS control, mice were treated with a single subcutaneous dose of test article accordingly.

Table 2: GalXC- lipid conjugate ALDH2 Tool Molecules

Oligo	DP #	Sequence Type	Sense Strand SEQ ID NO	Antisense strand SEQ ID NO	Conjugate
GalXC-ALDH2-C18	DP15543P:DP11674G	Unmodified	1	2	C18
		Modified	3	4	C18
GalXC-ALDH2-C22	DP15545P:DP11674G	Unmodified	5	6	C22
		Modified	7	8	C22

[00558] Dose response and duration of activity were determined by measuring the mouse and human *Aldh2*/*ALDH2* mRNA levels on days 3, 7- and 14 post treatment. In parallel, the activity of GalXC-ALDH2-C22 in non-tumor bearing mice was also investigated at 25 mg/kg dose level on days 3 and 14 post treatment (**FIG. 4B**). As observed previously, no target knockdown was observed in human tumor epithelial parenchyma at any dose level, including the high dose of 50 mg/kg (**FIG. 3A**). However, robust knockdown of *Aldh2* mRNA was observed in mouse host tissue (tumor microenvironment) (**FIG. 3B**). Nadir for mRNA knockdown in the

murine TME was observed at one-week post-dose. ED_{50} at nadir was observed to be between 10 and 25 mg/kg with the max knockdown was greater than 75%. Robust mRNA knockdown was maintained for at least two weeks post-dose. In the same study, tumor draining lymph nodes (axillary and inguinal) from the mice were also collected and analyzed by qPCR for mRNA levels of mouse *Aldh2*. As demonstrated in **FIG. 4A**, potent and durable activity was observed regardless of dose level. The ED_{50} in tumor draining lymph nodes (TdLN) was determined to be <10 mg/kg. The absence of a dose related response suggests that there was saturation of activity even at the lowest dose level of GalXC-ALDH2-C22. **FIG. 4B** shows that no target knockdown was observed in the lymph nodes (LNs) of non-tumor bearing mice treated with GalXC-ALDH2-C22. Without being bound by theory, it is possible that lack of activity in control LNs suggests that the activity demonstrated in TdLN is tumor mediated and that GalXC-ALDH-C22 conjugate gained access to the LNs through the tumor lymphatic drainage. To examine whether target knockdown was also observed across different lymph nodes types in tumor bearing mice, the non- draining lymph nodes (LNs on the opposite side of the body to the TdLN), were also collected and analyzed for target mRNA levels at all 3 time points. As shown in **FIG. 5A**, the target mRNA levels in non-TdLN were reduced 20% on day 3, 50% on day 7 and reached the same level (60%) of knockdown as observed in TdLN on day 14. The level of immune suppressive characteristics of cell populations was assessed by determining the ratio of mRNA markers *CD11b* and *Pdl1* in a given cell population. In this experiment, the murine mRNA ratio of these markers was found to be significantly lower in non-TdLN compared to TdLN on day 14 (**FIG. 5B**), suggesting that the cell population present in TdLN is more suppressive than the cell population present in Non-TdLN.

Example 5: GalXC lipid Conjugates Mediate Target Knockdown in Tumor-associated Myeloid Cells

[00559] Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of cells that expand during tumorigenesis and which have the remarkable ability to suppress T-cell responses. Collectively, MDSCs are characterized by the co-expression of cell surface or mRNA markers CD11b (a marker for the myeloid cells of the macrophage lineage) and Gr-1(a marker for the myeloid lineage differentiation antigen) and denoted as $CD11b^{+}Gr\text{-}1^{+}$ cells. Gr-1 is further comprised of 2 components Ly6G and Ly6C. MDSCs consist of two subsets:

Granulocytic MDSC (G-MDSC), further characterized as $CD11b^{+}Ly6G^{+}Ly6C^{lo}$, and monocytic MDSC (M-MDSC) characterized as $CD11b^{+}Ly6G^{-}Ly6C^{hi}$. To elucidate the cell populations susceptible to target knockdown mediated by GalXC lipid conjugates in mouse host tissue, specifically to investigate target knockdown in the $CD11b^{+}$ MDSCs of the TME, LS411N human xenograft tumors were implanted in nude mice as described in Example 3. After randomization mice were treated with a single dose of either GalXC-ALDH2-C22 conjugate at 25 mg/kg or PBS. At 3 days post dose, the murine host $CD11b^{+}$ cells (myeloid derived suppressor cells or MDSC) and human tumor cells were isolated from single cell suspensions of tumors through positive and negative magnetic separation methods, respectively, using MACS separation technology (Miltenyi Biotec Inc, Auburn, CA). To isolate the CD11b positive cells, a single cell suspension of tumor was made using gentle MACS dissociator. CD11b positive cells in the single cell suspension were then magnetically labeled with MACS microbeads and enriched by passing through MACS columns and subsequently eluting the retained labeled cells in the column as positively selected fractions (CD11b MicroBeads UltraPure, mouse kit Cat# 130-126-725). For tumor cell separation, non-target cells in the cell suspension were magnetically labeled with a cocktail of microbeads and passed through the MACS columns. During this process, the unwanted labeled cells were retained in the column and the unlabeled target cells (tumor cells) were collected in the flow-through as pure fraction. (Tumor Cell Isolation Kit, human Cat # 130-108-339). $CD11b^{+}$ cells were also isolated from the single cell suspensions of spleens of normal mice to compare the suppressive activity of the $CD11b^{+}$ populations from different tissue types. Assuming comparable *Aldh2* expression across cell types, CD11b+ MDSC preps were shown to be >90% pure. Upon isolation of the immune cell population, *CD11b* and *Arg1* (markers characterizing immune suppression capabilities) mRNA levels were measured in both populations and the relative levels determined. In this analysis, *CD11b* mRNA was set to 100% in tumor and spleen subpopulations. While *Arg1* was highly expressed in isolated MDSCs, it was not expressed (Ct >35) in spleen myeloid cells using the same affinity separation protocol, suggesting that the MDSCs in TME have high immune suppressive capabilities as compared to other myeloid derived cells, as this is one of the mechanisms that MDSCs use to inactivate tumor T-cells to suppress antitumor immune responses (**FIG. 6**). To determine if the GalXC-ALDH2-C22 mediated target knockdown was observed in the isolated $CD11b^{+}$ cells and/or tumor cells, qPCR was performed, and the *Aldh2/ALDH2* mRNA levels were determined. As demonstrated in

FIGs. 7A and 7B, there was roughly 42% target knockdown observed in isolated $CD11b^+$ cells, however there was no target knockdown observed in the isolated tumor cells. These data confirm the observation previously made in data collected from bulk tumor samples.

Example 6: Using SAR to Identify a GalXC Lipid Conjugate Favorable for Delivery of siRNA to the Tumor Microenvironment and Tumor Draining Lymph Nodes

[00560] To identify a lipid conjugate with the most favorable properties to deliver payload and mediate target knockdown with the highest selectivity to myeloid cells in TME, a series of GalXC lipid conjugates as demonstrated in Scheme 1 (C16, C18, C22 and C24) were generated. To investigate these test articles, Pan02 murine pancreatic tumor cells were implanted in nude mice. When the tumors reached a volume of 300-400 mm^3, the mice were randomized into groups and treated with either a single dose of PBS or a GalXC lipid conjugate (C16, C18, C22 and C24) at 25 mg/kg. Target knockdown was assessed on day 3 in bulk tumor and in liver **(FIGs. 8A and 8B)** to identify a GalXC lipid a conjugate with selectivity towards the target tissue (MDSCs) as compared to normal liver tissue. On day 3 post dose, *Aldh2* mRNA levels in the tumors of all the treatment groups were decreased to a similar degree. There was a trend observed in the *Aldh2* levels in livers of GalXC-ALDH2-lipid conjugate groups of a correlation of higher lipid acyl chain length with lower target knockdown (C24>C22>C18>C16), suggesting that these conjugates may use different mechanisms to traffic to TME versus Liver. Since the shorter lipid acyl chain conjugates C16 and C18 seem to be more liver sparing without compromising TME activity, as compared to longer acyl chain conjugates C22 and C24, the C16/C18 lipid conjugates were further explored in a separate study to further characterize their activity. Pan02 tumor bearing mice were treated with a single subcutaneous dose of GalXC-ALDH2- C16 or GalXC-ALDH-C18 at 25 mg/kg, or PBS and activity was monitored in bulk tumor tissue and TdLN on days 7 and 14. As shown in **FIGs. 8C and 8D**, the C18 conjugate outperformed C16 in target knockdown in bulk tumor at both time points. Although both test articles showed similar activity in TdLN on day 7, the C16 conjugate mediated activity was significantly reduced on day14 while C18 mediated activity was maintained. Based on these data, the GalXC-ALDH2-C18 conjugate was selected for further studies.

Example 7: Differences in the Onset of Activity and Dose-dependence in Myeloid Derived Suppressor Cell Subsets

[00561] While it has been demonstrated GalXC-ALDH2-lipid conjugates mediate delivery and silence the *Aldh2* gene in $CD11b^+$ cells, it is critical to determine whether knockdown is mediated in either of the cell types or in both subsets of cells. Since these cell population subsets use different mechanisms to exert immune suppressive activity, it is important to identify which cell populations the GalXC lipid conjugates show activity toward to identify appropriate therapeutic targets. As demonstrated in the literature, signaling through GM-CSF along with STAT3 or STAT5 plays a key role in recruiting granulocytic-MDSCs (G-MDSCs) to the TME and is heavily involved in their expansion and suppression by increasing the FATP2 receptors (SLC27A2; gene encoding FATP2) on G-MDSC and allowing for efficient uptake of long chain fatty acids. according to recent findings (Veglia et al, NATURE (2019) 569:73–78(2019), one of the fatty acids, arachidonic acid, when metabolized to PGE_2 by COX-2 enzyme (gene encoding COX-2; PTGS2), is involved in T-cell suppression. Monocytic MDSCs (M-MDSCs), on the other hand, are also recruited to the TME from bone marrow where they become suppressive. M-MDSCs are known to have a higher-level expression of lipid trafficking receptors such as SCARB1 and LDLR that are likely to be involving in lipid uptake. Once each of the myeloid cell subsets become suppressive, they heavily express suppression associated markers such as ARG1, TGFβ, IDO, ROS and many others.

[00562] To determine whether the GalXC lipid conjugates mediate knockdown in either G-MDSC or M-MDSC cells or both, the gentle MACS magnetic separation method was used to isolate these cells as outlined for CD11b cell separation. As described above, a single cell suspension of tumor was made using gentle MACS dissociator. The $Ly\text{-}6G^+$ fraction (or G-MDSC) was then isolated from the single cell suspension by magnetically labeling the Ly6G+ cells with MACS microbeads and passing through MACS columns and subsequently eluting the labeled cells as positively selected fractions. For separation of M-MDSCs ($Ly6G^-Gr\text{-}1^+$), the $Gr\text{-}1^+$ cells present in the remaining flow through after Ly6G separation were magnetically labeled with MACS microbeads and passed through MACS columns to isolate the pure fraction by positive selection (Miltenyi Biotec Inc, Auburn CA, MDSC kit Cat # 130-094-538). Through multiple positive and negative selection steps, pure MDSC subpopulations were isolated. These isolated populations were characterized by measuring multiple key markers that

are expressed when G-MDSCs are differentiated from M-MDSCs as demonstrated in **FIGs. 9 and 10**. mRNA markers *Ly6G, CxCr2, Slc27a2* and *Ptgs2* are preferentially expressed by G-MDSCs and not by M-MDSCs. Expression of specific markers such as *CxCr2, Scl27a2* and *Ptgs2* suggest the recruitment and suppression activity of G-MDSCs in the TME. Likewise, mRNA markers *Ly6C, Scarb1*, *Ldlr* and *Arg1* are highly expressed by M-MDSCs (**FIGs. 11 and 12**) compared to G-MDSCs. Higher expression of lipid trafficking receptors such as Scarb1 and Ldlr in M-MDSCs may play key role in lipid uptake. These mRNA marker profiles of isolated cell subpopulations were found to be consistent with the literature.

[00563] To identify in which cell populations knockdown can be mediated, Pan02 tumors were grown in nude mice as described in Example 3. After randomization into treatment groups mice received a single dose of either with GalXC-ALDH2-C18 at 25 mg/kg or a PBS control. At 3 days post treatment, tumors were collected, and the G-MDSC and M-MDSC populations were isolated. qPCR was used to determine the target mRNA levels. At this dose level, ~40% *Aldh2* mRNA knockdown was observed in only the G-MDSC subset and not in the M-MDSC subset. A follow-up study conducted in the same manner with a different tumor model, B16F10 (murine melanoma tumor) was performed to assess target knockdown pattern across tumor types. B16F10 tumors were implanted into nude mice as in Example 3 and when the tumors reached a volume of ~300 mm^3 size, the mice were randomized into treatment groups and treated with a single dose of the GalXC-ALDH2-C18 conjugate at 25 mg/kg, or PBS. At 3 days post treatment, mRNA levels were analyzed as described previously. As shown in **FIGs. 13A and 13B**, *Aldh2* knockdown was observed only in G-MDSCs collected from both Pan02 and B16F10 tumors. To understand further how the dose level of GalXC lipid conjugate plays a role in delivery, the higher dose of 50 mg/kg was included in Pan02 tumor bearing mice and target knockdown was monitored on days 3 and 7. As shown in **FIG. 13C**, at a higher dose, the target knockdown in the G-MDSC population remained the same as the knockdown observed with 25 mg/kg. In addition, there was roughly 50% knockdown observed in the M-MDSC subset as well. The activity in each cell subset was maintained for a week post dose (**FIG. 13D**) suggesting that the delivery could be happening to G-MDSC first, likely through the FATP2 receptors, and once that population is saturated delivery shifts to the M-MDSCs (through Scarb1 and Ldlr) to mediate knockdown in this cell type. This suggests that the onset of activity and dose dependence maybe different between these two MDSC cell subsets.

Example 8: Tissue Specific Targets in MDSC Cell Populations and Tumor Draining Lymph Nodes.

[00564] The data above demonstrate that the two MDSC subsets mediate immune suppression through different mechanisms. While CXCR2, SCL27A2 and PTGS2 are identified as specific potential targets on G-MDSCs, and PD-L1 would be a more specific target for cells residing in the TdLN, there are few targets that are expressed on both subsets of MDSC cells in the TME and cell types residing in TdLN. STAT3 is one such target that is expressed in all tissues of interest (i.e., tumor cells and immune cells in the tumor microenvironment). Expression of STAT3 was measured in Pan02 tumors (**FIGs. 14A-14C**). STAT3 is involved in immune suppression with examples abundantly reported in literature. Targeting *STAT3* transcription through an RNAi mechanism could potentially overcome the challenges in the development of pharmacological STAT3 inhibitors. For these reasons STAT3 was selected as a proof-of-concept target to demonstrate tissue specific activity in the tissues of interest. *STAT3* sequences were designed in the GalXC format with described modification patterns and screening for target knockdown in liver tissue was performed in normal CD-1 mice. Eighteen STAT3-GalXC conjugates (**Table 3**) were dosed once subcutaneously at 3 mg/kg.

Table 3: **GalXC Compound Candidates for Identifying Tool Compounds for Proof-of-concept Studies in Mice:**

Oligo	DP #	Sequence Type	Sense strand SEQ ID NO	Antisense strand SEQ ID NO	Conjugate
GalXC-STAT3-838	DP21679P: DP21678G	Unmodified	9	10	GalNAc
		Modified	11	12	GalNAc
GalXC-STAT3-1390	DP21697P: DP21696G	Unmodified	13	14	GalNAc
		Modified	15	16	GalNAc
GalXC-STAT3-1394	DP21677P: DP21676G	Unmodified	17	18	GalNAc
		Modified	19	20	GalNAc
GalXC-STAT3-1398	DP21691P: DP21690G	Unmodified	21	22	GalNAc
		Modified	23	24	GalNAc
GalXC-STAT3-1399	DP21671P: DP21670G	Unmodified	25	26	GalNAc
		Modified	27	28	GalNAc

GalXC-STAT3-1400	DP21673P: DP21672G	Unmodified	29	30	GalNAc
		Modified	31	32	GalNAc
GalXC-STAT3-1401	DP21687P: DP21686G	Unmodified	33	34	GalNAc
		Modified	35	36	GalNAc
GalXC-STAT3-1402	DP21675P: DP21674G	Unmodified	37	38	GalNAc
		Modified	39	40	GalNAc
GalXC-STAT3-1759	DP21701P: DP21700G	Unmodified	41	42	GalNAc
		Modified	43	44	GalNAc
GalXC-STAT3-2029	DP21689P: DP21688G	Unmodified	45	46	GalNAc
		Modified	47	48	GalNAc
GalXC-STAT3-2034	DP21693P: DP21692G	Unmodified	49	50	GalNAc
		Modified	51	52	GalNAc
GalXC-STAT3-2448	DP21699P: DP21698G	Unmodified	53	54	GalNAc
		Modified	55	56	GalNAc
GalXC-STAT3-2527	DP21695P: DP21694G	Unmodified	57	58	GalNAc
		Modified	59	60	GalNAc
GalXC-STAT3-4107	DP21683P: DP21682G	Unmodified	61	62	GalNAc
		Modified	63	64	GalNAc
GalXC-STAT3-4110	DP21669P: DP21668G	Unmodified	65	66	GalNAc
		Modified	67	68	GalNAc
GalXC-STAT3-4123	DP21667P: DP21666G	Unmodified	69	70	GalNAc
		Modified	71	72	GalNAc
GalXC-STAT3-4435	DP21685P: DP21684G	Unmodified	73	74	GalNAc
		Modified	75	76	GalNAc
GalXC-STAT3-4474	DP21681P: DP21680G	Unmodified	77	78	GalNAc
		Modified	79	80	GalNAc

Modification Key for Table 3

Symbol	**Modification/linkage**
mX	2'-*O*-methyl modified nucleotide
fX	2'- fluoro modified nucleotide
-*S*-	phosphorothioate linkage
-	phosphodiester linkage
[MePhosphonate-4O-mX]	4'-O-monomethylphosphonate-2'-O-methyl modified nucleotide
ademX-GalNAc	2′-aminodiethoxymethanol-nucleotide-GalNAc (GalNAc-conjugated nucleotide)

[00565] Five days post injection, livers were collected and subjected to mRNA analysis by qPCR. As a result of the screen, four sequences (GalXC -STAT3-838, GalXC-STAT3-1402, GalXC-STAT3-4110 and GalXC-STAT3-4123) that showed >85% target knockdown in liver were selected for further evaluation (**FIG. 15A**). Of these sequences three were identified as mouse specific and one was identified as human-mouse cross-reactive. These 4 sequences were further screened in CD-1 mice at 3 different doses (0.3, 1 and 3 mg/kg) to assess the dose response. GalXC-STAT3-4110 and 4123 were identified as the most potent sequences after the dose response screen, each with ED_{50} of 0.3 mg/kg and thus these molecules were selected for further studies (**FIG. 15B**). C18 lipid conjugation was performed for both GalXC-STAT3-4110 or 4123 for proof-of-concept studies (**Table 4**).

Table 4: **GalXC-STAT3 Lipid Conjugates**

SEQ ID	Oligonucleotide	Sequence Type	Ligand
81	GalXC-STAT3-4110-C18	Modified Sense strand	C18
82		Modified Antisense strand	C18
83	GalXC-STAT3-4123-C18	Modified Sense strand	C18
84		Modified Antisense strand	C18

Table 5: GalXC-STAT3 Lipid Conjugates

Oligo	Sequence Type	Sense strand SEQ ID NO	Antisense strand SEQ ID NO	Conjugate
GalXC-STAT3-4110-C18	Unmodified	65	66	C18
	Modified	67	68	C18
GalXC-STAT3-4123-C18	Unmodified	69	70	C18
	Modified	71	72	C18

Modification Key for Tables 2, 4 and 5

Symbol	Modification/linkage
mX	2'-*O*-methyl modified nucleotide

fX	2'- fluoro modified nucleotide
-*S*-	phosphorothioate linkage
-	phosphodiester linkage
[MePhosphonate-4O-mX]	4'-O-monomethylphosphonate-2'-O-methyl modified nucleotide
ademX-C#	2′-aminodiethoxymethanol-nucleotide-hydrocarbon chain (Lipid conjugate attached to a nucleotide (e.g. C16 or C18))

[00566] To evaluate the performance of GalXC-STAT3-C18 conjugates, Pan02 tumors were implanted in nude mice and upon reaching sufficient tumor volume mice were subjected to randomization as previously described. Mice received either a single dose of GalXC-STAT3-C18 4110 and 4123 subcutaneously at 25 mg/kg, 50 mg/kg, or PBS. At 3 days post injection, bulk tumors were collected. MDSC subsets were isolated as described in Example 5 and target mRNA was analyzed by qPCR (**FIGs. 16A and 16B**). *Stat3* mRNA levels were reduced by ~40% in G-MDSC and M-MDSCs by GalXC-STAT3-C18-4123. GalXC-STAT3-C18-4110 reduced the *Stat3* mRNA levels only by 20% in both MDSC subsets. It is worth noting that the *Aldh2* levels were reduced only in G-MDSC by the GalXC-ALDH2-lipid conjugates at the given dose and time point and the level of knockdown was comparable to the reduction of *Stat3* levels in G-MDSC that were observed in the current experiment. *Stat3* levels in M-MDSCs were reduced after GalXC-STAT3-C18 as compared to no reduction of *Aldh2* levels in M-MDSC after GalXC-ALDH2-lipid conjugate treatment. The higher overall *Aldh2* expression levels in M-MDSC compared to *Stat3* levels may explain the difference in activity.

[00567] To understand how the dose level of GalXC-STAT3-C18 conjugates plays a role in trafficking of these molecules to different tissues and cell subsets, a follow-up study was performed as previously described with the same tumor model. Pan02 tumor bearing mice were treated with a single subcutaneous dose of either GalXC-STAT3-C18-4123 at 50 mg/kg, or PBS and *Stat3* mRNA levels were measured after 3 days. The *Stat3* knockdown in G-MDSC was not significantly altered as compared to the knockdown observed at the 25 mg/kg dose, however there was a significant improvement in *Stat3* silencing observed in M-MDSC subset at this same dose level. In parallel study performed as previously described, *Stat3* knockdown was assessed in bulk tumors and TdLNs on day 7 (**FIGs. 17A and 17B**). Dose dependent *Stat3* mRNA knockdown was observed in bulk tumor with both GalXC-STAT3-C18 sequences. In TdLNs *Stat3* mRNA levels were reduced by ~60-65% by GalXC-STAT3-C18-4123, ~25-30% by

GalXC-STAT3-C18-4110 at both doses suggesting a saturation effect at these dose levels. Based on the data, GalXC-STAT3-C18-4123 was selected for further efficacy evaluations in immunocompetent mice.

Example 9: STAT3 Inhibition Decreases the PD-L1 Levels in MDSCs and Mediates Acute Tumor Effects

[00568] The transcriptional signature of phosphorylated STAT3 has been positively correlated with PD-L1 expression in tumors (Song et al, JOURNAL OF CELL PHYSIOLOGY (2020), Zerdes et al, CANCERS (2019), Song et al, BLOOD (2018). To extrapolate this correlation to STAT3 expressed by MDSCs, isolated populations of MDSCs treated with either PBS or a GalXC-STAT3 conjugate were assayed for *Pdl1* mRNA. *Pdl1* mRNA levels were decreased by ~80% in both G-MDSC and M-MDSC populations treated with either 25 or 50 mg/kg of a GalXC-STAT3 (**FIG. 18A**). The *Pdl1* levels were also dramatically reduced in TdLN after treatment with the GalXC-STAT3 conjugate, specifically GalXC-STAT3-C18-4123 (**FIG. 18B**). These data suggest a potential for downstream immunomodulation of PD-L1 after knockdown of STAT3.

[00569] In a separate study, a Pan02 (murine pancreatic syngeneic model) tumor bearing C57BL/6 mice (n=4 per group) were treated subcutaneously with GalXC-STAT3-C18 conjugate following a split dosing model where all animals received a total dose of 50 mg/kg, dosed as either 25 mg/kg x 2 doses or 12.5 mg/kg x 4 doses. Tumors treated using the 25 mg/kg split dose showed acute tumor regression, even after the first dose (**FIG. 19B**). After the second dose of 25 mg/kg, tumors from 3 out of 4 mice regressed to sizes that were too small to be collected for further processing. The anti-tumor effect of the GalXC-STAT3 treatment was also observed in mice that received the 12.5 mg/kg split doses (**FIG. 19A**). These data suggest that STAT3 mediated regulation of PD-L1 results in an acute and dramatic effect on tumor growth in the Pan02 tumor bearing immunocompetent mice.

Example 10: Preparation of Double-Stranded RNAi Oligonucleotides

Oligonucleotide Synthesis and Purification

[00570] The double-stranded RNAi (dsRNA) oligonucleotides described in the foregoing Examples were chemically synthesized using methods described herein. Generally, dsRNAi

oligonucleotides were synthesized using solid phase oligonucleotide synthesis methods as described for 19-23mer siRNAs (*see, e.g.*, Scaringe *et al.* (1990) NUCLEIC ACIDS RES.. 18:5433-41 and Usman *et al.* (1987) J. AM. CHEM. SOC. 109:p,7845; *see also*, US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,008,400; 6,111,086; 6,117,657; 6,353,098; 6,362,323; 6,437,117 and 6,469,158) in addition to using known phosphoramidite synthesis (*see, e.g.* Hughes and Ellington (2017) COLD SPRING HARB PERSPECT BIOL. 9(1):a023812; Beaucage S.L., Caruthers M.H. *Studies on Nucleotide Chemistry V: Deoxynucleoside Phosphoramidites—A New Class of Key Intermediates for Deoxypolynucleotide Synthesis.* TETRAHEDRON LETT. 1981;22:1859–62. doi: 10.1016/S0040-4039(01)90461-7). dsRNAi oligonucleotides having a 19mer core sequence were formatted into constructs having a 25mer sense strand and a 27mer antisense strand to allow for processing by the RNAi machinery. The 19mer core sequence is complementary to a region in the *STAT3* mRNA.

[00571] Individual RNA strands were synthesized and HPLC purified according to standard methods (Integrated DNA Technologies; Coralville, IA). For example, RNA oligonucleotides were synthesized using solid phase phosphoramidite chemistry, deprotected and desalted on NAP-5 columns (Amersham Pharmacia Biotech; Piscataway, NJ) using standard techniques (Damha & Olgivie (1993) METHODS MOL. BIOL. 20:81-114; Wincott *et al.* (1995) NUCLEIC ACIDS RES. 23:2677-2684). The oligomers were purified using ion-exchange high performance liquid chromatography (IE-HPLC) on an Amersham Source 15Q column (1.0 cm×25 cm; Amersham Pharmacia Biotech) using a 15 min step-linear gradient. The gradient varied from 90:10 Buffers A:B to 52:48 Buffers A:B, where Buffer A is 100 mM Tris pH 8.5 and Buffer B is 100 mM Tris pH 8.5, 1 M NaCl. Samples were monitored at 260 nm and peaks corresponding to the full-length oligonucleotide species were collected, pooled, desalted on NAP-5 columns, and lyophilized.

[00572] The purity of each oligomer was determined by capillary electrophoresis (CE) on a Beckman PACE 5000 (Beckman Coulter, Inc.; Fullerton, CA). The CE capillaries have a 100 μm inner diameter and contain ssDNA 100R Gel (Beckman-Coulter). Typically, about 0.6 nmole of oligonucleotide was injected into a capillary, run in an electric field of 444 V/cm and was detected by UV absorbance at 260 nm. Denaturing Tris-Borate-7 M-urea running buffer was purchased from Beckman-Coulter. Oligoribonucleotides were obtained that were at least 90% pure as assessed by CE for use in experiments described below. Compound identity was

verified by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectroscopy on a Voyager DE™ Biospectometry Work Station (Applied Biosystems; Foster City, CA) following the manufacturer's recommended protocol. Relative molecular masses of all oligomers were obtained, often within 0.2% of expected molecular mass.

Preparation of Duplexes

[00573] Single strand RNA oligomers were resuspended (*e.g.,* at 100 μM concentration) in duplex buffer consisting of 100 mM potassium acetate, 30 mM HEPES, pH 7.5. Complementary sense and antisense strands were mixed in equal molar amounts to yield a final solution of, for example, 50 μM duplex. Samples were heated to 100°C for 5′ in RNA buffer (IDT) and were allowed to cool to room temperature before use. The dsRNA oligonucleotides were stored at −20° C. Single strand RNA oligomers were stored lyophilized or in nuclease-free water at −80° C.

Example 11: **Generation of *STAT3*-Targeting Double-Stranded RNAi Oligonucleotides**

Identification of STAT3 mRNA Target Sequences

[00574] Signal transducer and activator of transcription 3 (STAT3) is a transcription factor involved in several development and disease functions. To generate RNAi oligonucleotide inhibitors of *STAT3* expression, a computer-based algorithm was used to computationally identify *STAT3* mRNA target sequences suitable for assaying inhibition of *STAT3* expression by the RNAi pathway. The algorithm provided RNAi oligonucleotide guide (antisense) strand sequences each having a region of complementarity to a suitable *STAT3* target sequence of human *STAT3* mRNA (e.g., SEQ ID NO:1217; **Table 6).** Some of the guide strand sequences identified by the algorithm were also complementary to the corresponding *STAT3* target sequence of monkey *STAT3* mRNA (SEQ ID NO: 1218 **Table 6**) and/or mouse *STAT3* mRNA. *STAT3* RNAi oligonucleotides comprising a region of complementarity to homologous *STAT3* mRNA target sequences with nucleotide sequence similarity are predicted to have the ability to target homologous *STAT3* mRNAs.

Table 6: Sequences of Human and Monkey *STAT3* mRNA

Species	**Ref Seq #**	**SEQ ID NO**
Human (Hs)	NM_139276.3	1217
M. Fascicularis (Mf)	XM_005584240.2	1218
Mus Musculus (Mm)	NM_213659.3	1229

[00575] RNAi oligonucleotides (formatted as DsiRNA oligonucleotides) were generated as described in **Example 10** for evaluation *in vitro*. Each DsiRNA was generated with the same modification pattern, and each with a unique guide strand having a region of complementarity to a *STAT3* target sequence identified by SEQ ID NOs: 89-280. Modifications for the sense and anti- sense DsiRNA included the following (*X*- any nucleotide ; *m*- 2'-O-methyl modified nucleotide; *r*- ribosyl modified nucleotide):

Sense Strand:

rXmXrXmXrXrXrXrXrXrXrXrXrXmXrXmXrXrXrXrXrXrXrXXX

Anti-sense Strand:

mXmXmXmXrXrXrXrXrXrXmXrXmXrXrXrXrXrXrXrXrXrXmXrXmXmXmX

[00576] The ability of each of the modified DsiRNA in **Table 7** to reduce *STAT3* mRNA was measured using *in vitro* cell-based assays. Briefly, human hepatocyte (Huh7) cells expressing endogenous human *STAT3* gene were transfected with each of the DsiRNAs listed in **Table 7** at 1 nM in separate wells of a multi-well cell-culture plate. Cells were maintained for 24 hours following transfection with the modified DsiRNA, and then the amount of remaining *STAT3* mRNA from the transfected cells was determined using TAQMAN®-based qPCR assays. Two qPCR assays, a 3′ assay and 5' assay (Forward 1- SEQ ID NO:1219), Reverse 1- SEQ ID NO:1220, Probe 1- SEQ ID NO: 1221; Forward 2- SEQ ID NO: 1222, Reverse 2- SEQ ID NO: 1223, Probe 2- SEQ ID NO: 1224) were used to determine *STAT3* mRNA levels as measured using PCR probes conjugated to 6-carboxy-fluorescein (FAM). Each primer pair was assayed for % remaining RNA as shown in **Table 7 and FIG. 20.** DsiRNAs resulting in less than or equal to 10% *STAT3* mRNA remaining in DsiRNA-transfected cells when compared to mock-transfected

cells were considered DsiRNA "hits". The Huh7 cell-based assay evaluating the ability of the DsiRNAs listed in **Table 7** to inhibit *STAT3* expression identified several candidate DsiRNAs.

[00577] Taken together, these results show that DsiRNAs designed to target human *STAT3* mRNA inhibit *STAT3* expression in cells, as determined by a reduced amount of *STAT3* mRNA in DsiRNA-transfected cells relative to control cells. These results demonstrate that the nucleotide sequences comprising the DsiRNA are useful for generating RNAi oligonucleotides to inhibit *STAT3* expression. Further, these results demonstrate that multiple *STAT3* mRNA target sequences are suitable for the RNAi-mediated inhibition of *STAT3* expression.

Table 7. Analysis of STAT3 mRNA in Huh7 cells

			Average		***STAT3*-5' Assay**		***STAT3*-3' Assay**	
SED ID NO (Sense Strand)	**SED ID NO (Anti-sense Strand)**	**DsiRNA name**	**% remain-ing**	**SEM**	**% remain-ing**	**SEM**	**% remai n-ing**	**SEM**
473	665	370	51.9	3.7	61.8	4.0	41.9	3.3
474	666	372	12.0	1.3	12.3	1.5	11.7	1.2
475	667	424	5.9	1.5	5.3	1.7	6.5	1.2
476	668	425	4.4	1.0	4.7	0.8	4.2	1.2
477	669	426	4.6	1.2	2.1	1.0	7.2	1.5
478	670	429	5.5	1.0	4.2	0.6	6.9	1.3
479	671	430	19.0	3.9	19.3	5.0	18.7	2.7
480	672	432	8.8	2.5	13.3	4.2	4.4	0.8
481	673	433	27.6	2.9	27.6	3.6	27.5	2.2
482	674	460	20.1	3.1	24.5	3.7	15.6	2.5
483	675	461	12.9	1.9	12.4	2.0	13.5	1.9
484	676	462	32.2	2.9	32.7	2.9	31.6	2.9
485	677	492	33.8	2.3	30.3	1.6	37.3	3.0
486	678	678	11.7	2.0	11.7	2.3	11.8	1.6
487	679	681	12.5	2.3	10.4	2.0	14.6	2.5
488	680	715	9.5	0.8	10.4	0.9	8.7	0.7
489	681	716	11.2	1.1	12.5	1.4	9.9	0.7
490	682	717	8.4	1.5	8.0	1.4	8.7	1.6
491	683	720	11.4	1.7	12.4	1.8	10.4	1.5
492	684	721	7.5	0.9	7.3	0.8	7.6	0.9
493	685	722	13.3	2.0	13.5	2.1	13.1	2.0
494	686	723	16.7	3.2	18.9	4.5	14.4	1.9
495	687	724	13.6	1.7	14.2	2.0	12.9	1.5
496	688	768	12.1	2.0	13.1	2.2	11.0	1.8

497	689	771	43.2	3.9	38.4	3.3	48.0	4.6
498	690	773	142.6	42.3	138.3	44.1	146.9	40.4
499	691	1000	19.3	2.9	22.0	3.9	16.5	2.0
500	692	1001	12.1	1.6	13.3	1.7	11.0	1.4
501	693	1003	51.3	6.5	62.8	8.3	39.8	4.7
502	694	1006	13.0	3.9	12.3	4.2	13.6	3.7
503	695	1008	93.5	12.0	90.0	13.1	96.9	11.0
504	696	1009	30.1	3.2	29.9	3.7	30.4	2.8
505	697	1010	22.1	3.5	22.7	4.4	21.5	2.6
506	698	1047	43.7	6.3	45.8	6.8	41.6	5.7
507	699	1067	15.3	1.3	16.0	1.5	14.5	1.1
508	700	1068	3.6	0.7	2.5	0.8	4.8	0.7
509	701	1145	9.2	2.2	8.4	2.5	9.9	1.8
510	702	1151	12.4	2.1	13.0	2.4	11.9	1.9
511	703	1241	6.7	1.9	8.3	1.9	5.1	1.8
512	704	1268	14.3	3.0	15.6	3.8	13.0	2.2
513	705	1272	85.2	16.3	104.4	20.9	66.1	11.8
514	706	1273	15.1	3.3	17.3	3.9	12.8	2.7
515	707	1275	14.7	1.7	13.7	1.8	15.8	1.7
516	708	1277	21.7	2.0	22.5	1.7	20.9	2.3
517	709	1278	10.8	1.4	9.4	1.9	12.1	0.9
518	710	1279	6.8	0.7	6.3	0.7	7.3	0.8
519	711	1280	9.9	1.0	8.2	1.0	11.5	1.0
520	712	1281	8.6	1.1	6.7	0.9	10.5	1.4
521	713	1282	17.0	1.9	15.8	1.6	18.1	2.1
522	714	1283	12.8	1.5	11.3	1.4	14.2	1.7
523	715	1284	7.8	1.0	6.2	0.8	9.4	1.3
524	716	1286	5.5	0.4	3.9	0.5	7.0	0.4
525	717	1287	5.1	0.6	4.6	0.9	5.6	0.3
526	718	1292	6.4	0.8	5.3	0.6	7.6	1.1
527	719	1293	7.3	0.8	5.9	0.9	8.7	0.6
528	720	1299	33.4	3.0	35.8	2.7	30.9	3.2
529	721	1305	27.5	1.9	26.7	0.6	28.3	3.1
530	722	1383	20.8	2.2	17.4	2.3	24.3	2.1
531	723	1388	4.0	0.8	1.6	0.6	6.3	0.9
532	724	1427	11.0	1.5	8.6	2.0	13.3	1.0
533	725	1485	11.6	2.3	12.4	2.1	10.8	2.6
534	726	1584	80.0	7.3	80.7	8.2	79.4	6.5
535	727	1586	22.0	2.8	18.6	2.6	25.4	3.0
536	728	1670	4.0	0.5	2.6	0.4	5.4	0.6
537	729	1671	9.9	2.6	10.8	3.1	8.9	2.1
538	730	1672	2.8	0.8	3.6	1.2	2.1	0.5
539	731	1673	3.7	0.9	3.1	1.0	4.2	0.9
540	732	1674	5.2	1.5	5.0	1.7	5.4	1.3
541	733	1676	11.5	2.3	13.0	2.1	10.1	2.4

542	734	1813	8.8	2.1	6.9	2.2	10.7	2.0
543	735	1815	7.0	1.9	8.9	2.7	5.0	1.1
544	736	1817	21.2	3.5	22.8	3.6	19.6	3.5
545	737	1819	13.3	1.9	15.0	1.9	11.5	1.8
546	738	1904	58.3	7.3	73.2	8.7	43.4	5.9
547	739	1906	24.6	3.5	30.2	3.8	18.9	3.2
548	740	1907	9.7	1.4	9.4	1.9	9.9	0.9
549	741	1908	9.0	1.4	9.2	1.5	8.9	1.3
550	742	1909	68.6	6.7	79.9	7.5	57.4	6.0
551	743	1910	4.3	0.6	3.3	0.6	5.4	0.6
552	744	1911	20.4	1.6	20.6	1.7	20.2	1.6
553	745	1912	15.6	1.6	16.6	2.4	14.7	0.8
554	746	1913	9.4	1.0	10.1	0.9	8.8	1.1
555	747	1914	46.2	3.6	52.5	4.2	39.8	3.0
556	748	1916	12.9	2.0	13.3	2.2	12.4	1.7
557	749	1917	13.3	1.4	13.4	1.5	13.3	1.3
558	750	1919	45.6	5.5	54.0	7.0	37.1	4.0
559	751	1920	47.5	2.8	49.9	2.3	45.1	3.4
560	752	2024	27.1	5.9	29.5	7.1	24.7	4.6
561	753	2135	35.1	3.7	37.4	3.4	32.8	3.9
562	754	2136	8.6	2.1	6.9	2.0	10.3	2.2
563	755	2138	54.0	12.5	49.8	16.5	58.1	8.5
564	756	2139	2.9	0.6	2.8	0.7	3.1	0.6
565	757	2143	53.2	9.7	67.0	11.8	39.3	7.7
566	758	2144	6.2	1.6	5.1	1.3	7.2	1.9
567	759	2145	21.4	2.1	23.1	2.2	19.8	2.0
568	760	2146	55.3	5.0	56.7	6.3	54.0	3.7
569	761	2147	18.2	1.9	15.6	1.4	20.8	2.4
570	762	2148	20.2	2.5	20.7	3.1	19.8	1.9
571	763	2151	36.9	3.0	33.2	2.0	40.7	3.9
572	764	2153	17.1	1.9	17.3	2.2	17.0	1.6
573	765	2154	13.7	1.3	13.9	1.6	13.6	0.9
574	766	2159	33.6	2.2	29.7	1.9	37.5	2.6
575	767	2322	20.1	1.8	21.3	2.5	18.8	1.2
576	768	2325	20.6	2.6	23.7	2.7	17.5	2.5
577	769	2327	12.1	1.4	11.8	1.4	12.4	1.4
578	770	2329	36.8	3.0	40.3	3.3	33.4	2.8
579	771	2333	18.9	3.1	18.5	4.2	19.4	2.0
580	772	2335	12.5	1.9	10.1	1.8	14.9	2.1
581	773	2404	9.8	2.2	8.7	3.0	10.8	1.3
582	774	2405	6.1	1.3	5.9	1.1	6.4	1.4
583	775	2407	36.0	2.7	33.2	2.6	38.9	2.9
584	776	2408	9.3	2.0	8.6	1.9	10.0	2.0
585	777	2411	43.2	3.7	46.9	3.7	39.6	3.6
586	778	2412	6.1	1.2	5.3	1.4	7.0	1.0

587	779	2413	36.9	5.5	39.0	5.8	34.8	5.3
588	780	2416	28.6	4.9	30.4	5.6	26.7	4.2
589	781	2418	15.5	1.9	15.0	2.1	16.0	1.7
590	782	2422	81.2	10.1	84.5	11.5	77.9	8.8
591	783	2427	45.3	7.7	53.2	9.4	37.3	5.9
592	784	2612	64.9	11.5	79.1	14.0	50.6	9.0
593	785	2615	153.3	24.5	170.0	27.8	136.6	21.1
594	786	2616	37.3	3.8	40.0	4.5	34.5	3.1
595	787	2617	28.9	4.1	30.8	4.8	27.0	3.3
596	788	2622	94.8	6.4	91.1	5.7	98.5	7.1
597	789	2625	60.0	4.2	53.6	3.9	66.4	4.4
598	790	2626	43.4	2.9	41.3	2.6	45.5	3.1
599	791	2627	17.1	1.0	15.0	0.6	19.2	1.4
600	792	2692	14.2	1.9	14.0	1.6	14.3	2.1
601	793	2693	13.6	1.4	14.0	1.4	13.2	1.5
602	794	2715	24.9	1.8	23.5	1.9	26.2	1.8
603	795	2719	28.7	2.3	28.2	2.6	29.3	2.0
604	796	2721	32.2	2.3	33.2	2.0	31.1	2.6
605	797	2735	39.4	2.2	36.7	1.7	42.0	2.6
606	798	2741	31.3	3.9	34.6	4.1	28.1	3.8
607	799	2801	31.4	2.7	33.7	3.3	29.0	2.1
608	800	2803	26.5	1.9	29.8	2.1	23.1	1.7
609	801	2804	37.3	2.2	40.7	2.4	33.9	2.1
610	802	2806	77.7	5.2	77.1	5.0	78.2	5.3
611	803	2807	60.9	4.2	65.4	4.7	56.3	3.8
612	804	2808	44.7	2.9	45.9	3.5	43.5	2.4
613	805	2809	41.7	1.9	41.0	1.9	42.3	1.8
614	806	2810	28.6	2.9	28.3	3.1	28.8	2.6
615	807	2811	58.2	3.1	62.4	4.1	54.0	2.1
616	808	2812	44.4	2.3	50.1	2.4	38.7	2.2
617	809	2813	26.7	1.6	30.0	1.8	23.5	1.3
618	810	2846	26.4	2.3	27.8	2.1	25.0	2.5
619	811	2848	30.9	1.4	31.3	1.4	30.5	1.5
620	812	2849	28.5	2.8	29.6	3.0	27.4	2.7
621	813	2850	46.7	3.4	48.2	3.5	45.2	3.4
622	814	2851	28.7	3.3	28.0	3.3	29.4	3.3
623	815	2852	25.0	4.1	20.3	4.2	29.8	3.9
624	816	2853	109.6	6.9	109.9	6.6	109.2	7.1
625	817	2854	79.0	7.6	73.6	6.4	84.3	8.7
626	818	2855	53.0	8.6	44.8	7.4	61.1	9.8
627	819	2856	101.8	31.5	115.1	38.1	88.4	24.9
628	820	2857	39.3	10.0	47.1	9.7	31.6	10.3
629	821	2858	41.4	5.1	38.8	4.0	44.0	6.2
630	822	2859	29.8	7.4	31.1	7.5	28.5	7.3
631	823	2860	27.2	6.4	19.8	5.9	34.6	6.9

632	824	2861	30.8	3.8	29.5	5.0	32.1	2.6
633	825	2862	38.3	8.0	37.1	6.5	39.6	9.6
634	826	2863	33.5	8.0	29.4	6.2	37.6	9.8
635	827	2865	50.2	15.0	48.2	12.7	52.1	17.2
636	828	2867	27.3	4.0	25.0	3.8	29.6	4.1
637	829	2868	47.0	13.0	32.6	10.1	61.4	16.0
638	830	2975	30.7	6.7	30.6	6.7	30.9	6.8
639	831	2979	37.2	9.9	39.7	11.8	34.8	8.1
640	832	2985	48.7	13.2	28.0	12.3	69.3	14.2
641	833	3025	39.6	5.1	33.9	4.6	45.3	5.6
642	834	3037	49.0	10.8	46.3	11.5	51.7	10.1
643	835	3038	42.1	8.1	36.0	6.6	48.2	9.6
644	836	3039	74.7	12.0	72.4	13.0	77.0	11.0
645	837	3041	54.7	11.6	54.4	11.0	54.9	12.1
646	838	3042	46.9	8.2	54.3	11.3	39.6	5.1
647	839	3043	44.9	9.5	47.5	10.3	42.2	8.8
648	840	3225	40.3	8.4	40.7	8.8	39.9	8.0
649	841	3226	41.0	12.2	34.7	11.5	47.2	12.9
650	842	3605	30.6	8.1	24.7	8.3	36.5	7.9
651	843	3611	51.3	8.2	59.5	12.2	43.1	4.1
652	844	3906	32.1	6.8	28.6	7.9	35.5	5.6
653	845	4311	37.2	8.0	41.7	7.8	32.6	8.2
654	846	4314	31.0	4.5	39.9	5.2	22.0	3.8
655	847	4317	32.1	4.8	31.9	5.3	32.3	4.3
656	848	4321	34.1	6.7	37.3	6.2	30.9	7.2
657	849	4465	46.3	11.0	48.9	11.3	43.8	10.8
658	850	4479	33.1	7.5	34.8	7.8	31.4	7.1
659	851	4480	34.7	7.3	36.0	6.7	33.5	7.9
660	852	4831	49.1	4.0	44.4	4.9	53.7	3.2
661	853	4833	87.3	14.1	75.5	11.0	99.1	17.2
662	854	4836	139.9	17.1	124.8	15.2	154.9	19.1
663	855	4837	175.2	39.6	185.9	41.5	164.5	37.7
664	856	4909	27.6	3.2	30.6	3.8	24.7	2.6
		PC (2412)	5.2	0.7	3.9	0.7	6.4	0.7

[00578] Following the initial *in vitro* screen, 48 constructs were selected for dosing studies. Huh7 cells were treated for 24 hours with 0.05nM, 0.3nM, or 1nM of oligonucleotide. mRNA was isolated and measured to determine a potent dose (**FIG. 21A**). Of the tested oligonucleotides, 34 sequences were selected for further testing *in vivo* (**Table 8** and **FIG. 21B**).

Table 8. Analysis of *STAT3* mRNA in Huh7 Dosing Study

	1nM		0.3nM		0.05nM	
	% Remaining mRNA	**Standard Deviation**	**% Remaining mRNA**	**Standard Deviation**	**% Remaining mRNA**	**Standard Deviation**
STAT3-372	18.7	2.0	62.7	7.0	81.3	20.0
STAT3-715	15.7	1.2	38.4	5.0	106.5	11.5
STAT3-716	17.6	1.3	36.1	3.4	99.3	10.2
STAT3-717	16.6	1.0	23.9	3.3	78.8	8.1
STAT3-720	18.6	2.3	33.2	4.3	111.2	9.0
STAT3-721	17.8	1.8	31.4	2.9	84.6	9.2
STAT3-722	17.8	2.4	56.3	5.4	109.4	11.7
STAT3-724	18.5	2.1	57.2	6.8	119.7	11.1
STAT3-768	15.6	2.3	36.0	4.8	78.4	10.4
STAT3-1001	14.7	2.1	36.3	5.6	88.5	13.2
STAT3-1006	25.2	3.0	48.5	5.2	105.4	14.0
STAT3-1068	10.5	2.7	40.5	4.5	144.0	37.7
STAT3-1145	15.7	2.4	29.3	4.6	61.6	4.3
STAT3-1151	19.4	2.2	31.0	3.3	103.5	7.8
STAT3-1268	19.7	1.8	33.1	3.1	101.6	10.4
STAT3-1273	16.2	1.1	37.1	3.9	93.4	9.3
STAT3-1275	29.1	2.5	61.6	21.5	89.1	8.3
STAT3-1278	22.2	5.7	67.4	7.6	98.0	8.8
STAT3-1279	15.3	2.0	44.9	5.1	83.6	7.1
STAT3-1280	19.8	1.5	37.9	4.7	85.3	10.4
STAT3-1281	20.2	2.2	36.3	4.5	71.9	7.0
STAT3-1283	21.8	2.4	58.1	9.1	78.3	16.1
STAT3-1284	18.8	2.6	42.7	9.3	75.2	8.0
STAT3-1286	15.0	2.2	61.9	33.7	86.9	19.8
STAT3-1287	13.7	2.0	33.3	10.9	85.0	36.0
STAT3-1292	17.0	2.3	43.4	4.7	88.3	10.9
STAT3-1293	15.0	2.1	32.8	3.1	72.9	7.9
STAT3-1388	11.0	2.3	34.1	2.2	111.9	28.3
STAT3-1427	23.5	2.3	78.1	5.4	90.6	15.0
STAT3-1485	24.4	2.1	62.2	3.5	114.1	12.6
STAT3-1676	31.5	4.2	54.1	4.4	102.3	9.4
STAT3-1819	28.9	3.6	47.8	2.6	82.0	6.2
STAT3-1907	29.5	3.8	51.2	3.4	96.7	13.5
STAT3-1908	32.4	3.6	47.2	3.0	86.4	10.0
STAT3-1910	15.9	2.2	43.8	4.1	91.6	19.2
STAT3-1913	16.8	3.1	50.9	4.7	106.2	20.7
STAT3-1916	27.4	3.2	57.4	3.2	153.0	18.1
STAT3-1917	21.2	2.3	53.3	2.4	117.9	27.1
STAT3-2139	9.9	3.3	29.1	3.2	91.8	15.7

STAT3-2144	16.3	2.3	34.9	2.8	105.9	37.8
STAT3-2154	23.2	2.6	37.1	3.4	113.4	24.6
STAT3-2327	18.2	1.9	25.7	4.7	76.6	31.2
STAT3-2335	30.5	3.6	49.7	4.0	84.3	28.4
STAT3-2408	19.4	2.0	29.8	3.4	74.6	16.2
STAT3-2412	17.0	4.1	30.3	1.9	105.7	29.5
STAT3-2418	24.2	4.2	42.0	4.5	90.7	28.0
STAT3-2692	17.8	2.3	43.8	4.2	91.1	19.3
STAT3-2693	14.8	1.5	47.8	4.6	124.5	25.5

Example 12: RNAi Oligonucleotide Inhibition of STAT3 *In Vivo*

[00579] The *in vitro* screening assay in **Example 11** validated the ability of *STAT3*-targeting DsiRNAs to knock-down target mRNA. To confirm the ability of the RNAi oligonucleotides to knockdown *STAT3 in vivo*, an HDI mouse model was used. A subset of the DsiRNAs identified in **Example 11** were used to generate corresponding double-stranded RNAi oligonucleotides comprising a nicked tetraloop GalNAc-conjugated structure (referred to herein as "GalNAc-conjugated *STAT3* oligonucleotides" or "GalNAc- *STAT3* oligonucleotides") having a 36-mer passenger strand and a 22-mer guide strand (**Table 10** and **Table 11**). Further, the nucleotide sequences comprising the passenger strand and guide strand have a distinct pattern of modified nucleotides and phosphorothioate linkages. Three of the nucleotides comprising the tetraloop were each conjugated to a GalNAc moiety (CAS#14131-60-3). The modification patterns used are illustrated below:

Pattern 1

Sense Strand: 5' mX-*S*-mX-mX-mX-mX-mX-mX-fX-fX-fX-fX[-mX-]$_{16}$-[ademX-GalNAc]-[ademX-GalNAc]-[ademX-GalNAc]-mX-mX-mX-mX-mX-mX 3'.

Hybridized to:

Antisense Strand: 5' [MePhosphonate-4O-mX]-*S*-fX-*S*-fX-fX-fX-mX-fX-mX-mX-fX-mX-mX-mX-fX-mX-mX-mX-mX-mX-mX-*S*-mX-*S*-mX 3'.

Or, represented as:

Sense Strand: [mXs][mX][mX][mX][mX][mX][mX][fX][fX][fX][fX][mX][mX][mX]

[mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mX][mX][mX][mX][mX][mX]

Hybridized to:

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fX][fX][fX][mX][fX][mX][mX][fX][mX][mX][mX][fX][mX][mX][mX][mX][mX][mXs][mXs][mX]

Pattern 2

Sense Strand: 5' mX-*S*-mX-mX-mX-mX-mX-mX-fX-fX-fX-fX[-mX-]$_{16}$-[ademX-GalNAc]-[ademX-GalNAc]-[ademX-GalNAc]-mX-mX-mX-mX-mX-mX 3'.

Hybridized to:

Antisense Strand: 5' [MePhosphonate-4O-mX]-*S*-fX-*S*-fX-*S*-fX-fX-mX-fX-mX-mX-fX-mX-mX-mX-fX-mX-mX-mX-mX-mX-mX-*S*-mX-*S*-mX 3'.

Or, represented as:

Sense Strand: [mXs][mX][mX][mX][mX][mX][mX][fX][fX][fX][fX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][mX][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mX][mX][mX][mX][mX][mX]

Hybridized to:

Antisense Strand: [MePhosphonate-4O-mXs][fXs][fXs][fX][fX][mX][fX][mX][mX][fX][mX][mX][mX][fX][mX][mX][mX][mX][mX][mXs][mXs][mX]

(Modification key: **Table 9**).

Symbol	**Modification/linkage**
Key 1	
mX	2'-*O*-methyl modified nucleotide
fX	2'- fluoro modified nucleotide
-*S*-	phosphorothioate linkage
-	phosphodiester linkage

[MePhosphonate-4O-mX]	4'-O-monomethylphosphonate-2'-O-methyl modified nucleotide
ademA-GalNAc	2′-aminodiethoxymethanol-adenine-GalNAc (GalNAc attached to an adenine nucleotide)
Key 2	
[mXs]	2'-*O*-methyl modified nucleotide with a phosphorothioate linkage to the neighboring nucleotide
[fXs]	2'- fluoro modified nucleotide with a phosphorothioate linkage to the neighboring nucleotide
[mX]	2'-*O*-methyl modified nucleotide with phosphodiester linkages to neighboring nucleotides
[fX]	2'- fluoro modified nucleotide with phosphodiester linkages to neighboring nucleotides

[00580] Oligonucleotides in **Table 10** and **Table 11** were evaluated in mice engineered to transiently express human *STAT3* mRNA in hepatocytes of the mouse liver. Briefly, 6-8-week-old female CD-1 mice (n = 4-5) were subcutaneously administered the indicated GalNAc-conjugated *STAT3* oligonucleotides at a dose of 1mg/kg formulated in PBS. A control group of mice (n = 3-4) were administered only PBS. Three days later (72 hours), the mice were hydrodynamically injected (HDI) with a DNA plasmid encoding the full human *STAT3* gene (25μg) under control of a ubiquitous cytomegalovirus (CMV) promoter sequence. One day after introduction of the DNA plasmid, liver samples from HDI mice were collected. Total RNA derived from these HDI mice were subjected to qRT-PCR analysis to determine *STAT3* mRNA levels as described in **Example 11**. mRNA levels were measured for human mRNA. The values were normalized for transfection efficiency using the NeoR gene included on the DNA plasmid. A benchmark control (STAT3-1388) comprising a different modification pattern, was used for both assays (Sense Strand SEQ ID NO: 1100; Antisense Strand SEQ ID NO: 1190).

Table 10. GalNAc-Conjugated *STAT3* RNAi Oligonucleotides for HDI screen

	Unmodified Sense Strand	**Unmodified Antisense strand**	**Modified Sense Strand**	**Modified Antisense strand**
STAT3-372	861	951	1041	1131
STAT3-715	857	947	1037	1127
STAT3-716	858	948	1038	1128
STAT3-717	859	949	1039	1129
STAT3-720	860	950	1040	1130
STAT3-721	862	952	1042	1132

STAT3-722	863	953	1043	1133
STAT3-768	864	954	1044	1134
STAT3-1001	865	955	1045	1135
STAT3-1006	866	956	1046	1136
STAT3-1145	867	957	1047	1137
STAT3-1151	868	958	1048	1138
STAT3-1268	869	959	1049	1139
STAT3-1273	870	960	1050	1140
STAT3-1279	871	961	1051	1141
STAT3-1280	872	962	1052	1142
STAT3-1281	873	963	1053	1143
STAT3-1388	920	1010	1100	1190

Table 11. GalNAc-Conjugated *STAT3* RNAi Oligonucleotides for HDI screen

	Unmodified Sense Strand	**Unmodified Antisense strand**	**Modified Sense Strand**	**Modified Antisense strand**
STAT3-1284	874	964	1054	1144
STAT3-1286	875	965	1055	1145
STAT3-1287	876	966	1056	1146
STAT3-1292	877	967	1057	1147
STAT3-1293	878	968	1058	1148
STAT3-1819	879	969	1059	1149
STAT3-1908	880	970	1060	1150
STAT3-1910	881	971	1061	1151
STAT3-1913	882	972	1062	1152
STAT3-2154	883	973	1063	1153
STAT3-2327	884	974	1064	1154
STAT3-2335	885	975	1065	1155
STAT3-2418	886	976	1066	1156
STAT3-2692	887	977	1067	1157
STAT3-2693	888	978	1068	1158
STAT3-2139	940	1030	1120	1210
STAT3-2408	896	986	1076	1166
STAT3-1388	920	1010	1100	1190

[00581] The results in **FIGs. 22A** and **22B** demonstrate that GalNAc-conjugated *STAT3* oligonucleotides designed to target human *STAT3* mRNA inhibited human *STAT3* mRNA expression in HDI mice, as determined by a reduction in the amount of human *STAT3* mRNA

expression in liver samples from HDI mice treated with GalNAc-conjugated *STAT3* oligonucleotides relative to control HDI mice treated with only PBS.

[00582] A subset of the GalNAc-conjugated *STAT3* oligonucleotides tested in **FIGs. 22A** and **22B** were further validated in a dosing study. Specifically, dosing studies were carried out using nine GalNAc-conjugated *STAT3* oligonucleotides (STAT3-715, STAT3-716, STAT3-717, STAT3-720, STAT3-721, STAT3-1145, STAT3- 1286, STAT3-1286, and STAT3-1287). Mice were hydrodynamically injected as described above and treated with 0.1mg/kg, 0.3mg/kg, or 1mg/kg of oligonucleotide. Livers were collected after one day, and *STAT3* expression was measured to determine a potent dose (**FIG. 23**). All GalNAc-conjugated *STAT3* oligonucleotides were able to reduce *STAT3* expression at a 1mg/kg dose and STAT3-1286 was able to reduce expression at a 0.3mg/kg dose. Overall, the HDI studies identified several potential GalNAc-conjugated *STAT3* oligonucleotides for inhibiting *STAT3* expression in liver.

Example 13: Species Specific RNAi Oligonucleotide Inhibition of STAT3 *In Vivo*

[00583] To confirm the ability of RNAi oligonucleotides to knockdown *STAT3 in vivo*, several cross species and species specific GalNAc-conjugated *STAT3* oligonucleotides were generated. Specifically, triple common (targeting human, non-human primate, and mouse; Hs/Mf/Mm), human/mouse (Hs/Mm), and human specific (Hs) oligonucleotides were evaluated.

Hs/Mf/Mm and Hs/Mm Commons

[00584] Mice expressing endogenous mouse *STAT3* in the liver were subcutaneously injected at a dose of 3mg/kg with the GalNAc-conjugated *STAT3* oligonucleotides set forth in **Table 12**. Livers were collected after five days, and *STAT3* expression was measured. Overall, the study identified several potential Hs/Mf/Mm GalNAc-conjugated *STAT3* oligonucleotides for inhibiting *STAT3* expression in liver (**FIG. 24**).

Table 12. GalNAc-Conjugated Human/Monkey/Mouse *STAT3* RNAi Oligonucleotides for Endogenous STAT3 screen.

	Unmodified Sense Strand	**Unmodified Antisense strand**	**Modified Sense Strand**	**Modified Antisense strand**
STAT3-461	901	991	1081	1171
STAT3-462	906	996	1086	1176
STAT3-492	905	995	1085	1175
STAT3-678	910	1000	1090	1180
STAT3-681	909	999	1089	1179
STAT3-771	908	998	1088	1178
STAT3-773	904	994	1084	1174
STAT3-1047	903	993	1083	1173
STAT3-1584	902	992	1082	1172
STAT3-1586	907	997	1087	1177
STAT3-2146	898	988	1078	1168
STAT3-2147	900	990	1080	1170
STAT3-2148	899	989	1079	1169
STAT3-2151	893	983	1073	1163
STAT3-2159	897	987	1077	1167
STAT3-2407	891	981	1071	1161
STAT3-2408	896	986	1076	1166
STAT3-2412	892	982	1072	1162
STAT3-2626	890	980	1070	1160
STAT3-2627	889	979	1069	1159
STAT3-4833	912	1002	1092	1182
STAT3-4836	895	985	1075	1165
STAT3-4837	911	1001	1091	1181

[00585] Human/Mouse GalNAc-conjugated *STAT3* oligonucleotides set forth in **Table 13** were tested in mice endogenously expressing mouse *STAT3*. As described above, mice were subcutaneously injected at a dose of 3mg/kg with oligonucleotide. Livers were collected after five days, and mouse *STAT3* expression was measured. Overall, the study identified several potential Hs/Mm GalNAc-conjugated *STAT3* oligonucleotides for inhibiting *STAT3* expression in liver (**FIG. 25**).

Table 13. GalNAc-Conjugated Human/Mouse *STAT3* RNAi Oligonucleotides for Endogenous *STAT3* Screen.

	Unmodified Sense Strand	**Unmodified Antisense strand**	**Modified Sense Strand**	**Modified Antisense strand**
STAT3-1383	946	1036	1126	1216
STAT3-2135	945	1035	1125	1206
STAT3-2136	935	1025	1115	1205
STAT3-2138	938	1028	1118	1208
STAT3-2139	940	1030	1120	1210
STAT3-2143	936	1026	1116	1206
STAT3-2144	937	1027	1117	1207
STAT3-2145	942	1032	1122	1212
STAT3-2411	941	1031	1121	1211
STAT3-2622	944	1034	1124	1214
STAT3-4831	943	1033	1123	1213
STAT3-4909	939	1029	1119	1209

[00586] A subset of the GalNAc-conjugated *STAT3* oligonucleotides tested in **FIGs. 24** and **25** were further validated in a dosing study. Specifically, dosing studies were carried out using ten GalNAc-conjugated *STAT3* oligonucleotides (STAT3-2626, STAT3-2627, STAT3-2408, STAT3-2412, STAT3-2139, STAT3-4909, STAT3- 461, STAT3-678, STAT3-2148, and STAT3-2144). Mice endogenously expressing mouse *STAT3* were subcutaneously injected with 0.3mg/kg, 1mg/kg, or 3mg/kg oligonucleotide. Livers were collected after five days, and mouse *STAT3* expression was measured to determine a potent dose (**FIGs. 26A** and **26B**). Overall, the endogenous mouse *STAT3* expression studies identified several potential GalNAc-conjugated *STAT3* oligonucleotides for inhibiting mouse *STAT3* expression in liver.

Hs Specific

[00587] Using the HDI model described in **Example 12,** human specific GalNAc-conjugated *STAT3* oligonucleotides were evaluated. Specifically, 6-8-week-old female CD-1 mice (n = 4-5) were subcutaneously administered the indicated GalNAc-conjugated *STAT3* oligonucleotides (**Table 14**) at a dose of 1mg/kg formulated in PBS. A control group of mice (n = 3-4) were administered only PBS. Three days later (72 hours), the mice were hydrodynamically injected (HDI) with a DNA plasmid encoding the full human *STAT3* gene (25μg) under control of a ubiquitous cytomegalovirus (CMV) promoter sequence. One day after

introduction of the DNA plasmid, liver samples from HDI mice were collected. Total RNA derived from these HDI mice were subjected to qRT-PCR analysis to determine *STAT3* mRNA levels.

Table 14. GalNAc-Conjugated Human *STAT3* RNAi Oligonucleotides for Exogenous *STAT3* Screen.

	Unmodified Sense Strand	**Unmodified Antisense strand**	**Modified Sense Strand**	**Modified Antisense strand**
STAT3-424	926	1016	1106	1196
STAT3-425	932	1022	1112	1202
STAT3-426	915	1005	1095	1185
STAT3-429	921	1011	1101	1191
STAT3-430	923	1013	1103	1193
STAT3-432	924	1014	1104	1194
STAT3-433	918	1008	1098	1188
STAT3-1067	917	1007	1097	1187
STAT3-1670	919	1009	1099	1189
STAT3-1241	930	1020	1110	1200
STAT3-1388	920	1010	1100	1190
STAT3-1671	934	1024	1114	1204
STAT3-1672	931	1021	1111	1201
STAT3-1673	914	1004	1094	1184
STAT3-1674	929	1019	1109	1199
STAT3-1813	928	1018	1108	1198
STAT3-1815	925	1015	1105	1195
STAT3-1817	933	1023	1113	1203
STAT3-2024	927	1017	1107	1197
STAT3-2404	916	1006	1096	1186
STAT3-2405	922	1012	1102	1192

[00588] The results in **FIG. 27** demonstrate that GalNAc-conjugated *STAT3* oligonucleotides designed to target human *STAT3* mRNA inhibited human *STAT3* mRNA expression in HDI mice, as determined by a reduction in the amount of human *STAT3* mRNA expression in liver samples from HDI mice treated with GalNAc-conjugated *STAT3* oligonucleotides relative to control HDI mice treated with only PBS.

[00589] A subset of the GalNAc-conjugated *STAT3* oligonucleotides tested in **FIG. 27** were further validated in a dosing study. Specifically, dosing studies were carried out using five GalNAc-conjugated *STAT3* oligonucleotides (STAT3-426, STAT3-432, STAT3-1068, STAT3-

1388, and STAT3-2404). Mice were hydrodynamically injected as described above and treated with 0.3mg/kg, 1 mg/kg, or 3mg/kg of oligonucleotide. Livers were collected after one day, and human *STAT3* expression was measured to determine a potent dose (**FIG. 28**). A dose of 1mg/kg was capable of reducing *STAT3* mRNA by about 75%, thereby identifying several potential GalNAc-conjugated *STAT3* oligonucleotides for inhibiting *STAT3* expression in liver. The best 2 sequences from FIG. 23 and the best sequence from FIG. 28 are tested in the final HDI screen (FIG. 29).

Example 14: Specific STAT3 Inhibition by GalNAc-Conjugated STAT3 Oligonucleotides

[00590] The specificity of the GalNAc-conjugated STAT3 oligonucleotides to inhibit *STAT3* rather than a family member (e.g. *STAT1*) was measured. Specifically, Huh7 cells expressing endogenous *STAT1* were treated for 24 hours with 0.05nM, 0.3nM, or 1nM of a GalNAc-conjugated STAT3 oligonucleotide (STAT3-721, STAT3-1286, and STAT3-1388) using lipofectamine as transfection agent. The percent (%) remaining mRNA was measured compared to a mock control (PBS; no lipofectamine or siRNA) and UTR (un-transfected; treated with lipofectamine but no siRNA) (**Table 15** and **FIG. 30**). STAT3 721 and 1286 did not downregulate human *STAT1* but STAT3 1388 did (Table 15). Oligonucleotides did not downregulate *STAT1* expression demonstrating a specificity for *STAT3* with limited off-target effects for *STAT1*.

Table 15. STAT1 Expression

Sample	Concentration	% Expression	SEM
Mock		100.0	10.8
UTR		107.5	8.4
STAT3-721	0.05nM	102.3	16.2
	0.3nM	113.6	12.8
	1nM	142.0	15.6
STAT3-1286	0.05nM	103.7	23.0
	0.3nM	133.8	9.6
	1nM	136.3	10.0
STAT3-1388	0.05nM	97.3	45.2
	0.3nM	86.8	14.6
	1nM	47.7	20.3

SEQUENCE LISTING

Name	Description	Species	Sequence	SEQ ID NO
GalXC-ALDH2-C18	Unmodified 36 mer		GGUGGAUGAAACUCAGUUUAGCAGCCG AAAGGCUGC	1
GalXC-ALDH2-C18	Unmodified 22 mer		UAAACUGAGUUUCAUCCACCGG	2
GalXC-ALDH2-C18	Modified 36mer		[mGs][mG][fU][mG][fG][mA][mU][fG][mA][fA][mA][fC][fU][mC][fA][mG][fU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-C18][mA][mA][mG][mG][mC][mU][mG][mC]	3
GalXC-ALDH2-C18	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fA][fA][fC][mU][fG][mA][mG][fU][mU][mU][mC][fA][mU][fC][mC][mA][fC][mCs][mGs][mG]	4
GalXC-ALDH2-C22	Unmodified 36 mer		GGUGGAUGAAACUCAGUUUAGCAGCCG AAAGGCUGC	5
GalXC-ALDH2-C22	Unmodified 22 mer		UAAACUGAGUUUCAUCCACCGG	6
GalXC-ALDH2-C22	Modified 36mer		[mGs][mG][fU][mG][fG][mA][mU][fG][mA][fA][mA][fC][fU][mC][fA][mG][fU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-C22][mA][mA][mG][mG][mC][mU][mG][mC]	7
GalXC-ALDH2-C22	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fA][fA][fC][mU][fG][mA][mG][fU][mU][mU][mC][fA][mU][fC][mC][mA][fC][mCs][mGs][mG]	8
GalXC-STAT3-838	Unmodified 36 mer		AGGACGACUUUGAUUUCAAAGCAGCCG AAAGGCUGC	9
GalXC-STAT3-838	Unmodified 22 mer		UUUGAAAUCAAAGUCGUCCUGG	10
GalXC-STAT3-838	Modified 36mer		[mAs][mG][mG][mA][mC][mG][mA][fC][fU][fU][fU][mG][mA][mU][mU][mU][mC][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	11

GalXC-STAT3-838	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fU][fG][fA][mA][fA][mU][mC][fA][mA][mA][mG][fU][mC][mG][mU][mC][mC][mUs][mGs][mG]	12
GalXC-STAT3-1390	Unmodified 36 mer		UCAAAUUUCCUGAGUUGAAAGCAGCCGAAAGGCUGC	13
GalXC-STAT3-1390	Unmodified 22 mer		UUUCAACUCAG GAAUUUGAGG	14
GalXC-STAT3-1390	Modified 36mer		[mUs][mC][mA][mA][mA][mU][mU][fU][fC][fC][fU][mG][mA][mG][mU][mU][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	15
GalXC-STAT3-1390	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fU][fC][fA][mA][fC][mU][mC][fA][mG][mG][mA][fA][mA][mU][mU][mU][mG][mAs][mGs][mG]	16
GalXC-STAT3-1394	Unmodified 36 mer		AUUUCCUGAGUUGAAUUAUAGCAGCCGAAAGGCUGC	17
GalXC-STAT3-1394	Unmodified 22 mer		UAUAAUUCAACUCAGGAAAUGG	18
GalXC-STAT3-1394	Modified 36mer		[mAs][mU][mU][mU][mC][mC][mU][fG][fA][fG][fU][mU][mG][mA][mA][mU][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	19
GalXC-STAT3-1394	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fU][fA][fA][mU][fU][mC][mA][fA][mC][mU][mC][fA][mG][mG][mA][mA][mA][mUs][mGs][mG]	20
GalXC-STAT3-1398	Unmodified 36 mer		CCUGAGUUGAAUUAUCAGCAGCAGCCGAAAGGCUGC	21
GalXC-STAT3-1398	Unmodified 22 mer		UGCUGAUAAUUCAACUCAGGGG	22
GalXC-STAT3-1398	Modified 36mer		[mCs][mC][mU][mG][mA][mG][mU][fU][fG][fA][fA][mU][mU][mA][mU][mC][mA][mG][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	23

GalXC-STAT3-1398	Modified 22mer		[MePhosphonate-4O-mUs][fGs][fC][fU][fG][mA][fU][mA][mA][fU][mU][mC][mA][fA][mC][mU][mC][mA][mG][mGs][mGs][mG]	24
GalXC-STAT3-1399	Unmodified 36 mer		CUGAGUUGAAUUAUCAGCUAGCAGCCGAAAGGCUGC	25
GalXC-STAT3-1399	Unmodified 22 mer		UAGCUGAUAAUUCAACUCAGGG	26
GalXC-STAT3-1399	Modified 36mer		[mCs][mU][mG][mA][mG][mU][mU][fG][fA][fA][fU][mU][mA][mU][mC][mA][mG][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	27
GalXC-STAT3-1399	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fG][fC][fU][mG][fA][mU][mA][fA][mU][mU][mC][fA][mA][mC][mU][mC][mA][mGs][mGs][mG]	28
GalXC-STAT3-1400	Unmodified 36 mer		UGAGUUGAAUUAUCAGCUUAGCAGCCGAAAGGCUGC	29
GalXC-STAT3-1400	Unmodified 22 mer		UAAGCUGAUAAUUCAACUCAGG	30
GalXC-STAT3-1400	Modified 36mer		[mUs][mG][mA][mG][mU][mU][mG][fA][fA][fU][fU][mA][mU][mC][mA][mG][mC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	31
GalXC-STAT3-1400	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fA][fG][fC][mU][fG][mA][mU][fA][mA][mU][mU][fC][mA][mA][mC][mU][mC][mAs][mGs][mG]	32
GalXC-STAT3-1401	Unmodified 36 mer		GAGUUGAAUUAUCAGCUUAAGCAGCCGAAAGGCUGC	33
GalXC-STAT3-1401	Unmodified 22 mer		UUAAGCUGAUAAUUCAACUCGG	34
GalXC-STAT3-1401	Modified 36mer		[mGs][mA][mG][mU][mU][mG][mA][fA][fU][fU][fA][mU][mC][mA][mG][mC][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	35

GalXC-STAT3-1401	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fA][fA][fG][mC][fU][mG][mA][fU][mA][mA][mU][fU][mC][mA][mA][mC][mU][mCs][mGs][mG]	36
GalXC-STAT3-1402	Unmodified 36 mer		AGUUGAAUUAUCAGCUUAAAGCAGCCGAAAGGCUGC	37
GalXC-STAT3-1402	Unmodified 22 mer		UUUAAGCUGAUAAUUCAACUGG	38
GalXC-STAT3-1402	Modified 36mer		[mAs][mG][mU][mU][mG][mA][mA][fU][fU][fA][fU][mC][mA][mG][mC][mU][mU][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	39
GalXC-STAT3-1402	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fU][fA][fA][mG][fC][mU][mG][fA][mU][mA][mA][fU][mU][mC][mA][mA][mC][mUs][mGs][mG]	40
GalXC-STAT3-1759	Unmodified 36 mer		CAAUCCUGUGGUAUAACAUAGCAGCCGAAAGGCUGC	41
GalXC-STAT3-1759	Unmodified 22 mer		UAUGUUAUACCACAGGAUUGGG	42
GalXC-STAT3-1759	Modified 36mer		[mCs][mA][mA][mU][mC][mC][mU][fG][fU][fG][fG][mU][mA][mU][mA][mA][mC][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	43
GalXC-STAT3-1759	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fU][fG][fU][mU][fA][mU][mA][fC][mC][mA][mC][fA][mG][mG][mA][mU][mU][mGs][mGs][mG]	44
GalXC-STAT3-2029	Unmodified 36 mer		ACAAUAUCAUCGACCUUGUAGCAGCCGAAAGGCUGC	45
GalXC-STAT3-2029	Unmodified 22 mer		UACAAGGUCGAUGAUAUUGUGG	46
GalXC-STAT3-2029	Modified 36mer		[mAs][mC][mA][mA][mU][mA][mU][fC][fA][fU][fC][mG][mA][mC][mC][mU][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	47

GalXC-STAT3-2029	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fC][fA][fA][mG][fG][mU][mC][fG][mA][mU][mG][fA][mU][mA][mU][mU][mG][mUs][mGs][mG]	48
GalXC-STAT3-2034	Unmodified 36 mer		AUCAUCGACCUUGUGAAAAAGCAGCCGAAAGGCUGC	49
GalXC-STAT3-2034	Unmodified 22 mer		UUUUUCACAAGGUCGAUGAUGG	50
GalXC-STAT3-2034	Modified 36mer		[mAs][mU][mC][mA][mU][mC][mG][fA][fC][fC][fU][mU][mG][mU][mG][mA][mA][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	51
GalXC-STAT3-2034	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fU][fU][fU][mC][fA][mC][mA][fA][mG][mG][mU][fC][mG][mA][mU][mG][mA][mUs][mGs][mG]	52
GalXC-STAT3-2448	Unmodified 36 mer		CUGAAGACCAAGUUCAUCUAGCAGCCGAAAGGCUGC	53
GalXC-STAT3-2448	Unmodified 22 mer		UAGAUGAACUU GGUCUUCAGGG	54
GalXC-STAT3-2448	Modified 36mer		[mCs][mU][mG][mA][mA][mG][mA][fC][fC][fA][fA][mG][mU][mU][mC][mA][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	55
GalXC-STAT3-2448	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fG][fA][fU][mG][fA][mA][mC][fU][mU][mG][mG][fU][mC][mU][mU][mC][mA][mGs][mGs][mG]	56
GalXC-STAT3-2527	Unmodified 36 mer		AUUCAUUGAUGCAGUUUGGAGCAGCCGAAAGGCUGC	57
GalXC-STAT3-2527	Unmodified 22 mer		UCCAAACUGCAUCAAUGAAUGG	58
GalXC-STAT3-2527	Modified 36mer		[mAs][mU][mU][mC][mA][mU][mU][fG][fA][fU][fG][mC][mA][mG][mU][mU][mU][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	59

GalXC-STAT3-2527	Modified 22mer		[MePhosphonate-4O-mUs][fCs][fC][fA][fA][mA][fC][mU][mG][fC][mA][mU][mC][fA][mA][mU][mG][mA][mA][mUs][mGs][mG]	60
GalXC-STAT3-4107	Unmodified 36 mer		CCCAUCAAUGUUCUUUAGUAGCAGCCGAAAGGCUGC	61
GalXC-STAT3-4107	Unmodified 22 mer		UACUAAAGAACAUUGAUGGGGG	62
GalXC-STAT3-4107	Modified 36mer		[mCs][mC][mC][mA][mU][mC][mA][fA][fU][fG][fU][mU][mC][mU][mU][mU][mA][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	63
GalXC-STAT3-4107	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fC][fU][fA][mA][fA][mG][mA][fA][mC][mA][mU][fU][mG][mA][mU][mG][mG][mGs][mGs][mG]	64
GalXC-STAT3-4110	Unmodified 36 mer		AUCAAUGUUCUUUAGUUAUAGCAGCCGAAAGGCUGC	65
GalXC-STAT3-4110	Unmodified 22 mer		UAUAACUAAAGAACAUUGAUGG	66
GalXC-STAT3-4110	Modified 36mer		[mAs][mU][mC][mA][mA][mU][mG][fU][fU][fC][fU][mU][mU][mA][mG][mU][mU][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	67
GalXC-STAT3-4110	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fU][fA][fA][mC][fU][mA][mA][fA][mG][mA][mA][fC][mA][mU][mU][mG][mA][mUs][mGs][mG]	68
GalXC-STAT3-4123	Unmodified 36 mer		AGUUAUACAAUAAGCUGAAAGCAGCCGAAAGGCUGC	69
GalXC-STAT3-4123	Unmodified 22 mer		UUUCAGCUUAUUGUAUAACUGG	70
GalXC-STAT3-4123	Modified 36mer		[mAs][mG][mU][mU][mA][mU][mA][fC][fA][fA][fU][mA][mA][mG][mC][mU][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	71

GalXC-STAT3-4123	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fU][fC][fA][mG][fC][mU][mU][fA][mU][mU][mG][fU][mA][mU][mA][mA][mC][mUs][mGs][mG]	72
GalXC-STAT3-4435	Unmodified 36 mer		AGUGUAAAAAUUUAUAUUAAGCAGCCGAAAGGCUGC	73
GalXC-STAT3-4435	Unmodified 22 mer		UUAAUAUAAAUUUUUACACUGG	74
GalXC-STAT3-4435	Modified 36mer		[mAs][mG][mU][mG][mU][mA][mA][fA][fA][fA][fU][mU][mU][mA][mU][mA][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	75
GalXC-STAT3-4435	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fA][fA][fU][mA][fU][mA][mA][fA][mU][mU][mU][fU][mU][mA][mC][mA][mC][mUs][mGs][mG]	76
GalXC-STAT3-4474	Unmodified 36 mer		UUGUUUGUUUUUGUAUAUUAGCAGCCGAAAGGCUGC	77
GalXC-STAT3-4474	Unmodified 22 mer		UUAAUAUAAAUUUUUACACUGG	78
GalXC-STAT3-4474	Modified 36mer		[mUs][mU][mG][mU][mU][mU][mG][fU][fU][fU][fU][mU][mG][mU][mA][mU][mA][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	79
GalXC-STAT3-4474	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fA][fU][fA][mU][fA][mC][mA][fA][mA][mA][mA][fC][mA][mA][mA][mC][mA][mAs][mGs][mG]	80
GalXC-STAT3-4110-C18	Modified 36mer		[mAs][mU][mC][mA][mA][mU][mG][fU][fU][fC][fU][mU][mU][mA][mG][mU][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-C18][mA][mA][mG][mG][mC][mU][mG][mC]	81
GalXC-STAT3-4110-C18	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fU][fA][fA][mC][fU][mA][mA][fA][mG][mA][mA][fC][mA][mU][mU][mG][mA][mUs][mGs][mG]	82
GalXC-STAT3-	Modified 36mer		[mAs][mG][mU][mU][mA][mU][mA][fC][fA][fA][fU][mA][mA][mG][mC][mU][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ade	83

4123-C18			mA-C18][mA][mA][mG][mG][mC][mU][mG][mC]	
GalXC-STAT3-4123-C18	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fU][fC][fA][mG][fC][mU][mU][fA][mU][mU][mG][fU][mA][mU][mA][mA][mC][mUs][mGs][mG]	84
	STAT3 Human (Hs) NM_001369512.1 (Genbank RefSeq #)		GTCGCAGCCGAGGGAACAAGCCCCAACC GGATCCTGGACAGGCACCCCGGCTTGGC GCTGTCTCTCCCCCTCGGCTCGGAGAGGC CCTTCGGCCTGAGGGAGCCTCGCCGCCC GTCCCCGGCACACGCGCAGCCCCGGCCT CTCGGCCTCTGCCGGAGAAACAGGATGG CCCAATGGAATCAGCTACAGCAGCTTGA CACACGGTACCTGGAGCAGCTCCATCAG CTCTACAGTGACAGCTTCCCAATGGAGCT GCGGCAGTTTCTGGCCCCTTGGATTGAGA GTCAAGATTGGGCATATGCGGCCAGCAA AGAATCACATGCCACTTTGGTGTTTCATA ATCTCCTGGGAGAGATTGACCAGCAGTA TAGCCGCTTCCTGCAAGAGTCGAATGTTC TCTATCAGCACAATCTACGAAGAATCAA GCAGTTTCTTCAGAGCAGGTATCTTGAGA AGCCAATGGAGATTGCCCGGATTGTGGC CCGGTGCCTGTGGGAAGAATCACGCCTT CTACAGACTGCAGCCACTGCGGCCCAGC AAGGGGGCCAGGCCAACCACCCCACAGC AGCCGTGGTGACGGAGAAGCAGCAGATG CTGGAGCAGCACCTTCAGGATGTCCGGA AGAGAGTGCAGGATCTAGAACAGAAAAT GAAAGTGGTAGAGAATCTCCAGGATGAC TTTGATTTCAACTATAAAACCCTCAAGAG TCAAGGAGACATGCAAGATCTGAATGGA AACAACCAGTCAGTGACCAGGCAGAAGA TGCAGCAGCTGGAACAGATGCTCACTGC GCTGGACCAGATGCGGAGAAGCATCGTG AGTGAGCTGGCGGGGCTTTTGTCAGCGA TGGAGTACGTGCAGAAAACTCTCACGGA CGAGGAGCTGGCTGACTGGAAGAGGCGG CAACAGATTGCCTGCATTGGAGGCCCGC CCAACATCTGCCTAGATCGGCTAGAAAA CTGGATAACGTCATTAGCAGAATCTCAA CTTCAGACCCGTCAACAAATTAAGAAAC TGGAGGAGTTGCAGCAAAAAGTTTCCTA CAAAGGGGACCCCATTGTACAGCACCGG CCGATGCTGGAGGAGAGAATCGTGGAGC TGTTTAGAAACTTAATGAAAAGTGCCTTT	85

			GTGGTGGAGCGGCAGCCCTGCATGCCCA TGCATCCTGACCGGCCCCTCGTCATCAAG ACCGGCGTCCAGTTCACTACTAAAGTCA GGTTGCTGGTCAAATTCCCTGAGTTGAAT TATCAGCTTAAAATTAAAGTGTGCATTGA CAAAGACTCTGGGGACGTTGCAGCTCTC AGAGGATCCCGGAAATTTAACATTCTGG GCACAAACACAAAAGTGATGAACATGGA AGAATCCAACAACGGCAGCCTCTCTGCA GAATTCAAACACTTGACCCTGAGGGAGC AGAGATGTGGGAATGGGGGCCGAGCCAA TTGTGATGCTTCCCTGATTGTGACTGAGG AGCTGCACCTGATCACCTTTGAGACCGA GGTGTATCACCAAGGCCTCAAGATTGAC CTAGAGACCCACTCCT TGCCAGTTGTGGTGATCTCCAACATCTGT CAGATGCCAAATGCCTGGGCGTCCATCCT GTGGTACAACATGCTGACCAACAATCCC AAGAATGTAAACTTTTTTACCAAGCCCCC AATTGGAACCTGGGATCAAGTGGCCGAG GTCCTGAGCTGGCAGTTCTCCTCCACCAC CAAGCGAGGACTGAGCATCGAGCAGCTG ACTACACTGGCAGAGAAACTCTTGGGAC CTGGTGTGAATTATTCAGGGTGTCAGATC ACATGGGCTAAATTTTGCAAAGAAAACA TGGCTGGCAAGGGCTTCTCCTTCTGGGTC TGGCTGGACAATATCATTGACCTTGTGAA AAAGTACATCCTGGCCCTTTGGAACGAA GGGTACATCATGGGCTTTATCAGTAAGG AGCGGGAGCGGGCCATCTTGAGCACTAA GCCTCCAGGCACCTTCCTGCTAAGATTCA GTGAAAGCAGCAAAGAAGGAGGCGTCAC TTTCACTTGGGTGGAGAAGGACATCAGC GGTAAGACCCAGATCCAGTCCGTGGAAC CATACACAAAGCAGCAGCTGAACAACAT GTCATTTGCTGAAATCATCATGGGCTATA AGATCATGGATGCTACCAATATCCTGGTG TCTCCACTGGTCTATCTCTATCCTGACAT TCCCAAGGAGGAGGCATTCGGAAAGTAT TGTCGGCCAGAGAGCCAGGAGCATCCTG AAGCTGACCCAGGTAGCGCTGCCCCATA CCTGAAGACCAAGTTTATCTGTGTGACAC CA ACGACCTGCAGCAATACCATTGACCTGC CGATGTCCCCCCGCACTTTAGATTCATTG ATGCAGTTTGGAAATAATGGTGAAGGTG	

			CTGAACCCTCAGCAGGAGGGCAGTTTGA GTCCCTCACCTTTGACATGGAGTTGACCT CGGAGTGCGCTACCTCCCCCATGTGAGG AGCTGAGAACGGAAGCTGCAGAAAGATA CGACTGAGGCGCCTACCTGCATTCTGCCA CCCCTCACACAGCCAAACCCCAGATCAT CTGAAACTACTAACTTTGTGGTTCCAGAT TTTTTTTAATCTCCTACTTCTGCTATCTTT GAGCAATCTGGGCACTTTTAAAAATAGA GAAATGAGTGAATGTGGGTGATCTGCTTT TATCTAAATGCAAATAAGGATGTGTTCTC TGAGACCCATGATCAGGGGATGTGGCGG GGGGTGGCTAGAGGGAGAAAAAGGAAA TGTCTTGTGTTGTTTTGTTCCCCTGCCCTC CTTTCTCAGCAGCTTTTTGTTATTGTTGTT GTTGTTCTTAGACAAGTGCCTCCTGGTGC CTGCGGCATCCTTCTGCCTGTTTCTGTAA GCAAATGCCACAGGCCACCTATAGCTAC ATACTCCTGGCATTGCACTTTTTAACCTT GCTGACATCCAAATAGAAGATAGGACTA TCTAAGCCCTAGGTTTCTTTTTAAATTAA GAAATAATAACAATTAAAGGGCAAAAAA CACTGTATCAGCATAGCCTTTCTGTATTT AAGAAACTTAAGCAGCCGGGCATGGTGG CTCACGCCTGTAATCCCAGCACTTTGGGA GGCCGAGGCGGATCATAAGGTCAGGAGA TCAAGACCATCCTGGCTAACACGGTGAA ACCCCGTCTCTACTAAAAGTACAAAAAA TTAGCTGGGTGTGGTGGTGGGCGCC TGTAGTCCCAGCTACTCGGGAGGCTGAG GCAGGAGAATCGCTTGAACCTGAGAGGC GGAGGTTGCAGTGAGCCAAAATTGCACC ACTGCACACTGCACTCCATCCTGGGCGAC AGTCTGAGACTCTGTCTCAAAAAAAAAA AAAAAAAAAAGAAACTTCAGTTAACAGC CTCCTTGGTGCTTTAAGCATTCAGCTTCC TTCAGGCTGGTAATTTATATAATCCCTGA AACGGGCTTCAGGTCAAACCCTTAAGAC ATCTGAAGCTGCAACCTGGCCTTTGGTGT TGAAATAGGAAGGTTTAAGGAGAATCTA AGCATTTTAGACTTTTTTTTATAAATAGA CTTATTTTCCTTTGTAATGTATTGGCCTTT TAGTGAGTAAGGCTGGGCAGAGGGTGCT TACAACCTTGACTCCCTTTCTCCCTGGAC TTGATCTGCTGTTTCAGAGGCTAGGTTGT TTCTGTGGGTGCCTTATCAGGGCTGGGAT	

			ACTTCTGATTCTGGCTTCCTTCCTGCCCC ACCCTCCCGACCCCAGTCCCCCTGATCCT GCTAGAGGCATGTCTCCTTGCGTGTCTAA AGGTCCCTCATCCTGTTTGTTTTAGGAAT CCTGGTCTCAGGACCTCATGGAAGAAGA GGGGGAGAGAGTTACAGGTTGGACATGA TGCACACTATGGGGCCCCAGCGACGTGT CTGGTTGAGCTCAGGGAATATGGTTCTTA GCCAGTTTCTTGGTGATATCCAGTGGCAC TTGTAATGGCGTCTTCATTCAGTTCA TGCAGGGCAAAGGCTTACTGATAAACTT GAGTCTGCCCTCGTATGAGGGTGTATACC TGGCCTCCCTCTGAGGCTGGTGACTCCTC CCTGCTGGGGCCCCACAGGTGAGGCAGA ACAGCTAGAGGGCCTCCCCGCCTGCCCG CCTTGGCTGGCTAGCTCGCCTCTCCTGTG CGTATGGGAACACCTAGCACGTGCTGGA TGGGCTGCCTCTGACTCAGAGGCATGGC CGGATTTGGCAACTCAAAACCACCTTGCC TCAGCTGATCAGAGTTTCTGTGGAATTCT GTTTGTTAAATCAAATTAGCTGGTCTCTG AATTAAGGGGGAGACGACCTTCTCTAAG ATGAACAGGGTTCGCCCCAGTCCTCCTGC CTGGAGACAGTTGATGTGTCATGCAGAG CTCTTACTTCTCCAGCAACACTCTTCAGT ACATAATAAGCTTAACTGATAAACAGAA TATTTAGAAAGGTGAGACTTGGGCTTACC ATTGGGTTTAAATCATAGGGACCTAGGG CGAGGGTTCAGGGCTTCTCTGGAGCAGA TATTGTCAAGTTCATGGCCTTAGGTAGCA TGTATCTGGTCTTAACTCTGATTGTAGCA AAAGTTCTGAGAGGAGCTGAGCCCTGTT GTGGCCCATTAAAGAACAGGGTCCTCAG GCCCTGCCCGCTTCCTGTCCACTGCCCCC TCCCCATCCCCAGCCCAGCCGAGGGAAT CCCGTGGGTTGCTTACCTACCTATAAGGT GGTTTATAAGCTGCTGTCCTGGCCACTGC ATTCAAATTCCAATGTGTACTTCATAGTG TAAAAATTTATATTATTGTGAGGTTTTTT GTCTTTTTTTTTTTTTTTTTTTTTTGGTATA TTGCTGTATCTACTTTAACTTCCAGAAAT AAACGTTATATAGGAACCGTC	
	Stem Loop		GCAGCCGAAAGGCUGC	86

GalXC-STAT3-2029	Modified 36mer		[mAs][mU][mC][mA][mA][mU][mG][fU][fU][fC][fU][mU][mU][mA][mG][mU][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-C18][mA][mA][mG][mG][mC][mU][mG][mC]	87
STAT3-4123-C18	Modified 36mer		[mAs][mG][mU][mU][mA][mU][mA][fC][fA][fA][fU][mA][mA][mG][mC][mU][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-C18][mA][mA][mG][mG][mC][mU][mG][mC]	88
STAT3-370	Sense 19mer		CACUUUGGUGUUUCAUAAU	89
STAT3-372	Sense 19mer		CUUUGGUGUUUCAUAAUCU	90
STAT3-424	Sense 19mer		CCUGCAAGAGUCGAAUGUU	91
STAT3-425	Sense 19mer		CUGCAAGAGUCGAAUGUUC	92
STAT3-426	Sense 19mer		UGCAAGAGUCGAAUGUUCU	93
STAT3-429	Sense 19mer		AAGAGUCGAAUGUUCUCUA	94
STAT3-430	Sense 19mer		AGAGUCGAAUGUUCUCUAU	95
STAT3-432	Sense 19mer		AGUCGAAUGUUCUCUAUCA	96
STAT3-433	Sense 19mer		GUCGAAUGUUCUCUAUCAG	97
STAT3-460	Sense 19mer		ACGAAGAAUCAAGCAGUUU	98
STAT3-461	Sense 19mer		CGAAGAAUCAAGCAGUUUC	99
STAT3-462	Sense 19mer		GAAGAAUCAAGCAGUUUCU	100
STAT3-492	Sense 19mer		AUCUUGAGAAGCCAAUGGA	101
STAT3-678	Sense 19mer		AGGAUCUAGAACAGAAAAU	102
STAT3-681	Sense 19mer		AUCUAGAACAGAAAAUGAA	103
STAT3-715	Sense 19mer		CCAGGAUGACUUUGAUUUC	104
STAT3-716	Sense 19mer		CAGGAUGACUUUGAUUUCA	105
STAT3-717	Sense 19mer		AGGAUGACUUUGAUUUCAA	106

STAT3-720	Sense 19mer		AUGACUUUGAUUUCAACUA	107
STAT3-721	Sense 19mer		UGACUUUGAUUUCAACUAU	108
STAT3-722	Sense 19mer		GACUUUGAUUUCAACUAUA	109
STAT3-723	Sense 19mer		ACUUUGAUUUCAACUAUAA	110
STAT3-724	Sense 19mer		CUUUGAUUUCAACUAUAAA	111
STAT3-768	Sense 19mer		AAGAUCUGAAUGGAAACAA	112
STAT3-771	Sense 19mer		AUCUGAAUGGAAACAACCA	113
STAT3-773	Sense 19mer		CUGAAUGGAAACAACCAGU	114
STAT3-1000	Sense 19mer		AGAAAACUGGAUAACGUCA	115
STAT3-1001	Sense 19mer		GAAAACUGGAUAACGUCAU	116
STAT3-1003	Sense 19mer		AAACUGGAUAACGUCAUUA	117
STAT3-1006	Sense 19mer		CUGGAUAACGUCAUUAGCA	118
STAT3-1008	Sense 19mer		GGAUAACGUCAUUAGCAGA	119
STAT3-1009	Sense 19mer		GAUAACGUCAUUAGCAGAA	120
STAT3-1010	Sense 19mer		AUAACGUCAUUAGCAGAAU	121
STAT3-1047	Sense 19mer		AACAAAUUAAGAAACUGGA	122
STAT3-1067	Sense 19mer		GAGUUGCAGCAAAAAGUUU	123
STAT3-1068	Sense 19mer		AGUUGCAGCAAAAAGUUUC	124
STAT3-1145	Sense 19mer		CUGUUUAGAAACUUAAUGA	125
STAT3-1151	Sense 19mer		AGAAACUUAAUGAAAAGUG	126
STAT3-1241	Sense 19mer		CAGUUCACUACUAAAGUCA	127
STAT3-1268	Sense 19mer		GUCAAAUUCCCUGAGUUGA	128
STAT3-1272	Sense 19mer		AAUUCCCUGAGUUGAAUUA	129

STAT3-1273	Sense 19mer		AUUCCCUGAGUUGAAUUAU	130
STAT3-1275	Sense 19mer		UCCCUGAGUUGAAUUAUCA	131
STAT3-1277	Sense 19mer		CCUGAGUUGAAUUAUCAGC	132
STAT3-1278	Sense 19mer		CUGAGUUGAAUUAUCAGCU	133
STAT3-1279	Sense 19mer		UGAGUUGAAUUAUCAGCUU	134
STAT3-1280	Sense 19mer		GAGUUGAAUUAUCAGCUUA	135
STAT3-1281	Sense 19mer		AGUUGAAUUAUCAGCUUAA	136
STAT3-1282	Sense 19mer		GUUGAAUUAUCAGCUUAAA	137
STAT3-1283	Sense 19mer		UUGAAUUAUCAGCUUAAAA	138
STAT3-1284	Sense 19mer		UGAAUUAUCAGCUUAAAAU	139
STAT3-1286	Sense 19mer		AAUUAUCAGCUUAAAAUUA	140
STAT3-1287	Sense 19mer		AUUAUCAGCUUAAAAUUAA	141
STAT3-1292	Sense 19mer		CAGCUUAAAAUUAAAGUGU	142
STAT3-1293	Sense 19mer		AGCUUAAAAUUAAAGUGUG	143
STAT3-1299	Sense 19mer		AAAUUAAAGUGUGCAUUGA	144
STAT3-1305	Sense 19mer		AAGUGUGCAUUGACAAAGA	145
STAT3-1383	Sense 19mer		CAAAAGUGAUGAACAUGGA	146
STAT3-1388	Sense 19mer		GUGAUGAACAUGGAAGAAU	147
STAT3-1427	Sense 19mer		GCAGAAUUCAAACACUUGA	148
STAT3-1485	Sense 19mer		AUUGUGAUGCUUCCCUGAU	149
STAT3-1584	Sense 19mer		CCUUGCCAGUUGUGGUGAU	150
STAT3-1586	Sense 19mer		UUGCCAGUUGUGGUGAUCU	151
STAT3-1670	Sense 19mer		CCCAAGAAUGUAAACUUUU	152

STAT3-1671	Sense 19mer		CCAAGAAUGUAAACUUUUU	153
STAT3-1672	Sense 19mer		CAAGAAUGUAAACUUUUUU	154
STAT3-1673	Sense 19mer		AAGAAUGUAAACUUUUUUA	155
STAT3-1674	Sense 19mer		AGAAUGUAAACUUUUUUAC	156
STAT3-1676	Sense 19mer		AAUGUAAACUUUUUUACCA	157
STAT3-1813	Sense 19mer		ACCUGGUGUGAAUUAUUCA	158
STAT3-1815	Sense 19mer		CUGGUGUGAAUUAUUCAGG	159
STAT3-1817	Sense 19mer		GGUGUGAAUUAUUCAGGGU	160
STAT3-1819	Sense 19mer		UGUGAAUUAUUCAGGGUGU	161
STAT3-1904	Sense 19mer		CUGGACAAUAUCAUUGACC	162
STAT3-1906	Sense 19mer		GGACAAUAUCAUUGACCUU	163
STAT3-1907	Sense 19mer		GACAAUAUCAUUGACCUUG	164
STAT3-1908	Sense 19mer		ACAAUAUCAUUGACCUUGU	165
STAT3-1909	Sense 19mer		CAAUAUCAUUGACCUUGUG	166
STAT3-1910	Sense 19mer		AAUAUCAUUGACCUUGUGA	167
STAT3-1911	Sense 19mer		AUAUCAUUGACCUUGUGAA	168
STAT3-1912	Sense 19mer		UAUCAUUGACCUUGUGAAA	169
STAT3-1913	Sense 19mer		AUCAUUGACCUUGUGAAAA	170
STAT3-1914	Sense 19mer		UCAUUGACCUUGUGAAAAA	171
STAT3-1916	Sense 19mer		AUUGACCUUGUGAAAAAGU	172
STAT3-1917	Sense 19mer		UUGACCUUGUGAAAAAGUA	173
STAT3-1919	Sense 19mer		GACCUUGUGAAAAAGUACA	174
STAT3-1920	Sense 19mer		ACCUUGUGAAAAAGUACAU	175

STAT3-2024	Sense 19mer		ACCUUCCUGCUAAGAUUCA	176
STAT3-2135	Sense 19mer		AAGCAGCAGCUGAACAACA	177
STAT3-2136	Sense 19mer		AGCAGCAGCUGAACAACAU	178
STAT3-2138	Sense 19mer		CAGCAGCUGAACAACAUGU	179
STAT3-2139	Sense 19mer		AGCAGCUGAACAACAUGUC	180
STAT3-2143	Sense 19mer		GCUGAACAACAUGUCAUUU	181
STAT3-2144	Sense 19mer		CUGAACAACAUGUCAUUUG	182
STAT3-2145	Sense 19mer		UGAACAACAUGUCAUUUGC	183
STAT3-2146	Sense 19mer		GAACAACAUGUCAUUUGCU	184
STAT3-2147	Sense 19mer		AACAACAUGUCAUUUGCUG	185
STAT3-2148	Sense 19mer		ACAACAUGUCAUUUGCUGA	186
STAT3-2151	Sense 19mer		ACAUGUCAUUUGCUGAAAU	187
STAT3-2153	Sense 19mer		AUGUCAUUUGCUGAAAUCA	188
STAT3-2154	Sense 19mer		UGUCAUUUGCUGAAAUCAU	189
STAT3-2159	Sense 19mer		UUUGCUGAAAUCAUCAUGG	190
STAT3-2322	Sense 19mer		CAUACCUGAAGACCAAGUU	191
STAT3-2325	Sense 19mer		ACCUGAAGACCAAGUUUAU	192
STAT3-2327	Sense 19mer		CUGAAGACCAAGUUUAUCU	193
STAT3-2329	Sense 19mer		GAAGACCAAGUUUAUCUGU	194
STAT3-2333	Sense 19mer		ACCAAGUUUAUCUGUGUGA	195
STAT3-2335	Sense 19mer		CAAGUUUAUCUGUGUGACA	196
STAT3-2404	Sense 19mer		AGAUUCAUUGAUGCAGUUU	197
STAT3-2405	Sense 19mer		GAUUCAUUGAUGCAGUUUG	198

STAT3-2407	Sense 19mer		UUCAUUGAUGCAGUUUGGA	199
STAT3-2408	Sense 19mer		UCAUUGAUGCAGUUUGGAA	200
STAT3-2411	Sense 19mer		UUGAUGCAGUUUGGAAAUA	201
STAT3-2412	Sense 19mer		UGAUGCAGUUUGGAAAUAA	202
STAT3-2413	Sense 19mer		GAUGCAGUUUGGAAAUAAU	203
STAT3-2416	Sense 19mer		GCAGUUUGGAAAUAAUGGU	204
STAT3-2418	Sense 19mer		AGUUUGGAAAUAAUGGUGA	205
STAT3-2422	Sense 19mer		UGGAAAUAAUGGUGAAGGU	206
STAT3-2427	Sense 19mer		AUAAUGGUGAAGGUGCUGA	207
STAT3-2612	Sense 19mer		CUGAAACUACUAACUUUGU	208
STAT3-2615	Sense 19mer		AAACUACUAACUUUGUGGU	209
STAT3-2616	Sense 19mer		AACUACUAACUUUGUGGUU	210
STAT3-2617	Sense 19mer		ACUACUAACUUUGUGGUUC	211
STAT3-2622	Sense 19mer		UAACUUUGUGGUUCCAGAU	212
STAT3-2625	Sense 19mer		CUUUGUGGUUCCAGAUUUU	213
STAT3-2626	Sense 19mer		UUUGUGGUUCCAGAUUUUU	214
STAT3-2627	Sense 19mer		UUGUGGUUCCAGAUUUUUU	215
STAT3-2692	Sense 19mer		AAAUAGAGAAAUGAGUGAA	216
STAT3-2693	Sense 19mer		AAUAGAGAAAUGAGUGAAU	217
STAT3-2715	Sense 19mer		GGUGAUCUGCUUUUAUCUA	218
STAT3-2719	Sense 19mer		AUCUGCUUUUAUCUAAAUG	219
STAT3-2721	Sense 19mer		CUGCUUUUAUCUAAAUGCA	220
STAT3-2735	Sense 19mer		AUGCAAAUAAGGAUGUGUU	221

STAT3-2741	Sense 19mer		AUAAGGAUGUGUUCUCUGA	222
STAT3-2801	Sense 19mer		GAAAAAGGAAAUGUCUUGU	223
STAT3-2803	Sense 19mer		AAAAGGAAAUGUCUUGUGU	224
STAT3-2804	Sense 19mer		AAAGGAAAUGUCUUGUGUU	225
STAT3-2806	Sense 19mer		AGGAAAUGUCUUGUGUUGU	226
STAT3-2807	Sense 19mer		GGAAAUGUCUUGUGUUGUU	227
STAT3-2808	Sense 19mer		GAAAUGUCUUGUGUUGUUU	228
STAT3-2809	Sense 19mer		AAAUGUCUUGUGUUGUUUU	229
STAT3-2810	Sense 19mer		AAUGUCUUGUGUUGUUUUG	230
STAT3-2811	Sense 19mer		AUGUCUUGUGUUGUUUUGU	231
STAT3-2812	Sense 19mer		UGUCUUGUGUUGUUUUGUU	232
STAT3-2813	Sense 19mer		GUCUUGUGUUGUUUUGUUC	233
STAT3-2846	Sense 19mer		CUCAGCAGCUUUUUGUUAU	234
STAT3-2848	Sense 19mer		CAGCAGCUUUUUGUUAUUG	235
STAT3-2849	Sense 19mer		AGCAGCUUUUUGUUAUUGU	236
STAT3-2850	Sense 19mer		GCAGCUUUUUGUUAUUGUU	237
STAT3-2851	Sense 19mer		CAGCUUUUUGUUAUUGUUG	238
STAT3-2852	Sense 19mer		AGCUUUUUGUUAUUGUUGU	239
STAT3-2853	Sense 19mer		GCUUUUUGUUAUUGUUGUU	240
STAT3-2854	Sense 19mer		CUUUUUGUUAUUGUUGUUG	241
STAT3-2855	Sense 19mer		UUUUUGUUAUUGUUGUUGU	242
STAT3-2856	Sense 19mer		UUUUGUUAUUGUUGUUGUU	243
STAT3-2857	Sense 19mer		UUUGUUAUUGUUGUUGUUG	244

STAT3-2858	Sense 19mer		UUGUUAUUGUUGUUGUUGU	245
STAT3-2859	Sense 19mer		UGUUAUUGUUGUUGUUGUU	246
STAT3-2860	Sense 19mer		GUUAUUGUUGUUGUUGUUC	247
STAT3-2861	Sense 19mer		UUAUUGUUGUUGUUGUUCU	248
STAT3-2862	Sense 19mer		UAUUGUUGUUGUUGUUCUU	249
STAT3-2863	Sense 19mer		AUUGUUGUUGUUGUUCUUA	250
STAT3-2865	Sense 19mer		UGUUGUUGUUGUUCUUAGA	251
STAT3-2867	Sense 19mer		UUGUUGUUGUUCUUAGACA	252
STAT3-2868	Sense 19mer		UGUUGUUGUUCUUAGACAA	253
STAT3-2975	Sense 19mer		CUUUUUAACCUUGCUGACA	254
STAT3-2979	Sense 19mer		UUAACCUUGCUGACAUCCA	255
STAT3-2985	Sense 19mer		UUGCUGACAUCCAAAUAGA	256
STAT3-3025	Sense 19mer		AGGUUUCUUUUUAAAUUAA	257
STAT3-3037	Sense 19mer		AAAUUAAGAAAUAAUAACA	258
STAT3-3038	Sense 19mer		AAUUAAGAAAUAAUAACAA	259
STAT3-3039	Sense 19mer		AUUAAGAAAUAAUAACAAU	260
STAT3-3041	Sense 19mer		UAAGAAAUAAUAACAAUUA	261
STAT3-3042	Sense 19mer		AAGAAAUAAUAACAAUUAA	262
STAT3-3043	Sense 19mer		AGAAAUAAUAACAAUUAAA	263
STAT3-3225	Sense 19mer		ACUAAAAGUACAAAAAAUU	264
STAT3-3226	Sense 19mer		CUAAAAGUACAAAAAAUUA	265
STAT3-3605	Sense 19mer		AGACUUAUUUUCCUUUGUA	266
STAT3-3611	Sense 19mer		AUUUUCCUUUGUAAUGUAU	267

STAT3-3906	Sense 19mer		AGUUACAGGUUGGACAUGA	268
STAT3-4311	Sense 19mer		UGUGGAAUUCUGUUUGUUA	269
STAT3-4314	Sense 19mer		GGAAUUCUGUUUGUUAAAU	270
STAT3-4317	Sense 19mer		AUUCUGUUUGUUAAAUCAA	271
STAT3-4321	Sense 19mer		UGUUUGUUAAAUCAAAUUA	272
STAT3-4465	Sense 19mer		ACAUAAUAAGCUUAACUGA	273
STAT3-4479	Sense 19mer		ACUGAUAAACAGAAUAUUU	274
STAT3-4480	Sense 19mer		CUGAUAAACAGAAUAUUUA	275
STAT3-4831	Sense 19mer		UAGUGUAAAAAUUUAUAUU	276
STAT3-4833	Sense 19mer		GUGUAAAAAUUUAUAUUAU	277
STAT3-4836	Sense 19mer		UAAAAAUUUAUAUUAUUGU	278
STAT3-4837	Sense 19mer		AAAAAUUUAUAUUAUUGUG	279
STAT3-4909	Sense 19mer		UUUAACUUCCAGAAAUAAA	280
STAT3-370	Antisense 19mer		AUUAUGAAACACCAAAGUG	281
STAT3-372	Antisense 19mer		AGAUUAUGAAACACCAAAG	282
STAT3-424	Antisense 19mer		AACAUUCGACUCUUGCAGG	283
STAT3-425	Antisense 19mer		GAACAUUCGACUCUUGCAG	284
STAT3-426	Antisense 19mer		AGAACAUUCGACUCUUGCA	285
STAT3-429	Antisense 19mer		UAGAGAACAUUCGACUCUU	286
STAT3-430	Antisense 19mer		AUAGAGAACAUUCGACUCU	287
STAT3-432	Antisense 19mer		UGAUAGAGAACAUUCGACU	288
STAT3-433	Antisense 19mer		CUGAUAGAGAACAUUCGAC	289
STAT3-460	Antisense 19mer		AAACUGCUUGAUUCUUCGU	290

STAT3-461	Antisense 19mer		GAAACUGCUUGAUUCUUCG	291
STAT3-462	Antisense 19mer		AGAAACUGCUUGAUUCUUC	292
STAT3-492	Antisense 19mer		UCCAUUGGCUUCUCAAGAU	293
STAT3-678	Antisense 19mer		AUUUUCUGUUCUAGAUCCU	294
STAT3-681	Antisense 19mer		UUCAUUUUCUGUUCUAGAU	295
STAT3-715	Antisense 19mer		GAAAUCAAAGUCAUCCUGG	296
STAT3-716	Antisense 19mer		UGAAAUCAAAGUCAUCCUG	297
STAT3-717	Antisense 19mer		UUGAAAUCAAAGUCAUCCU	298
STAT3-720	Antisense 19mer		UAGUUGAAAUCAAAGUCAU	299
STAT3-721	Antisense 19mer		AUAGUUGAAAUCAAAGUCA	300
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STAT3-723	Antisense 19mer		UUAUAGUUGAAAUCAAAGU	302
STAT3-724	Antisense 19mer		UUUAUAGUUGAAAUCAAAG	303
STAT3-768	Antisense 19mer		UUGUUUCCAUUCAGAUCUU	304
STAT3-771	Antisense 19mer		UGGUUGUUUCCAUUCAGAU	305
STAT3-773	Antisense 19mer		ACUGGUUGUUUCCAUUCAG	306
STAT3-1000	Antisense 19mer		UGACGUUAUCCAGUUUUCU	307
STAT3-1001	Antisense 19mer		AUGACGUUAUCCAGUUUUC	308
STAT3-1003	Antisense 19mer		UAAUGACGUUAUCCAGUUU	309
STAT3-1006	Antisense 19mer		UGCUAAUGACGUUAUCCAG	310
STAT3-1008	Antisense 19mer		UCUGCUAAUGACGUUAUCC	311
STAT3-1009	Antisense 19mer		UUCUGCUAAUGACGUUAUC	312
STAT3-1010	Antisense 19mer		AUUCUGCUAAUGACGUUAU	313

STAT3-1047	Antisense 19mer		UCCAGUUUCUUAAUUUGUU	314
STAT3-1067	Antisense 19mer		AAACUUUUUGCUGCAACUC	315
STAT3-1068	Antisense 19mer		GAAACUUUUUGCUGCAACU	316
STAT3-1145	Antisense 19mer		UCAUUAAGUUUCUAAACAG	317
STAT3-1151	Antisense 19mer		CACUUUUCAUUAAGUUUCU	318
STAT3-1241	Antisense 19mer		UGACUUUAGUAGUGAACUG	319
STAT3-1268	Antisense 19mer		UCAACUCAGGGAAUUUGAC	320
STAT3-1272	Antisense 19mer		UAAUUCAACUCAGGGAAUU	321
STAT3-1273	Antisense 19mer		AUAAUUCAACUCAGGGAAU	322
STAT3-1275	Antisense 19mer		UGAUAAUUCAACUCAGGGA	323
STAT3-1277	Antisense 19mer		GCUGAUAAUUCAACUCAGG	324
STAT3-1278	Antisense 19mer		AGCUGAUAAUUCAACUCAG	325
STAT3-1279	Antisense 19mer		AAGCUGAUAAUUCAACUCA	326
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STAT3-1281	Antisense 19mer		UUAAGCUGAUAAUUCAACU	328
STAT3-1282	Antisense 19mer		UUUAAGCUGAUAAUUCAAC	329
STAT3-1283	Antisense 19mer		UUUUAAGCUGAUAAUUCAA	330
STAT3-1284	Antisense 19mer		AUUUUAAGCUGAUAAUUCA	331
STAT3-1286	Antisense 19mer		UAAUUUUAAGCUGAUAAUU	332
STAT3-1287	Antisense 19mer		UUAAUUUUAAGCUGAUAAU	333
STAT3-1292	Antisense 19mer		ACACUUUAAUUUUAAGCUG	334
STAT3-1293	Antisense 19mer		CACACUUUAAUUUUAAGCU	335
STAT3-1299	Antisense 19mer		UCAAUGCACACUUUAAUUU	336

STAT3-1305	Antisense 19mer		UCUUUGUCAAUGCACACUU	337
STAT3-1383	Antisense 19mer		UCCAUGUUCAUCACUUUUG	338
STAT3-1388	Antisense 19mer		AUUCUUCCAUGUUCAUCAC	339
STAT3-1427	Antisense 19mer		UCAAGUGUUUGAAUUCUGC	340
STAT3-1485	Antisense 19mer		AUCAGGGAAGCAUCACAAU	341
STAT3-1584	Antisense 19mer		AUCACCACAACUGGCAAGG	342
STAT3-1586	Antisense 19mer		AGAUCACCACAACUGGCAA	343
STAT3-1670	Antisense 19mer		AAAAGUUUACAUUCUUGGG	344
STAT3-1671	Antisense 19mer		AAAAAGUUUACAUUCUUGG	345
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STAT3-1674	Antisense 19mer		GUAAAAAAGUUUACAUUCU	348
STAT3-1676	Antisense 19mer		UGGUAAAAAAGUUUACAUU	349
STAT3-1813	Antisense 19mer		UGAAUAAUUCACACCAGGU	350
STAT3-1815	Antisense 19mer		CCUGAAUAAUUCACACCAG	351
STAT3-1817	Antisense 19mer		ACCCUGAAUAAUUCACACC	352
STAT3-1819	Antisense 19mer		ACACCCUGAAUAAUUCACA	353
STAT3-1904	Antisense 19mer		GGUCAAUGAUAUUGUCCAG	354
STAT3-1906	Antisense 19mer		AAGGUCAAUGAUAUUGUCC	355
STAT3-1907	Antisense 19mer		CAAGGUCAAUGAUAUUGUC	356
STAT3-1908	Antisense 19mer		ACAAGGUCAAUGAUAUUGU	357
STAT3-1909	Antisense 19mer		CACAAGGUCAAUGAUAUUG	358
STAT3-1910	Antisense 19mer		UCACAAGGUCAAUGAUAUU	359

STAT3-1911	Antisense 19mer		UUCACAAGGUCAAUGAUAU	360
STAT3-1912	Antisense 19mer		UUUCACAAGGUCAAUGAUA	361
STAT3-1913	Antisense 19mer		UUUUCACAAGGUCAAUGAU	362
STAT3-1914	Antisense 19mer		UUUUUCACAAGGUCAAUGA	363
STAT3-1916	Antisense 19mer		ACUUUUUCACAAGGUCAAU	364
STAT3-1917	Antisense 19mer		UACUUUUUCACAAGGUCAA	365
STAT3-1919	Antisense 19mer		UGUACUUUUUCACAAGGUC	366
STAT3-1920	Antisense 19mer		AUGUACUUUUUCACAAGGU	367
STAT3-2024	Antisense 19mer		UGAAUCUUAGCAGGAAGGU	368
STAT3-2135	Antisense 19mer		UGUUGUUCAGCUGCUGCUU	369
STAT3-2136	Antisense 19mer		AUGUUGUUCAGCUGCUGCU	370
STAT3-2138	Antisense 19mer		ACAUGUUGUUCAGCUGCUG	371
STAT3-2139	Antisense 19mer		GACAUGUUGUUCAGCUGCU	372
STAT3-2143	Antisense 19mer		AAAUGACAUGUUGUUCAGC	373
STAT3-2144	Antisense 19mer		CAAAUGACAUGUUGUUCAG	374
STAT3-2145	Antisense 19mer		GCAAAUGACAUGUUGUUCA	375
STAT3-2146	Antisense 19mer		AGCAAAUGACAUGUUGUUC	376
STAT3-2147	Antisense 19mer		CAGCAAAUGACAUGUUGUU	377
STAT3-2148	Antisense 19mer		UCAGCAAAUGACAUGUUGU	378
STAT3-2151	Antisense 19mer		AUUUCAGCAAAUGACAUGU	379
STAT3-2153	Antisense 19mer		UGAUUUCAGCAAAUGACAU	380
STAT3-2154	Antisense 19mer		AUGAUUUCAGCAAAUGACA	381
STAT3-2159	Antisense 19mer		CCAUGAUGAUUUCAGCAAA	382

STAT3-2322	Antisense 19mer		AACUUGGUCUUCAGGUAUG	383
STAT3-2325	Antisense 19mer		AUAAACUUGGUCUUCAGGU	384
STAT3-2327	Antisense 19mer		AGAUAAACUUGGUCUUCAG	385
STAT3-2329	Antisense 19mer		ACAGAUAAACUUGGUCUUC	386
STAT3-2333	Antisense 19mer		UCACACAGAUAAACUUGGU	387
STAT3-2335	Antisense 19mer		UGUCACACAGAUAAACUUG	388
STAT3-2404	Antisense 19mer		AAACUGCAUCAAUGAAUCU	389
STAT3-2405	Antisense 19mer		CAAACUGCAUCAAUGAAUC	390
STAT3-2407	Antisense 19mer		UCCAAACUGCAUCAAUGAA	391
STAT3-2408	Antisense 19mer		UUCCAAACUGCAUCAAUGA	392
STAT3-2411	Antisense 19mer		UAUUUCCAAACUGCAUCAA	393
STAT3-2412	Antisense 19mer		UUAUUUCCAAACUGCAUCA	394
STAT3-2413	Antisense 19mer		AUUAUUUCCAAACUGCAUC	395
STAT3-2416	Antisense 19mer		ACCAUUAUUUCCAAACUGC	396
STAT3-2418	Antisense 19mer		UCACCAUUAUUUCCAAACU	397
STAT3-2422	Antisense 19mer		ACCUUCACCAUUAUUUCCA	398
STAT3-2427	Antisense 19mer		UCAGCACCUUCACCAUUAU	399
STAT3-2612	Antisense 19mer		ACAAAGUUAGUAGUUUCAG	400
STAT3-2615	Antisense 19mer		ACCACAAAGUUAGUAGUUU	401
STAT3-2616	Antisense 19mer		AACCACAAAGUUAGUAGUU	402
STAT3-2617	Antisense 19mer		GAACCACAAAGUUAGUAGU	403
STAT3-2622	Antisense 19mer		AUCUGGAACCACAAAGUUA	404
STAT3-2625	Antisense 19mer		AAAAUCUGGAACCACAAAG	405

STAT3-2626	Antisense 19mer		AAAAAUCUGGAACCACAAA	406
STAT3-2627	Antisense 19mer		AAAAAAUCUGGAACCACAA	407
STAT3-2692	Antisense 19mer		UUCACUCAUUUCUCUAUUU	408
STAT3-2693	Antisense 19mer		AUUCACUCAUUUCUCUAUU	409
STAT3-2715	Antisense 19mer		UAGAUAAAAGCAGAUCACC	410
STAT3-2719	Antisense 19mer		CAUUUAGAUAAAAGCAGAU	411
STAT3-2721	Antisense 19mer		UGCAUUUAGAUAAAAGCAG	412
STAT3-2735	Antisense 19mer		AACACAUCCUUAUUUGCAU	413
STAT3-2741	Antisense 19mer		UCAGAGAACACAUCCUUAU	414
STAT3-2801	Antisense 19mer		ACAAGACAUUUCCUUUUUC	415
STAT3-2803	Antisense 19mer		ACACAAGACAUUUCCUUUU	416
STAT3-2804	Antisense 19mer		AACACAAGACAUUUCCUUU	417
STAT3-2806	Antisense 19mer		ACAACACAAGACAUUUCCU	418
STAT3-2807	Antisense 19mer		AACAACACAAGACAUUUCC	419
STAT3-2808	Antisense 19mer		AAACAACACAAGACAUUUC	420
STAT3-2809	Antisense 19mer		AAAACAACACAAGACAUUU	421
STAT3-2810	Antisense 19mer		CAAAACAACACAAGACAUU	422
STAT3-2811	Antisense 19mer		ACAAAACAACACAAGACAU	423
STAT3-2812	Antisense 19mer		AACAAAACAACACAAGACA	424
STAT3-2813	Antisense 19mer		GAACAAAACAACACAAGAC	425
STAT3-2846	Antisense 19mer		AUAACAAAAAGCUGCUGAG	426
STAT3-2848	Antisense 19mer		CAAUAACAAAAAGCUGCUG	427
STAT3-2849	Antisense 19mer		ACAAUAACAAAAAGCUGCU	428

STAT3-2850	Antisense 19mer		AACAAUAACAAAAAGCUGC	429
STAT3-2851	Antisense 19mer		CAACAAUAACAAAAAGCUG	430
STAT3-2852	Antisense 19mer		ACAACAAUAACAAAAAGCU	431
STAT3-2853	Antisense 19mer		AACAACAAUAACAAAAAGC	432
STAT3-2854	Antisense 19mer		CAACAACAAUAACAAAAAG	433
STAT3-2855	Antisense 19mer		ACAACAACAAUAACAAAAA	434
STAT3-2856	Antisense 19mer		AACAACAACAAUAACAAAA	435
STAT3-2857	Antisense 19mer		CAACAACAACAAUAACAAA	436
STAT3-2858	Antisense 19mer		ACAACAACAACAAUAACAA	437
STAT3-2859	Antisense 19mer		AACAACAACAACAAUAACA	438
STAT3-2860	Antisense 19mer		GAACAACAACAACAAUAAC	439
STAT3-2861	Antisense 19mer		AGAACAACAACAACAAUAA	440
STAT3-2862	Antisense 19mer		AAGAACAACAACAACAAUA	441
STAT3-2863	Antisense 19mer		UAAGAACAACAACAACAAU	442
STAT3-2865	Antisense 19mer		UCUAAGAACAACAACAACA	443
STAT3-2867	Antisense 19mer		UGUCUAAGAACAACAACAA	444
STAT3-2868	Antisense 19mer		UUGUCUAAGAACAACAACA	445
STAT3-2975	Antisense 19mer		UGUCAGCAAGGUUAAAAAG	446
STAT3-2979	Antisense 19mer		UGGAUGUCAGCAAGGUUAA	447
STAT3-2985	Antisense 19mer		UCUAUUUGGAUGUCAGCAA	448
STAT3-3025	Antisense 19mer		UUAAUUUAAAAAGAAACCU	449
STAT3-3037	Antisense 19mer		UGUUAUUAUUUCUUAAUUU	450
STAT3-3038	Antisense 19mer		UUGUUAUUAUUUCUUAAUU	451

STAT3-3039	Antisense 19mer		AUUGUUAUUAUUUCUUAAU	452
STAT3-3041	Antisense 19mer		UAAUUGUUAUUAUUUCUUA	453
STAT3-3042	Antisense 19mer		UUAAUUGUUAUUAUUUCUU	454
STAT3-3043	Antisense 19mer		UUUAAUUGUUAUUAUUUCU	455
STAT3-3225	Antisense 19mer		AAUUUUUUGUACUUUUAGU	456
STAT3-3226	Antisense 19mer		UAAUUUUUUGUACUUUUAG	457
STAT3-3605	Antisense 19mer		UACAAAGGAAAAUAAGUCU	458
STAT3-3611	Antisense 19mer		AUACAUUACAAAGGAAAAU	459
STAT3-3906	Antisense 19mer		UCAUGUCCAACCUGUAACU	460
STAT3-4311	Antisense 19mer		UAACAAACAGAAUUCCACA	461
STAT3-4314	Antisense 19mer		AUUUAACAAACAGAAUUCC	462
STAT3-4317	Antisense 19mer		UUGAUUUAACAAACAGAAU	463
STAT3-4321	Antisense 19mer		UAAUUUGAUUUAACAAACA	464
STAT3-4465	Antisense 19mer		UCAGUUAAGCUUAUUAUGU	465
STAT3-4479	Antisense 19mer		AAAUAUUCUGUUUAUCAGU	466
STAT3-4480	Antisense 19mer		UAAAUAUUCUGUUUAUCAG	467
STAT3-4831	Antisense 19mer		AAUAUAAAUUUUUACACUA	468
STAT3-4833	Antisense 19mer		AUAAUAUAAAUUUUUACAC	469
STAT3-4836	Antisense 19mer		ACAAUAAUAUAAAUUUUUA	470
STAT3-4837	Antisense 19mer		CACAAUAAUAUAAAUUUUU	471
STAT3-4909	Antisense 19mer		UUUAUUUCUGGAAGUUAAA	472
STAT3-370	25 mer Sense Strand		CACUUUGGUGUUUCAUAAUAGCAGC	473

STAT3-372	25 mer Sense Strand		CUUUGGUGUUUCAUAAUCUAGCAGC	474
STAT3-424	25 mer Sense Strand		CCUGCAAGAGUCGAAUGUUAGCAGC	475
STAT3-425	25 mer Sense Strand		CUGCAAGAGUCGAAUGUUCAGCAGC	476
STAT3-426	25 mer Sense Strand		UGCAAGAGUCGAAUGUUCUAGCAGC	477
STAT3-429	25 mer Sense Strand		AAGAGUCGAAUGUUCUCUAAGCAGC	478
STAT3-430	25 mer Sense Strand		AGAGUCGAAUGUUCUCUAUAGCAGC	479
STAT3-432	25 mer Sense Strand		AGUCGAAUGUUCUCUAUCAAGCAGC	480
STAT3-433	25 mer Sense Strand		GUCGAAUGUUCUCUAUCAGAGCAGC	481
STAT3-460	25 mer Sense Strand		ACGAAGAAUCAAGCAGUUUAGCAGC	482
STAT3-461	25 mer Sense Strand		CGAAGAAUCAAGCAGUUUCAGCAGC	483
STAT3-462	25 mer Sense Strand		GAAGAAUCAAGCAGUUUCUAGCAGC	484
STAT3-492	25 mer Sense Strand		AUCUUGAGAAGCCAAUGGAAGCAGC	485
STAT3-678	25 mer Sense Strand		AGGAUCUAGAACAGAAAAUAGCAGC	486
STAT3-681	25 mer Sense Strand		AUCUAGAACAGAAAAUGAAAGCAGC	487
STAT3-715	25 mer Sense Strand		CCAGGAUGACUUUGAUUUCAGCAGC	488

STAT3-716	25 mer Sense Strand		CAGGAUGACUUUGAUUUCAAGCAGC	489
STAT3-717	25 mer Sense Strand		AGGAUGACUUUGAUUUCAAAGCAGC	490
STAT3-720	25 mer Sense Strand		AUGACUUUGAUUUCAACUAAGCAGC	491
STAT3-721	25 mer Sense Strand		UGACUUUGAUUUCAACUAUAGCAGC	492
STAT3-722	25 mer Sense Strand		GACUUUGAUUUCAACUAUAAGCAGC	493
STAT3-723	25 mer Sense Strand		ACUUUGAUUUCAACUAUAAAGCAGC	494
STAT3-724	25 mer Sense Strand		CUUUGAUUUCAACUAUAAAAGCAGC	495
STAT3-768	25 mer Sense Strand		AAGAUCUGAAUGGAAACAAAGCAGC	496
STAT3-771	25 mer Sense Strand		AUCUGAAUGGAAACAACCAAGCAGC	497
STAT3-773	25 mer Sense Strand		CUGAAUGGAAACAACCAGUAGCAGC	498
STAT3-1000	25 mer Sense Strand		AGAAAACUGGAUAACGUCAAGCAGC	499
STAT3-1001	25 mer Sense Strand		GAAAACUGGAUAACGUCAUAGCAGC	500
STAT3-1003	25 mer Sense Strand		AAACUGGAUAACGUCAUUAAGCAGC	501
STAT3-1006	25 mer Sense Strand		CUGGAUAACGUCAUUAGCAAGCAGC	502
STAT3-1008	25 mer Sense Strand		GGAUAACGUCAUUAGCAGAAGCAGC	503

STAT3-1009	25 mer Sense Strand		GAUAACGUCAUUAGCAGAAAGCAGC	504
STAT3-1010	25 mer Sense Strand		AUAACGUCAUUAGCAGAAUAGCAGC	505
STAT3-1047	25 mer Sense Strand		AACAAAUUAAGAAACUGGAAGCAGC	506
STAT3-1067	25 mer Sense Strand		GAGUUGCAGCAAAAAGUUUAGCAGC	507
STAT3-1068	25 mer Sense Strand		AGUUGCAGCAAAAAGUUUCAGCAGC	508
STAT3-1145	25 mer Sense Strand		CUGUUUAGAAACUUAAUGAAGCAGC	509
STAT3-1151	25 mer Sense Strand		AGAAACUUAAUGAAAAGUGAGCAGC	510
STAT3-1241	25 mer Sense Strand		CAGUUCACUACUAAAGUCAAGCAGC	511
STAT3-1268	25 mer Sense Strand		GUCAAAUUCCCUGAGUUGAAGCAGC	512
STAT3-1272	25 mer Sense Strand		AAUUCCCUGAGUUGAAUUAAGCAGC	513
STAT3-1273	25 mer Sense Strand		AUUCCCUGAGUUGAAUUAUAGCAGC	514
STAT3-1275	25 mer Sense Strand		UCCCUGAGUUGAAUUAUCAAGCAGC	515
STAT3-1277	25 mer Sense Strand		CCUGAGUUGAAUUAUCAGCAGCAGC	516
STAT3-1278	25 mer Sense Strand		CUGAGUUGAAUUAUCAGCUAGCAGC	517
STAT3-1279	25 mer Sense Strand		UGAGUUGAAUUAUCAGCUUAGCAGC	518

STAT3-1280	25 mer Sense Strand		GAGUUGAAUUAUCAGCUUAAGCAGC	519
STAT3-1281	25 mer Sense Strand		AGUUGAAUUAUCAGCUUAAAGCAGC	520
STAT3-1282	25 mer Sense Strand		GUUGAAUUAUCAGCUUAAAAGCAGC	521
STAT3-1283	25 mer Sense Strand		UUGAAUUAUCAGCUUAAAAAGCAGC	522
STAT3-1284	25 mer Sense Strand		UGAAUUAUCAGCUUAAAAUAGCAGC	523
STAT3-1286	25 mer Sense Strand		AAUUAUCAGCUUAAAAUUAAGCAGC	524
STAT3-1287	25 mer Sense Strand		AUUAUCAGCUUAAAAUUAAAGCAGC	525
STAT3-1292	25 mer Sense Strand		CAGCUUAAAAUUAAAGUGUAGCAGC	526
STAT3-1293	25 mer Sense Strand		AGCUUAAAAUUAAAGUGUGAGCAGC	527
STAT3-1299	25 mer Sense Strand		AAAUUAAAGUGUGCAUUGAAGCAGC	528
STAT3-1305	25 mer Sense Strand		AAGUGUGCAUUGACAAAGAAGCAGC	529
STAT3-1383	25 mer Sense Strand		CAAAAGUGAUGAACAUGGAAGCAGC	530
STAT3-1388	25 mer Sense Strand		GUGAUGAACAUGGAAGAAUAGCAGC	531
STAT3-1427	25 mer Sense Strand		GCAGAAUUCAAACACUUGAAGCAGC	532
STAT3-1485	25 mer Sense Strand		AUUGUGAUGCUUCCCUGAUAGCAGC	533

STAT3-1584	25 mer Sense Strand		CCUUGCCAGUUGUGGUGAUAGCAGC	534
STAT3-1586	25 mer Sense Strand		UUGCCAGUUGUGGUGAUCUAGCAGC	535
STAT3-1670	25 mer Sense Strand		CCCAAGAAUGUAAACUUUUAGCAGC	536
STAT3-1671	25 mer Sense Strand		CCAAGAAUGUAAACUUUUUAGCAGC	537
STAT3-1672	25 mer Sense Strand		CAAGAAUGUAAACUUUUUUAGCAGC	538
STAT3-1673	25 mer Sense Strand		AAGAAUGUAAACUUUUUUAAGCAGC	539
STAT3-1674	25 mer Sense Strand		AGAAUGUAAACUUUUUUACAGCAGC	540
STAT3-1676	25 mer Sense Strand		AAUGUAAACUUUUUUACCAAGCAGC	541
STAT3-1813	25 mer Sense Strand		ACCUGGUGUGAAUUAUUCAAGCAGC	542
STAT3-1815	25 mer Sense Strand		CUGGUGUGAAUUAUUCAGGAGCAGC	543
STAT3-1817	25 mer Sense Strand		GGUGUGAAUUAUUCAGGGUAGCAGC	544
STAT3-1819	25 mer Sense Strand		UGUGAAUUAUUCAGGGUGUAGCAGC	545
STAT3-1904	25 mer Sense Strand		CUGGACAAUAUCAUUGACCAGCAGC	546
STAT3-1906	25 mer Sense Strand		GGACAAUAUCAUUGACCUUAGCAGC	547
STAT3-1907	25 mer Sense Strand		GACAAUAUCAUUGACCUUGAGCAGC	548

STAT3-1908	25 mer Sense Strand		ACAAUAUCAUUGACCUUGUAGCAGC	549
STAT3-1909	25 mer Sense Strand		CAAUAUCAUUGACCUUGUGAGCAGC	550
STAT3-1910	25 mer Sense Strand		AAUAUCAUUGACCUUGUGAAGCAGC	551
STAT3-1911	25 mer Sense Strand		AUAUCAUUGACCUUGUGAAAGCAGC	552
STAT3-1912	25 mer Sense Strand		UAUCAUUGACCUUGUGAAAAGCAGC	553
STAT3-1913	25 mer Sense Strand		AUCAUUGACCUUGUGAAAAAGCAGC	554
STAT3-1914	25 mer Sense Strand		UCAUUGACCUUGUGAAAAAAGCAGC	555
STAT3-1916	25 mer Sense Strand		AUUGACCUUGUGAAAAAGUAGCAGC	556
STAT3-1917	25 mer Sense Strand		UUGACCUUGUGAAAAAGUAAGCAGC	557
STAT3-1919	25 mer Sense Strand		GACCUUGUGAAAAAGUACAAGCAGC	558
STAT3-1920	25 mer Sense Strand		ACCUUGUGAAAAAGUACAUAGCAGC	559
STAT3-2024	25 mer Sense Strand		ACCUUCCUGCUAAGAUUCAAGCAGC	560
STAT3-2135	25 mer Sense Strand		AAGCAGCAGCUGAACAACAAGCAGC	561
STAT3-2136	25 mer Sense Strand		AGCAGCAGCUGAACAACAUAGCAGC	562
STAT3-2138	25 mer Sense Strand		CAGCAGCUGAACAACAUGUAGCAGC	563

STAT3-2139	25 mer Sense Strand		AGCAGCUGAACAACAUGUCAGCAGC	564
STAT3-2143	25 mer Sense Strand		GCUGAACAACAUGUCAUUUAGCAGC	565
STAT3-2144	25 mer Sense Strand		CUGAACAACAUGUCAUUUGAGCAGC	566
STAT3-2145	25 mer Sense Strand		UGAACAACAUGUCAUUUGCAGCAGC	567
STAT3-2146	25 mer Sense Strand		GAACAACAUGUCAUUUGCUAGCAGC	568
STAT3-2147	25 mer Sense Strand		AACAACAUGUCAUUUGCUGAGCAGC	569
STAT3-2148	25 mer Sense Strand		ACAACAUGUCAUUUGCUGAAGCAGC	570
STAT3-2151	25 mer Sense Strand		ACAUGUCAUUUGCUGAAAUAGCAGC	571
STAT3-2153	25 mer Sense Strand		AUGUCAUUUGCUGAAAUCAAGCAGC	572
STAT3-2154	25 mer Sense Strand		UGUCAUUUGCUGAAAUCAUAGCAGC	573
STAT3-2159	25 mer Sense Strand		UUUGCUGAAAUCAUCAUGGAGCAGC	574
STAT3-2322	25 mer Sense Strand		CAUACCUGAAGACCAAGUUAGCAGC	575
STAT3-2325	25 mer Sense Strand		ACCUGAAGACCAAGUUUAUAGCAGC	576
STAT3-2327	25 mer Sense Strand		CUGAAGACCAAGUUUAUCUAGCAGC	577
STAT3-2329	25 mer Sense Strand		GAAGACCAAGUUUAUCUGUAGCAGC	578

STAT3-2333	25 mer Sense Strand		ACCAAGUUUAUCUGUGUGAAGCAGC	579
STAT3-2335	25 mer Sense Strand		CAAGUUUAUCUGUGUGACAAGCAGC	580
STAT3-2404	25 mer Sense Strand		AGAUUCAUUGAUGCAGUUUAGCAGC	581
STAT3-2405	25 mer Sense Strand		GAUUCAUUGAUGCAGUUUGAGCAGC	582
STAT3-2407	25 mer Sense Strand		UUCAUUGAUGCAGUUUGGAAGCAGC	583
STAT3-2408	25 mer Sense Strand		UCAUUGAUGCAGUUUGGAAAGCAGC	584
STAT3-2411	25 mer Sense Strand		UUGAUGCAGUUUGGAAAUAAGCAGC	585
STAT3-2412	25 mer Sense Strand		UGAUGCAGUUUGGAAAUAAAGCAGC	586
STAT3-2413	25 mer Sense Strand		GAUGCAGUUUGGAAAUAAUAGCAGC	587
STAT3-2416	25 mer Sense Strand		GCAGUUUGGAAAUAAUGGUAGCAGC	588
STAT3-2418	25 mer Sense Strand		AGUUUGGAAAUAAUGGUGAAGCAGC	589
STAT3-2422	25 mer Sense Strand		UGGAAAUAAUGGUGAAGGUAGCAGC	590
STAT3-2427	25 mer Sense Strand		AUAAUGGUGAAGGUGCUGAAGCAGC	591
STAT3-2612	25 mer Sense Strand		CUGAAACUACUAACUUUGUAGCAGC	592
STAT3-2615	25 mer Sense Strand		AAACUACUAACUUUGUGGUAGCAGC	593

STAT3-2616	25 mer Sense Strand		AACUACUAACUUUGUGGUUAGCAGC	594
STAT3-2617	25 mer Sense Strand		ACUACUAACUUUGUGGUUCAGCAGC	595
STAT3-2622	25 mer Sense Strand		UAACUUUGUGGUUCCAGAUAGCAGC	596
STAT3-2625	25 mer Sense Strand		CUUUGUGGUUCCAGAUUUUAGCAGC	597
STAT3-2626	25 mer Sense Strand		UUUGUGGUUCCAGAUUUUUAGCAGC	598
STAT3-2627	25 mer Sense Strand		UUGUGGUUCCAGAUUUUUUAGCAGC	599
STAT3-2692	25 mer Sense Strand		AAAUAGAGAAAUGAGUGAAAGCAGC	600
STAT3-2693	25 mer Sense Strand		AAUAGAGAAAUGAGUGAAUAGCAGC	601
STAT3-2715	25 mer Sense Strand		GGUGAUCUGCUUUUAUCUAAGCAGC	602
STAT3-2719	25 mer Sense Strand		AUCUGCUUUUAUCUAAAUGAGCAGC	603
STAT3-2721	25 mer Sense Strand		CUGCUUUUAUCUAAAUGCAAGCAGC	604
STAT3-2735	25 mer Sense Strand		AUGCAAAUAAGGAUGUGUUAGCAGC	605
STAT3-2741	25 mer Sense Strand		AUAAGGAUGUGUUCUCUGAAGCAGC	606
STAT3-2801	25 mer Sense Strand		GAAAAAGGAAAUGUCUUGUAGCAGC	607
STAT3-2803	25 mer Sense Strand		AAAAGGAAAUGUCUUGUGUAGCAGC	608

STAT3-2804	25 mer Sense Strand		AAAGGAAAUGUCUUGUGUUAGCAGC	609
STAT3-2806	25 mer Sense Strand		AGGAAAUGUCUUGUGUUGUAGCAGC	610
STAT3-2807	25 mer Sense Strand		GGAAAUGUCUUGUGUUGUUAGCAGC	611
STAT3-2808	25 mer Sense Strand		GAAAUGUCUUGUGUUGUUUAGCAGC	612
STAT3-2809	25 mer Sense Strand		AAAUGUCUUGUGUUGUUUUAGCAGC	613
STAT3-2810	25 mer Sense Strand		AAUGUCUUGUGUUGUUUUGAGCAGC	614
STAT3-2811	25 mer Sense Strand		AUGUCUUGUGUUGUUUUGUAGCAGC	615
STAT3-2812	25 mer Sense Strand		UGUCUUGUGUUGUUUUGUUAGCAGC	616
STAT3-2813	25 mer Sense Strand		GUCUUGUGUUGUUUUGUUCAGCAGC	617
STAT3-2846	25 mer Sense Strand		CUCAGCAGCUUUUUGUUAUAGCAGC	618
STAT3-2848	25 mer Sense Strand		CAGCAGCUUUUUGUUAUUGAGCAGC	619
STAT3-2849	25 mer Sense Strand		AGCAGCUUUUUGUUAUUGUAGCAGC	620
STAT3-2850	25 mer Sense Strand		GCAGCUUUUUGUUAUUGUUAGCAGC	621
STAT3-2851	25 mer Sense Strand		CAGCUUUUUGUUAUUGUUGAGCAGC	622
STAT3-2852	25 mer Sense Strand		AGCUUUUUGUUAUUGUUGUAGCAGC	623

STAT3-2853	25 mer Sense Strand		GCUUUUUGUUAUUGUUGUUAGCAGC	624
STAT3-2854	25 mer Sense Strand		CUUUUUGUUAUUGUUGUUGAGCAGC	625
STAT3-2855	25 mer Sense Strand		UUUUUGUUAUUGUUGUUGUAGCAGC	626
STAT3-2856	25 mer Sense Strand		UUUUGUUAUUGUUGUUGUUAGCAGC	627
STAT3-2857	25 mer Sense Strand		UUUGUUAUUGUUGUUGUUGAGCAGC	628
STAT3-2858	25 mer Sense Strand		UUGUUAUUGUUGUUGUUGUAGCAGC	629
STAT3-2859	25 mer Sense Strand		UGUUAUUGUUGUUGUUGUUAGCAGC	630
STAT3-2860	25 mer Sense Strand		GUUAUUGUUGUUGUUGUUCAGCAGC	631
STAT3-2861	25 mer Sense Strand		UUAUUGUUGUUGUUGUUCUAGCAGC	632
STAT3-2862	25 mer Sense Strand		UAUUGUUGUUGUUGUUCUUAGCAGC	633
STAT3-2863	25 mer Sense Strand		AUUGUUGUUGUUGUUCUUAAGCAGC	634
STAT3-2865	25 mer Sense Strand		UGUUGUUGUUGUUCUUAGAAGCAGC	635
STAT3-2867	25 mer Sense Strand		UUGUUGUUGUUCUUAGACAAGCAGC	636
STAT3-2868	25 mer Sense Strand		UGUUGUUGUUCUUAGACAAAGCAGC	637
STAT3-2975	25 mer Sense Strand		CUUUUUAACCUUGCUGACAAGCAGC	638

STAT3-2979	25 mer Sense Strand		UUAACCUUGCUGACAUCCAAGCAGC	639
STAT3-2985	25 mer Sense Strand		UUGCUGACAUCCAAAUAGAAGCAGC	640
STAT3-3025	25 mer Sense Strand		AGGUUUCUUUUUAAAUUAAAGCAGC	641
STAT3-3037	25 mer Sense Strand		AAAUUAAGAAAUAAUAACAAGCAGC	642
STAT3-3038	25 mer Sense Strand		AAUUAAGAAAUAAUAACAAAGCAGC	643
STAT3-3039	25 mer Sense Strand		AUUAAGAAAUAAUAACAAUAGCAGC	644
STAT3-3041	25 mer Sense Strand		UAAGAAAUAAUAACAAUUAAGCAGC	645
STAT3-3042	25 mer Sense Strand		AAGAAAUAAUAACAAUUAAAGCAGC	646
STAT3-3043	25 mer Sense Strand		AGAAAUAAUAACAAUUAAAAGCAGC	647
STAT3-3225	25 mer Sense Strand		ACUAAAAGUACAAAAAAUUAGCAGC	648
STAT3-3226	25 mer Sense Strand		CUAAAAGUACAAAAAAUUAAGCAGC	649
STAT3-3605	25 mer Sense Strand		AGACUUAUUUUCCUUUGUAAGCAGC	650
STAT3-3611	25 mer Sense Strand		AUUUUCCUUUGUAAUGUAUAGCAGC	651
STAT3-3906	25 mer Sense Strand		AGUUACAGGUUGGACAUGAAGCAGC	652
STAT3-4311	25 mer Sense Strand		UGUGGAAUUCUGUUUGUUAAGCAGC	653

STAT3-4314	25 mer Sense Strand		GGAAUUCUGUUUGUUAAAUAGCAGC	654
STAT3-4317	25 mer Sense Strand		AUUCUGUUUGUUAAAUCAAAGCAGC	655
STAT3-4321	25 mer Sense Strand		UGUUUGUUAAAUCAAAUUAAGCAGC	656
STAT3-4465	25 mer Sense Strand		ACAUAAUAAGCUUAACUGAAGCAGC	657
STAT3-4479	25 mer Sense Strand		ACUGAUAAACAGAAUAUUUAGCAGC	658
STAT3-4480	25 mer Sense Strand		CUGAUAAACAGAAUAUUUAAGCAGC	659
STAT3-4831	25 mer Sense Strand		UAGUGUAAAAAUUUAUAUUAGCAGC	660
STAT3-4833	25 mer Sense Strand		GUGUAAAAAUUUAUAUUAUAGCAGC	661
STAT3-4836	25 mer Sense Strand		UAAAAAUUUAUAUUAUUGUAGCAGC	662
STAT3-4837	25 mer Sense Strand		AAAAAUUUAUAUUAUUGUGAGCAGC	663
STAT3-4909	25 mer Sense Strand		UUUAACUUCCAGAAAUAAAAGCAGC	664
STAT3-370	27 mer Antisense Strand		GCUGCUAUUAUGAAACACCAAAGUGGG	665
STAT3-372	27 mer Antisense Strand		GCUGCUAGAUUAUGAAACACCAAAGGG	666
STAT3-424	27 mer Antisense Strand		GCUGCUAACAUUCGACUCUUGCAGGGG	667
STAT3-425	27 mer Antisense Strand		GCUGCUGAACAUUCGACUCUUGCAGGG	668

STAT3-426	27 mer Antisense Strand		GCUGCUAGAACAUUCGACUCUUGCAGG	669
STAT3-429	27 mer Antisense Strand		GCUGCUUAGAGAACAUUCGACUCUUGG	670
STAT3-430	27 mer Antisense Strand		GCUGCUAUAGAGAACAUUCGACUCUGG	671
STAT3-432	27 mer Antisense Strand		GCUGCUUGAUAGAGAACAUUCGACUGG	672
STAT3-433	27 mer Antisense Strand		GCUGCUCUGAUAGAGAACAUUCGACGG	673
STAT3-460	27 mer Antisense Strand		GCUGCUAAACUGCUUGAUUCUUCGUGG	674
STAT3-461	27 mer Antisense Strand		GCUGCUGAAACUGCUUGAUUCUUCGGG	675
STAT3-462	27 mer Antisense Strand		GCUGCUAGAAACUGCUUGAUUCUUCGG	676
STAT3-492	27 mer Antisense Strand		GCUGCUUCCAUUGGCUUCUCAAGAUGG	677
STAT3-678	27 mer Antisense Strand		GCUGCUAUUUUCUGUUCUAGAUCCUGG	678
STAT3-681	27 mer Antisense Strand		GCUGCUUUCAUUUUCUGUUCUAGAUGG	679
STAT3-715	27 mer Antisense Strand		GCUGCUGAAAUCAAAGUCAUCCUGGGG	680
STAT3-716	27 mer Antisense Strand		GCUGCUUGAAAUCAAAGUCAUCCUGGG	681
STAT3-717	27 mer Antisense Strand		GCUGCUUUGAAAUCAAAGUCAUCCUGG	682
STAT3-720	27 mer Antisense Strand		GCUGCUUAGUUGAAAUCAAAGUCAUGG	683

STAT3-721	27 mer Antisense Strand		GCUGCUAUAGUUGAAAUCAAAGUCAGG	684
STAT3-722	27 mer Antisense Strand		GCUGCUUAUAGUUGAAAUCAAAGUCGG	685
STAT3-723	27 mer Antisense Strand		GCUGCUUUAUAGUUGAAAUCAAAGUGG	686
STAT3-724	27 mer Antisense Strand		GCUGCUUUUAUAGUUGAAAUCAAAGGG	687
STAT3-768	27 mer Antisense Strand		GCUGCUUUGUUUCCAUUCAGAUCUUGG	688
STAT3-771	27 mer Antisense Strand		GCUGCUUGGUUGUUUCCAUUCAGAUGG	689
STAT3-773	27 mer Antisense Strand		GCUGCUACUGGUUGUUUCCAUUCAGGG	690
STAT3-1000	27 mer Antisense Strand		GCUGCUUGACGUUAUCCAGUUUUCUGG	691
STAT3-1001	27 mer Antisense Strand		GCUGCUAUGACGUUAUCCAGUUUUCGG	692
STAT3-1003	27 mer Antisense Strand		GCUGCUUAAUGACGUUAUCCAGUUUGG	693
STAT3-1006	27 mer Antisense Strand		GCUGCUUGCUAAUGACGUUAUCCAGGG	694
STAT3-1008	27 mer Antisense Strand		GCUGCUUCUGCUAAUGACGUUAUCCGG	695
STAT3-1009	27 mer Antisense Strand		GCUGCUUUCUGCUAAUGACGUUAUCGG	696
STAT3-1010	27 mer Antisense Strand		GCUGCUAUUCUGCUAAUGACGUUAUGG	697
STAT3-1047	27 mer Antisense Strand		GCUGCUUCCAGUUUCUUAAUUUGUUGG	698

STAT3-1067	27 mer Antisense Strand		GCUGCUAAACUUUUUGCUGCAACUCGG	699
STAT3-1068	27 mer Antisense Strand		GCUGCUGAAACUUUUUGCUGCAACUGG	700
STAT3-1145	27 mer Antisense Strand		GCUGCUUCAUUAAGUUUCUAAACAGGG	701
STAT3-1151	27 mer Antisense Strand		GCUGCUCACUUUUCAUUAAGUUUCUGG	702
STAT3-1241	27 mer Antisense Strand		GCUGCUUGACUUUAGUAGUGAACUGGG	703
STAT3-1268	27 mer Antisense Strand		GCUGCUUCAACUCAGGGAAUUUGACGG	704
STAT3-1272	27 mer Antisense Strand		GCUGCUUAAUUCAACUCAGGGAAUUGG	705
STAT3-1273	27 mer Antisense Strand		GCUGCUAUAAUUCAACUCAGGGAAUGG	706
STAT3-1275	27 mer Antisense Strand		GCUGCUUGAUAAUUCAACUCAGGGAGG	707
STAT3-1277	27 mer Antisense Strand		GCUGCUGCUGAUAAUUCAACUCAGGGG	708
STAT3-1278	27 mer Antisense Strand		GCUGCUAGCUGAUAAUUCAACUCAGGG	709
STAT3-1279	27 mer Antisense Strand		GCUGCUAAGCUGAUAAUUCAACUCAGG	710
STAT3-1280	27 mer Antisense Strand		GCUGCUUAAGCUGAUAAUUCAACUCGG	711
STAT3-1281	27 mer Antisense Strand		GCUGCUUUAAGCUGAUAAUUCAACUGG	712
STAT3-1282	27 mer Antisense Strand		GCUGCUUUUAAGCUGAUAAUUCAACGG	713

STAT3-1283	27 mer Antisense Strand		GCUGCUUUUUAAGCUGAUAAUUCAAGG	714
STAT3-1284	27 mer Antisense Strand		GCUGCUAUUUUAAGCUGAUAAUUCAGG	715
STAT3-1286	27 mer Antisense Strand		GCUGCUUAAUUUUAAGCUGAUAAUUGG	716
STAT3-1287	27 mer Antisense Strand		GCUGCUUUAAUUUUAAGCUGAUAAUGG	717
STAT3-1292	27 mer Antisense Strand		GCUGCUACACUUUAAUUUUAAGCUGGG	718
STAT3-1293	27 mer Antisense Strand		GCUGCUCACACUUUAAUUUUAAGCUGG	719
STAT3-1299	27 mer Antisense Strand		GCUGCUUCAAUGCACACUUUAAUUUGG	720
STAT3-1305	27 mer Antisense Strand		GCUGCUUCUUUGUCAAUGCACACUUGG	721
STAT3-1383	27 mer Antisense Strand		GCUGCUUCCAUGUUCAUCACUUUUGGG	722
STAT3-1388	27 mer Antisense Strand		GCUGCUAUUCUUCCAUGUUCAUCACGG	723
STAT3-1427	27 mer Antisense Strand		GCUGCUUCAAGUGUUUGAAUUCUGCGG	724
STAT3-1485	27 mer Antisense Strand		GCUGCUAUCAGGGAAGCAUCACAAUGG	725
STAT3-1584	27 mer Antisense Strand		GCUGCUAUCACCACAACUGGCAAGGGG	726
STAT3-1586	27 mer Antisense Strand		GCUGCUAGAUCACCACAACUGGCAAGG	727
STAT3-1670	27 mer Antisense Strand		GCUGCUAAAAGUUUACAUUCUUGGGGG	728

STAT3-1671	27 mer Antisense Strand		GCUGCUAAAAAGUUUACAUUCUUGGGG	729
STAT3-1672	27 mer Antisense Strand		GCUGCUAAAAAAGUUUACAUUCUUGGG	730
STAT3-1673	27 mer Antisense Strand		GCUGCUUAAAAAAGUUUACAUUCUUGG	731
STAT3-1674	27 mer Antisense Strand		GCUGCUGUAAAAAAGUUUACAUUCUGG	732
STAT3-1676	27 mer Antisense Strand		GCUGCUUGGUAAAAAAGUUUACAUUGG	733
STAT3-1813	27 mer Antisense Strand		GCUGCUUGAAUAAUUCACACCAGGUGG	734
STAT3-1815	27 mer Antisense Strand		GCUGCUCCUGAAUAAUUCACACCAGGG	735
STAT3-1817	27 mer Antisense Strand		GCUGCUACCCUGAAUAAUUCACACCGG	736
STAT3-1819	27 mer Antisense Strand		GCUGCUACACCCUGAAUAAUUCACAGG	737
STAT3-1904	27 mer Antisense Strand		GCUGCUGGUCAAUGAUAUUGUCCAGGG	738
STAT3-1906	27 mer Antisense Strand		GCUGCUAAGGUCAAUGAUAUUGUCCGG	739
STAT3-1907	27 mer Antisense Strand		GCUGCUCAAGGUCAAUGAUAUUGUCGG	740
STAT3-1908	27 mer Antisense Strand		GCUGCUACAAGGUCAAUGAUAUUGUGG	741
STAT3-1909	27 mer Antisense Strand		GCUGCUCACAAGGUCAAUGAUAUUGGG	742
STAT3-1910	27 mer Antisense Strand		GCUGCUUCACAAGGUCAAUGAUAUUGG	743

STAT3-1911	27 mer Antisense Strand		GCUGCUUUCACAAGGUCAAUGAUAUGG	744
STAT3-1912	27 mer Antisense Strand		GCUGCUUUUCACAAGGUCAAUGAUAGG	745
STAT3-1913	27 mer Antisense Strand		GCUGCUUUUUCACAAGGUCAAUGAUGG	746
STAT3-1914	27 mer Antisense Strand		GCUGCUUUUUUCACAAGGUCAAUGAGG	747
STAT3-1916	27 mer Antisense Strand		GCUGCUACUUUUUCACAAGGUCAAUGG	748
STAT3-1917	27 mer Antisense Strand		GCUGCUUACUUUUUCACAAGGUCAAGG	749
STAT3-1919	27 mer Antisense Strand		GCUGCUUGUACUUUUUCACAAGGUCGG	750
STAT3-1920	27 mer Antisense Strand		GCUGCUAUGUACUUUUUCACAAGGUGG	751
STAT3-2024	27 mer Antisense Strand		GCUGCUUGAAUCUUAGCAGGAAGGUGG	752
STAT3-2135	27 mer Antisense Strand		GCUGCUUGUUGUUCAGCUGCUGCUUGG	753
STAT3-2136	27 mer Antisense Strand		GCUGCUAUGUUGUUCAGCUGCUGCUGG	754
STAT3-2138	27 mer Antisense Strand		GCUGCUACAUGUUGUUCAGCUGCUGGG	755
STAT3-2139	27 mer Antisense Strand		GCUGCUGACAUGUUGUUCAGCUGCUGG	756
STAT3-2143	27 mer Antisense Strand		GCUGCUAAAUGACAUGUUGUUCAGCGG	757
STAT3-2144	27 mer Antisense Strand		GCUGCUCAAAUGACAUGUUGUUCAGGG	758

STAT3-2145	27 mer Antisense Strand		GCUGCUGCAAAUGACAUGUUGUUCAGG	759
STAT3-2146	27 mer Antisense Strand		GCUGCUAGCAAAUGACAUGUUGUUCGG	760
STAT3-2147	27 mer Antisense Strand		GCUGCUCAGCAAAUGACAUGUUGUUGG	761
STAT3-2148	27 mer Antisense Strand		GCUGCUUCAGCAAAUGACAUGUUGUGG	762
STAT3-2151	27 mer Antisense Strand		GCUGCUAUUUCAGCAAAUGACAUGUGG	763
STAT3-2153	27 mer Antisense Strand		GCUGCUUGAUUUCAGCAAAUGACAUGG	764
STAT3-2154	27 mer Antisense Strand		GCUGCUAUGAUUUCAGCAAAUGACAGG	765
STAT3-2159	27 mer Antisense Strand		GCUGCUCCAUGAUGAUUUCAGCAAAGG	766
STAT3-2322	27 mer Antisense Strand		GCUGCUAACUUGGUCUUCAGGUAUGGG	767
STAT3-2325	27 mer Antisense Strand		GCUGCUAUAAACUUGGUCUUCAGGUGG	768
STAT3-2327	27 mer Antisense Strand		GCUGCUAGAUAAACUUGGUCUUCAGGG	769
STAT3-2329	27 mer Antisense Strand		GCUGCUACAGAUAAACUUGGUCUUCGG	770
STAT3-2333	27 mer Antisense Strand		GCUGCUUCACACAGAUAAACUUGGUGG	771
STAT3-2335	27 mer Antisense Strand		GCUGCUUGUCACACAGAUAAACUUGGG	772
STAT3-2404	27 mer Antisense Strand		GCUGCUAAACUGCAUCAAUGAAUCUGG	773

STAT3-2405	27 mer Antisense Strand		GCUGCUCAAACUGCAUCAAUGAAUCGG	774
STAT3-2407	27 mer Antisense Strand		GCUGCUUCCAAACUGCAUCAAUGAAGG	775
STAT3-2408	27 mer Antisense Strand		GCUGCUUUCCAAACUGCAUCAAUGAGG	776
STAT3-2411	27 mer Antisense Strand		GCUGCUUAUUUCCAAACUGCAUCAAGG	777
STAT3-2412	27 mer Antisense Strand		GCUGCUUUAUUUCCAAACUGCAUCAGG	778
STAT3-2413	27 mer Antisense Strand		GCUGCUAUUAUUUCCAAACUGCAUCGG	779
STAT3-2416	27 mer Antisense Strand		GCUGCUACCAUUAUUUCCAAACUGCGG	780
STAT3-2418	27 mer Antisense Strand		GCUGCUUCACCAUUAUUUCCAAACUGG	781
STAT3-2422	27 mer Antisense Strand		GCUGCUACCUUCACCAUUAUUUCCAGG	782
STAT3-2427	27 mer Antisense Strand		GCUGCUUCAGCACCUUCACCAUUAUGG	783
STAT3-2612	27 mer Antisense Strand		GCUGCUACAAAGUUAGUAGUUUCAGGG	784
STAT3-2615	27 mer Antisense Strand		GCUGCUACCACAAAGUUAGUAGUUUGG	785
STAT3-2616	27 mer Antisense Strand		GCUGCUAACCACAAAGUUAGUAGUUGG	786
STAT3-2617	27 mer Antisense Strand		GCUGCUGAACCACAAAGUUAGUAGUGG	787
STAT3-2622	27 mer Antisense Strand		GCUGCUAUCUGGAACCACAAAGUUAGG	788

STAT3-2625	27 mer Antisense Strand		GCUGCUAAAAUCUGGAACCACAAAGGG	789
STAT3-2626	27 mer Antisense Strand		GCUGCUAAAAAUCUGGAACCACAAAGG	790
STAT3-2627	27 mer Antisense Strand		GCUGCUAAAAAAUCUGGAACCACAAGG	791
STAT3-2692	27 mer Antisense Strand		GCUGCUUUCACUCAUUUCUCUAUUUGG	792
STAT3-2693	27 mer Antisense Strand		GCUGCUAUUCACUCAUUUCUCUAUUGG	793
STAT3-2715	27 mer Antisense Strand		GCUGCUUAGAUAAAAGCAGAUCACCGG	794
STAT3-2719	27 mer Antisense Strand		GCUGCUCAUUUAGAUAAAAGCAGAUGG	795
STAT3-2721	27 mer Antisense Strand		GCUGCUUGCAUUUAGAUAAAAGCAGGG	796
STAT3-2735	27 mer Antisense Strand		GCUGCUAACACAUCCUUAUUUGCAUGG	797
STAT3-2741	27 mer Antisense Strand		GCUGCUUCAGAGAACACAUCCUUAUGG	798
STAT3-2801	27 mer Antisense Strand		GCUGCUACAAGACAUUUCCUUUUUCGG	799
STAT3-2803	27 mer Antisense Strand		GCUGCUACACAAGACAUUUCCUUUUGG	800
STAT3-2804	27 mer Antisense Strand		GCUGCUAACACAAGACAUUUCCUUUGG	801
STAT3-2806	27 mer Antisense Strand		GCUGCUACAACACAAGACAUUUCCUGG	802
STAT3-2807	27 mer Antisense Strand		GCUGCUAACAACACAAGACAUUUCCGG	803

STAT3-2808	27 mer Antisense Strand		GCUGCUAAACAACACAAGACAUUUCGG	804
STAT3-2809	27 mer Antisense Strand		GCUGCUAAAACAACACAAGACAUUUGG	805
STAT3-2810	27 mer Antisense Strand		GCUGCUCAAAACAACACAAGACAUUGG	806
STAT3-2811	27 mer Antisense Strand		GCUGCUACAAAACAACACAAGACAUGG	807
STAT3-2812	27 mer Antisense Strand		GCUGCUAACAAAACAACACAAGACAGG	808
STAT3-2813	27 mer Antisense Strand		GCUGCUGAACAAAACAACACAAGACGG	809
STAT3-2846	27 mer Antisense Strand		GCUGCUAUAACAAAAAGCUGCUGAGGG	810
STAT3-2848	27 mer Antisense Strand		GCUGCUCAAUAACAAAAAGCUGCUGGG	811
STAT3-2849	27 mer Antisense Strand		GCUGCUACAAUAACAAAAAGCUGCUGG	812
STAT3-2850	27 mer Antisense Strand		GCUGCUAACAAUAACAAAAAGCUGCGG	813
STAT3-2851	27 mer Antisense Strand		GCUGCUCAACAAUAACAAAAAGCUGGG	814
STAT3-2852	27 mer Antisense Strand		GCUGCUACAACAAUAACAAAAAGCUGG	815
STAT3-2853	27 mer Antisense Strand		GCUGCUAACAACAAUAACAAAAAGCGG	816
STAT3-2854	27 mer Antisense Strand		GCUGCUCAACAACAAUAACAAAAAGGG	817
STAT3-2855	27 mer Antisense Strand		GCUGCUACAACAACAAUAACAAAAAGG	818

STAT3-2856	27 mer Antisense Strand		GCUGCUAACAACAACAAUAACAAAAGG	819
STAT3-2857	27 mer Antisense Strand		GCUGCUCAACAACAACAAUAACAAAGG	820
STAT3-2858	27 mer Antisense Strand		GCUGCUACAACAACAACAAUAACAAGG	821
STAT3-2859	27 mer Antisense Strand		GCUGCUAACAACAACAACAAUAACAGG	822
STAT3-2860	27 mer Antisense Strand		GCUGCUGAACAACAACAACAAUAACGG	823
STAT3-2861	27 mer Antisense Strand		GCUGCUAGAACAACAACAACAAUAAGG	824
STAT3-2862	27 mer Antisense Strand		GCUGCUAAGAACAACAACAACAAUAGG	825
STAT3-2863	27 mer Antisense Strand		GCUGCUUAAGAACAACAACAACAAUGG	826
STAT3-2865	27 mer Antisense Strand		GCUGCUUCUAAGAACAACAACAACAGG	827
STAT3-2867	27 mer Antisense Strand		GCUGCUUGUCUAAGAACAACAACAAGG	828
STAT3-2868	27 mer Antisense Strand		GCUGCUUUGUCUAAGAACAACAACAGG	829
STAT3-2975	27 mer Antisense Strand		GCUGCUUGUCAGCAAGGUUAAAAAGGG	830
STAT3-2979	27 mer Antisense Strand		GCUGCUUGGAUGUCAGCAAGGUUAAGG	831
STAT3-2985	27 mer Antisense Strand		GCUGCUUCUAUUUGGAUGUCAGCAAGG	832
STAT3-3025	27 mer Antisense Strand		GCUGCUUUAAUUUAAAAAGAAACCUGG	833

STAT3-3037	27 mer Antisense Strand		GCUGCUUGUUAUUAUUUCUUAAUUUGG	834
STAT3-3038	27 mer Antisense Strand		GCUGCUUUGUUAUUAUUUCUUAAUUGG	835
STAT3-3039	27 mer Antisense Strand		GCUGCUAUUGUUAUUAUUUCUUAAUGG	836
STAT3-3041	27 mer Antisense Strand		GCUGCUUAAUUGUUAUUAUUUCUUAGG	837
STAT3-3042	27 mer Antisense Strand		GCUGCUUUAAUUGUUAUUAUUUCUUGG	838
STAT3-3043	27 mer Antisense Strand		GCUGCUUUUAAUUGUUAUUAUUUCUGG	839
STAT3-3225	27 mer Antisense Strand		GCUGCUAAUUUUUUGUACUUUUAGUGG	840
STAT3-3226	27 mer Antisense Strand		GCUGCUUAAUUUUUUGUACUUUUAGGG	841
STAT3-3605	27 mer Antisense Strand		GCUGCUUACAAAGGAAAAUAAGUCUGG	842
STAT3-3611	27 mer Antisense Strand		GCUGCUAUACAUUACAAAGGAAAAUGG	843
STAT3-3906	27 mer Antisense Strand		GCUGCUUCAUGUCCAACCUGUAACUGG	844
STAT3-4311	27 mer Antisense Strand		GCUGCUUAACAAACAGAAUUCCACAGG	845
STAT3-4314	27 mer Antisense Strand		GCUGCUAUUUAACAAACAGAAUUCCGG	846
STAT3-4317	27 mer Antisense Strand		GCUGCUUUGAUUUAACAAACAGAAUGG	847
STAT3-4321	27 mer Antisense Strand		GCUGCUUAAUUUGAUUUAACAAACAGG	848

STAT3-4465	27 mer Antisense Strand		GCUGCUUCAGUUAAGCUUAUUAUGUGG	849
STAT3-4479	27 mer Antisense Strand		GCUGCUAAAUAUUCUGUUUAUCAGUGG	850
STAT3-4480	27 mer Antisense Strand		GCUGCUUAAAUAUUCUGUUUAUCAGGG	851
STAT3-4831	27 mer Antisense Strand		GCUGCUAAUAUAAAUUUUUACACUAGG	852
STAT3-4833	27 mer Antisense Strand		GCUGCUAUAAUAUAAAUUUUUACACGG	853
STAT3-4836	27 mer Antisense Strand		GCUGCUACAAUAAUAUAAAUUUUUAGG	854
STAT3-4837	27 mer Antisense Strand		GCUGCUCACAAUAAUAUAAAUUUUUGG	855
STAT3-4909	27 mer Antisense Strand		GCUGCUUUUAUUUCUGGAAGUUAAAGG	856
STAT3-715	Unmodified 36 mer		CCAGGAUGACUUUGAUUUCAGCAGCCG AAAGGCUGC	857
STAT3-716	Unmodified 36 mer		CAGGAUGACUUUGAUUUCAAGCAGCCG AAAGGCUGC	858
STAT3-717	Unmodified 36 mer		AGGAUGACUUUGAUUUCAAAGCAGCCG AAAGGCUGC	859
STAT3-720	Unmodified 36 mer		AUGACUUUGAUUUCAACUAAGCAGCCG AAAGGCUGC	860
STAT3-372	Unmodified 36 mer		CUUUGGUGUUUCAUAAUCUAGCAGCCG AAAGGCUGC	861
STAT3-721	Unmodified 36 mer		UGACUUUGAUUUCAACUAUAGCAGCCG AAAGGCUGC	862
STAT3-722	Unmodified 36 mer		GACUUUGAUUUCAACUAUAAGCAGCCG AAAGGCUGC	863

STAT3-768	Unmodified 36 mer		AAGAUCUGAAUGGAAACAAAGCAGCCG AAAGGCUGC	864
STAT3-1001	Unmodified 36 mer		GAAAACUGGAUAACGUCAUAGCAGCCG AAAGGCUGC	865
STAT3-1006	Unmodified 36 mer		CUGGAUAACGUCAUUAGCAAGCAGCCG AAAGGCUGC	866
STAT3-1145	Unmodified 36 mer		CUGUUUAGAAACUUAAUGAAGCAGCCG AAAGGCUGC	867
STAT3-1151	Unmodified 36 mer		AGAAACUUAAUGAAAAGUGAGCAGCCG AAAGGCUGC	868
STAT3-1268	Unmodified 36 mer		GUCAAAUUCCCUGAGUUGAAGCAGCCG AAAGGCUGC	869
STAT3-1273	Unmodified 36 mer		AUUCCCUGAGUUGAAUUAUAGCAGCCG AAAGGCUGC	870
STAT3-1279	Unmodified 36 mer		UGAGUUGAAUUAUCAGCUUAGCAGCCG AAAGGCUGC	871
STAT3-1280	Unmodified 36 mer		GAGUUGAAUUAUCAGCUUAAGCAGCCG AAAGGCUGC	872
STAT3-1281	Unmodified 36 mer		GAGUUGAAUUAUCAGCUUAAGCAGCCG AAAGGCUGC	873
STAT3-1284	Unmodified 36 mer		UGAAUUAUCAGCUUAAAAUAGCAGCCG AAAGGCUGC	874
STAT3-1286	Unmodified 36 mer		AAUUAUCAGCUUAAAAUUAAGCAGCCG AAAGGCUGC	875
STAT3-1287	Unmodified 36 mer		AUUAUCAGCUUAAAAUUAAAGCAGCCG AAAGGCUGC	876
STAT3-1292	Unmodified 36 mer		CAGCUUAAAAUUAAAGUGUAGCAGCCG AAAGGCUGC	877
STAT3-1293	Unmodified 36 mer		AGCUUAAAAUUAAAGUGUGAGCAGCCG AAAGGCUGC	878

STAT3-1819	Unmodified 36 mer		UGUGAAUUAUUCAGGGUGUAGCAGCCG AAAGGCUGC	879
STAT3-1908	Unmodified 36 mer		ACAAUAUCAUUGACCUUGUAGCAGCCG AAAGGCUGC	880
STAT3-1910	Unmodified 36 mer		AAUAUCAUUGACCUUGUGAAGCAGCCG AAAGGCUGC	881
STAT3-1913	Unmodified 36 mer		AUCAUUGACCUUGUGAAAAAGCAGCCG AAAGGCUGC	882
STAT3-2154	Unmodified 36 mer		UGUCAUUUGCUGAAAUCAUAGCAGCCG AAAGGCUGC	883
STAT3-2327	Unmodified 36 mer		CUGAAGACCAAGUUUAUCUAGCAGCCG AAAGGCUGC	884
STAT3-2335	Unmodified 36 mer		CAAGUUUAUCUGUGUGACAAGCAGCCG AAAGGCUGC	885
STAT3-2418	Unmodified 36 mer		AGUUUGGAAAUAAUGGUGAAGCAGCCG AAAGGCUGC	886
STAT3-2692	Unmodified 36 mer		AAAUAGAGAAAUGAGUGAAAGCAGCCG AAAGGCUGC	887
STAT3-2693	Unmodified 36 mer		AAUAGAGAAAUGAGUGAAUAGCAGCCG AAAGGCUGC	888
STAT3-2627	Unmodified 36 mer	Hs-Mf-Mm	UUGUGGUUCCAGAUUUUUUAGCAGCCG AAAGGCUGC	889
STAT3-2626	Unmodified 36 mer	Hs-Mf-Mm	UUUGUGGUUCCAGAUUUUUAGCAGCCG AAAGGCUGC	890
STAT3-2407	Unmodified 36 mer	Hs-Mf-Mm	UUCAUUGAUGCAGUUUGGAAGCAGCCG AAAGGCUGC	891
STAT3-2412	Unmodified 36 mer	Hs-Mf-Mm	UGAUGCAGUUUGGAAAUAAAGCAGCCG AAAGGCUGC	892
STAT3-2151	Unmodified 36 mer	Hs-Mf-Mm	ACAUGUCAUUUGCUGAAAUAGCAGCCG AAAGGCUGC	893

STAT3-2625	Unmodified 36 mer	Hs-Mf-Mm	CUUUGUGGUUCCAGAUUUUAGCAGCCGAAAGGCUGC	894
STAT3-4836	Unmodified 36 mer	Hs-Mf-Mm	UAAAAAUUUAUAUUAUUGUAGCAGCCGAAAGGCUGC	895
STAT3-2408	Unmodified 36 mer	Hs-Mf-Mm	UCAUUGAUGCAGUUUGGAAAGCAGCCGAAAGGCUGC	896
STAT3-2159	Unmodified 36 mer	Hs-Mf-Mm	UUUGCUGAAAUCAUCAUGGAGCAGCCGAAAGGCUGC	897
STAT3-2146	Unmodified 36 mer	Hs-Mf-Mm	GAACAACAUGUCAUUUGCUAGCAGCCGAAAGGCUGC	898
STAT3-2148	Unmodified 36 mer	Hs-Mf-Mm	ACAACAUGUCAUUUGCUGAAGCAGCCGAAAGGCUGC	899
STAT3-2147	Unmodified 36 mer	Hs-Mf-Mm	AACAACAUGUCAUUUGCUGAGCAGCCGAAAGGCUGC	900
STAT3-0461	Unmodified 36 mer	Hs-Mf-Mm	CGAAGAAUCAAGCAGUUUCAGCAGCCGAAAGGCUGC	901
STAT3-1584	Unmodified 36 mer	Hs-Mf-Mm	CCUUGCCAGUUGUGGUGAUAGCAGCCGAAAGGCUGC	902
STAT3-1047	Unmodified 36 mer	Hs-Mf-Mm	AACAAAUUAAGAAACUGGAAGCAGCCGAAAGGCUGC	903
STAT3-0773	Unmodified 36 mer	Hs-Mf-Mm	CUGAAUGGAAACAACCAGUAGCAGCCGAAAGGCUGC	904
STAT3-0492	Unmodified 36 mer	Hs-Mf-Mm	AUCUUGAGAAGCCAAUGGAAGCAGCCGAAAGGCUGC	905
STAT3-0462	Unmodified 36 mer	Hs-Mf-Mm	GAAGAAUCAAGCAGUUUCUAGCAGCCGAAAGGCUGC	906
STAT3-1586	Unmodified 36 mer	Hs-Mf-Mm	UUGCCAGUUGUGGUGAUCUAGCAGCCGAAAGGCUGC	907
STAT3-0771	Unmodified 36 mer	Hs-Mf-Mm	AUCUGAAUGGAAACAACCAAGCAGCCGAAAGGCUGC	908

STAT3-0681	Unmodified 36 mer	Hs-Mf-Mm	AUCUAGAACAGAAAAUGAAAGCAGCCG AAAGGCUGC	909
STAT3-0678	Unmodified 36 mer	Hs-Mf-Mm	AGGAUCUAGAACAGAAAAUAGCAGCCG AAAGGCUGC	910
STAT3-4837	Unmodified 36 mer	Hs-Mf-Mm	AAAAAUUUAUAUUAUUGUGAGCAGCCG AAAGGCUGC	911
STAT3-4833	Unmodified 36 mer	Hs-Mf-Mm	GUGUAAAAAUUUAUAUUAUAGCAGCCG AAAGGCUGC	912
STAT3-1068	Unmodified 36 mer	Hs	AGUUGCAGCAAAAAGUUUCAGCAGCCG AAAGGCUGC	913
STAT3-1673	Unmodified 36 mer	Hs	AAGAAUGUAAACUUUUUUAAGCAGCCG AAAGGCUGC	914
STAT3-0426	Unmodified 36 mer	Hs	UGCAAGAGUCGAAUGUUCUAGCAGCCG AAAGGCUGC	915
STAT3-2404	Unmodified 36 mer	Hs	AGAUUCAUUGAUGCAGUUUAGCAGCCG AAAGGCUGC	916
STAT3-1067	Unmodified 36 mer	Hs	GAGUUGCAGCAAAAAGUUUAGCAGCCG AAAGGCUGC	917
STAT3-0433	Unmodified 36 mer	Hs	GUCGAAUGUUCUCUAUCAGAGCAGCCG AAAGGCUGC	918
STAT3-1670	Unmodified 36 mer	Hs	CCCAAGAAUGUAAACUUUUAGCAGCCG AAAGGCUGC	919
STAT3-1388	Unmodified 36 mer	Hs	GUGAUGAACAUGGAAGAAUAGCAGCCG AAAGGCUGC	920
STAT3-0429	Unmodified 36 mer	Hs	AAGAGUCGAAUGUUCUCUAAGCAGCCG AAAGGCUGC	921
STAT3-2405	Unmodified 36 mer	Hs	GAUUCAUUGAUGCAGUUUGAGCAGCCG AAAGGCUGC	922
STAT3-0430	Unmodified 36 mer	Hs	AGAGUCGAAUGUUCUCUAUAGCAGCCG AAAGGCUGC	923

STAT3-0432	Unmodified 36 mer	Hs	AGUCGAAUGUUCUCUAUCAAGCAGCCGAAAGGCUGC	924
STAT3-1815	Unmodified 36 mer	Hs	CUGGUGUGAAUUAUUCAGGAGCAGCCGAAAGGCUGC	925
STAT3-0424	Unmodified 36 mer	Hs	CCUGCAAGAGUCGAAUGUUAGCAGCCGAAAGGCUGC	926
STAT3-2024	Unmodified 36 mer	Hs	ACCUUCCUGCUAAGAUUCAAGCAGCCGAAAGGCUGC	927
STAT3-1813	Unmodified 36 mer	Hs	ACCUGGUGUGAAUUAUUCAAGCAGCCGAAAGGCUGC	928
STAT3-1674	Unmodified 36 mer	Hs	AGAAUGUAAACUUUUUUACAGCAGCCGAAAGGCUGC	929
STAT3-1241	Unmodified 36 mer	Hs	CAGUUCACUACUAAAGUCAAGCAGCCGAAAGGCUGC	930
STAT3-1672	Unmodified 36 mer	Hs	CAAGAAUGUAAACUUUUUUAGCAGCCGAAAGGCUGC	931
STAT3-0425	Unmodified 36 mer	Hs	CUGCAAGAGUCGAAUGUUCAGCAGCCGAAAGGCUGC	932
STAT3-1817	Unmodified 36 mer	Hs	GGUGUGAAUUAUUCAGGGUAGCAGCCGAAAGGCUGC	933
STAT3-1671	Unmodified 36 mer	Hs	CCAAGAAUGUAAACUUUUUAGCAGCCGAAAGGCUGC	934
STAT3-2136	Unmodified 36 mer	Hs-Mm	AGCAGCAGCUGAACAACAUAGCAGCCGAAAGGCUGC	935
STAT3-2143	Unmodified 36 mer	Hs-Mm	GCUGAACAACAUGUCAUUUAGCAGCCGAAAGGCUGC	936
STAT3-2144	Unmodified 36 mer	Hs-Mm	CUGAACAACAUGUCAUUUGAGCAGCCGAAAGGCUGC	937
STAT3-2138	Unmodified 36 mer	Hs-Mm	CAGCAGCUGAACAACAUGUAGCAGCCGAAAGGCUGC	938

STAT3-4909	Unmodified 36 mer	Hs-Mm	UUUAACUUCCAGAAAUAAAAGCAGCCGAAAGGCUGC	939
STAT3-2139	Unmodified 36 mer	Hs-Mm	AGCAGCUGAACAACAUGUCAGCAGCCGAAAGGCUGC	940
STAT3-2411	Unmodified 36 mer	Hs-Mm	UUGAUGCAGUUUGGAAAUAAGCAGCCGAAAGGCUGC	941
STAT3-2145	Unmodified 36 mer	Hs-Mm	UGAACAACAUGUCAUUUGCAGCAGCCGAAAGGCUGC	942
STAT3-4831	Unmodified 36 mer	Hs-Mm	UAGUGUAAAAAUUUAUAUUAGCAGCCGAAAGGCUGC	943
STAT3-2622	Unmodified 36 mer	Hs-Mm	UAACUUUGUGGUUCCAGAUAGCAGCCGAAAGGCUGC	944
STAT3-2135	Unmodified 36 mer	Hs-Mm	AAGCAGCAGCUGAACAACAAGCAGCCGAAAGGCUGC	945
STAT3-1383	Unmodified 36 mer	Hs-Mm	CAAAAGUGAUGAACAUGGAAGCAGCCGAAAGGCUGC	946
STAT3-715	Unmodified 22 mer		UGAAAUCAAAGUCAUCCUGGGG	947
STAT3-716	Unmodified 22 mer		UUGAAAUCAAAGUCAUCCUGGG	948
STAT3-717	Unmodified 22 mer		UUUGAAAUCAAAGUCAUCCUGG	949
STAT3-720	Unmodified 22 mer		UUAGUUGAAAUCAAAGUCAUGG	950
STAT3-372	Unmodified 22 mer		UAGAUUAUGAAACACCAAAGGG	951
STAT3-721	Unmodified 22 mer		UAUAGUUGAAAUCAAAGUCAGG	952
STAT3-722	Unmodified 22 mer		UUAUAGUUGAAAUCAAAGUCGG	953
STAT3-768	Unmodified 22 mer		UUUGUUUCCAUUCAGAUCUUGG	954
STAT3-1001	Unmodified 22 mer		UAUGACGUUAUCCAGUUUUCGG	955
STAT3-1006	Unmodified 22 mer		UUGCUAAUGACGUUAUCCAGGG	956

STAT3-1145	Unmodified 22 mer		UUCAUUAAGUUUCUAAACAGGG	957
STAT3-1151	Unmodified 22 mer		UCACUUUUCAUUAAGUUUCUGG	958
STAT3-1268	Unmodified 22 mer		UUCAACUCAGGGAAUUUGACGG	959
STAT3-1273	Unmodified 22 mer		UAUAAUUCAACUCAGGGAAUGG	960
STAT3-1279	Unmodified 22 mer		UAAGCUGAUAAUUCAACUCAGG	961
STAT3-1280	Unmodified 22 mer		UUAAGCUGAUAAUUCAACUCGG	962
STAT3-1281	Unmodified 22 mer		UUUAAGCUGAUAAUUCAACUGG	963
STAT3-1284	Unmodified 22 mer		UAUUUUAAGCUGAUAAUUCAGG	964
STAT3-1286	Unmodified 22 mer		UUAAUUUUAAGCUGAUAAUUGG	965
STAT3-1287	Unmodified 22 mer		UUUAAUUUUAAGCUGAUAAUGG	966
STAT3-1292	Unmodified 22 mer		UACACUUUAAUUUUAAGCUGGG	967
STAT3-1293	Unmodified 22 mer		UCACACUUUAAUUUUAAGCUGG	968
STAT3-1819	Unmodified 22 mer		UACACCCUGAAUAAUUCACAGG	969
STAT3-1908	Unmodified 22 mer		UACAAGGUCAAUGAUAUUGUGG	970
STAT3-1910	Unmodified 22 mer		UUCACAAGGUCAAUGAUAUUGG	971
STAT3-1913	Unmodified 22 mer		UUUUUCACAAGGUCAAUGAUGG	972
STAT3-2154	Unmodified 22 mer		UAUGAUUUCAGCAAAUGACAGG	973
STAT3-2327	Unmodified 22 mer		UAGAUAAACUUGGUCUUCAGGG	974
STAT3-2335	Unmodified 22 mer		UUGUCACACAGAUAAACUUGGG	975
STAT3-2418	Unmodified 22 mer		UUCACCAUUAUUUCCAAACUGG	976

STAT3-2692	Unmodified 22 mer		UUUCACUCAUUUCUCUAUUUGG	977
STAT3-2693	Unmodified 22 mer		UAUUCACUCAUUUCUCUAUUGG	978
STAT3-2627	Unmodified 22 mer	Hs-Mf-Mm	UAAAAAAUCUGGAACCACAAGG	979
STAT3-2626	Unmodified 22 mer	Hs-Mf-Mm	UAAAAAUCUGGAACCACAAAGG	980
STAT3-2407	Unmodified 22 mer	Hs-Mf-Mm	UUCCAAACUGCAUCAAUGAAGG	981
STAT3-2412	Unmodified 22 mer	Hs-Mf-Mm	UUUAUUUCCAAACUGCAUCAGG	982
STAT3-2151	Unmodified 22 mer	Hs-Mf-Mm	UAUUUCAGCAAAUGACAUGUGG	983
STAT3-2625	Unmodified 22 mer	Hs-Mf-Mm	UAAAAUCUGGAACCACAAAGGG	984
STAT3-4836	Unmodified 22 mer	Hs-Mf-Mm	UACAAUAAUAUAAAUUUUUAGG	985
STAT3-2408	Unmodified 22 mer	Hs-Mf-Mm	UUUCCAAACUGCAUCAAUGAGG	986
STAT3-2159	Unmodified 22 mer	Hs-Mf-Mm	UCCAUGAUGAUUUCAGCAAAGG	987
STAT3-2146	Unmodified 22 mer	Hs-Mf-Mm	UAGCAAAUGACAUGUUGUUCGG	988
STAT3-2148	Unmodified 22 mer	Hs-Mf-Mm	UUCAGCAAAUGACAUGUUGUGG	989
STAT3-2147	Unmodified 22 mer	Hs-Mf-Mm	UCAGCAAAUGACAUGUUGUUGG	990
STAT3-0461	Unmodified 22 mer	Hs-Mf-Mm	UGAAACUGCUUGAUUCUUCGGG	991
STAT3-1584	Unmodified 22 mer	Hs-Mf-Mm	UAUCACCACAACUGGCAAGGGG	992
STAT3-1047	Unmodified 22 mer	Hs-Mf-Mm	UUCCAGUUUCUUAAUUUGUUGG	993
STAT3-0773	Unmodified 22 mer	Hs-Mf-Mm	UACUGGUUGUUUCCAUUCAGGG	994
STAT3-0492	Unmodified 22 mer	Hs-Mf-Mm	UUCCAUUGGCUUCUCAAGAUGG	995
STAT3-0462	Unmodified 22 mer	Hs-Mf-Mm	UAGAAACUGCUUGAUUCUUCGG	996
STAT3-1586	Unmodified 22 mer	Hs-Mf-Mm	UAGAUCACCACAACUGGCAAGG	997
STAT3-0771	Unmodified 22 mer	Hs-Mf-Mm	UUGGUUGUUUCCAUUCAGAUGG	998
STAT3-0681	Unmodified 22 mer	Hs-Mf-Mm	UUUCAUUUUCUGUUCUAGAUGG	999

STAT3-0678	Unmodified 22 mer	Hs-Mf-Mm	UAUUUUCUGUUCUAGAUCCUGG	1000
STAT3-4837	Unmodified 22 mer	Hs-Mf-Mm	UCACAAUAAUAUAAAUUUUUGG	1001
STAT3-4833	Unmodified 22 mer	Hs-Mf-Mm	UAUAAUAUAAAUUUUUACACGG	1002
STAT3-1068	Unmodified 22 mer	Hs	UGAAACUUUUUGCUGCAACUGG	1003
STAT3-1673	Unmodified 22 mer	Hs	UUAAAAAAGUUUACAUUCUUGG	1004
STAT3-0426	Unmodified 22 mer	Hs	UAGAACAUUCGACUCUUGCAGG	1005
STAT3-2404	Unmodified 22 mer	Hs	UAAACUGCAUCAAUGAAUCUGG	1006
STAT3-1067	Unmodified 22 mer	Hs	UAAACUUUUUGCUGCAACUCGG	1007
STAT3-0433	Unmodified 22 mer	Hs	UCUGAUAGAGAACAUUCGACGG	1008
STAT3-1670	Unmodified 22 mer	Hs	UAAAAGUUUACAUUCUUGGGGG	1009
STAT3-1388	Unmodified 22 mer	Hs	UAUUCUUCCAUGUUCAUCACGG	1010
STAT3-0429	Unmodified 22 mer	Hs	UUAGAGAACAUUCGACUCUUGG	1011
STAT3-2405	Unmodified 22 mer	Hs	UCAAACUGCAUCAAUGAAUCGG	1012
STAT3-0430	Unmodified 22 mer	Hs	UAUAGAGAACAUUCGACUCUGG	1013
STAT3-0432	Unmodified 22 mer	Hs	UUGAUAGAGAACAUUCGACUGG	1014
STAT3-1815	Unmodified 22 mer	Hs	UCCUGAAUAAUUCACACCAGGG	1015
STAT3-0424	Unmodified 22 mer	Hs	UAACAUUCGACUCUUGCAGGGG	1016
STAT3-2024	Unmodified 22 mer	Hs	UUGAAUCUUAGCAGGAAGGUGG	1017
STAT3-1813	Unmodified 22 mer	Hs	UUGAAUAAUUCACACCAGGUGG	1018
STAT3-1674	Unmodified 22 mer	Hs	UGUAAAAAAGUUUACAUUCUGG	1019
STAT3-1241	Unmodified 22 mer	Hs	UUGACUUUAGUAGUGAACUGGG	1020
STAT3-1672	Unmodified 22 mer	Hs	UAAAAAAGUUUACAUUCUUGGG	1021
STAT3-0425	Unmodified 22 mer	Hs	UGAACAUUCGACUCUUGCAGGG	1022

STAT3-1817	Unmodified 22 mer	Hs	UACCCUGAAUAAUUCACACCGG	1023
STAT3-1671	Unmodified 22 mer	Hs	UAAAAAGUUUACAUUCUUGGGG	1024
STAT3-2136	Unmodified 22 mer	Hs-Mm	UAUGUUGUUCAGCUGCUGCUGG	1025
STAT3-2143	Unmodified 22 mer	Hs-Mm	UAAAUGACAUGUUGUUCAGCGG	1026
STAT3-2144	Unmodified 22 mer	Hs-Mm	UCAAAUGACAUGUUGUUCAGGG	1027
STAT3-2138	Unmodified 22 mer	Hs-Mm	UACAUGUUGUUCAGCUGCUGGG	1028
STAT3-4909	Unmodified 22 mer	Hs-Mm	UUUUAUUUCUGGAAGUUAAAGG	1029
STAT3-2139	Unmodified 22 mer	Hs-Mm	UGACAUGUUGUUCAGCUGCUGG	1030
STAT3-2411	Unmodified 22 mer	Hs-Mm	UUAUUUCCAAACUGCAUCAAGG	1031
STAT3-2145	Unmodified 22 mer	Hs-Mm	UGCAAAUGACAUGUUGUUCAGG	1032
STAT3-4831	Unmodified 22 mer	Hs-Mm	UAAUAUAAAUUUUUACACUAGG	1033
STAT3-2622	Unmodified 22 mer	Hs-Mm	UAUCUGGAACCACAAAGUUAGG	1034
STAT3-2135	Unmodified 22 mer	Hs-Mm	UUGUUGUUCAGCUGCUGCUUGG	1035
STAT3-1383	Unmodified 22 mer	Hs-Mm	UUCCAUGUUCAUCACUUUUGGG	1036
STAT3-715	Modified 36 mer		[mCs][mC][mA][mG][mG][mA][mU][fG][fA][fC][fU][mU][mU][mG][mA][mU][mU][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1037
STAT3-716	Modified 36 mer		[mCs][mA][mG][mG][mA][mU][mG][fA][fC][fU][fU][mU][mG][mA][mU][mU][mU][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1038
STAT3-717	Modified 36 mer		[mAs][mG][mG][mA][mU][mG][mA][fC][fU][fU][fU][mG][mA][mU][mU][mU][mC][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1039

STAT3-720	Modified 36 mer		[mAs][mU][mG][mA][mC][mU][mU][fU][fG][fA][fU][mU][mU][mC][mA][mA][mC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1040
STAT3-372	Modified 36 mer		[mCs][mU][mU][mU][mG][mG][mU][fG][fU][fU][fU][mC][mA][mU][mA][mA][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1041
STAT3-721	Modified 36 mer		[mUs][mG][mA][mC][mU][mU][mU][fG][fA][fU][fU][mU][mC][mA][mA][mC][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1042
STAT3-722	Modified 36 mer		[mGs][mA][mC][mU][mU][mU][mG][fA][fU][fU][fU][mC][mA][mA][mC][mU][mA][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1043
STAT3-768	Modified 36 mer		[mAs][mA][mG][mA][mU][mC][mU][fG][fA][fA][fU][mG][mG][mA][mA][mA][mC][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1044
STAT3-1001	Modified 36 mer		[mGs][mA][mA][mA][mA][mC][mU][fG][fG][fA][fU][mA][mA][mC][mG][mU][mC][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1045
STAT3-1006	Modified 36 mer		[mCs][mU][mG][mG][mA][mU][mA][fA][fC][fG][fU][mC][mA][mU][mU][mA][mG][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1046
STAT3-1145	Modified 36 mer		[mCs][mU][mG][mU][mU][mU][mA][fG][fA][fA][fA][mC][mU][mU][mA][mA][mU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ade	1047

			mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
STAT3-1151	Modified 36 mer		[mAs][mG][mA][mA][mA][mC][mU][fU][fA][fA][fU][mG][mA][mA][mA][mA][mG][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1048
STAT3-1268	Modified 36 mer		[mGs][mU][mC][mA][mA][mA][mU][fU][fC][fC][fC][mU][mG][mA][mG][mU][mU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1049
STAT3-1273	Modified 36 mer		[mAs][mU][mU][mC][mC][mC][mU][fG][fA][fG][fU][mU][mG][mA][mA][mU][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1050
STAT3-1279	Modified 36 mer		[mUs][mG][mA][mG][mU][mU][mG][fA][fA][fU][fU][mA][mU][mC][mA][mG][mC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1051
STAT3-1280	Modified 36 mer		[mGs][mA][mG][mU][mU][mG][mA][fA][fU][fU][fA][mU][mC][mA][mG][mC][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1052
STAT3-1281	Modified 36 mer		[mAs][mG][mU][mU][mG][mA][mA][fU][fU][fA][fU][mC][mA][mG][mC][mU][mU][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1053
STAT3-1284	Modified 36 mer		[mUs][mG][mA][mA][mU][mU][mA][fU][fC][fA][fG][mC][mU][mU][mA][mA][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1054

STAT3-1286	Modified 36 mer		[mAs][mA][mU][mU][mA][mU][mC][fA][fG][fC][fU][mU][mA][mA][mA][mA][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1055
STAT3-1287	Modified 36 mer		[mAs][mU][mU][mA][mU][mC][mA][fG][fC][fU][fU][mA][mA][mA][mA][mU][mU][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1056
STAT3-1292	Modified 36 mer		[mCs][mA][mG][mC][mU][mU][mA][fA][fA][fA][fU][mU][mA][mA][mA][mG][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1057
STAT3-1293	Modified 36 mer		[mAs][mG][mC][mU][mU][mA][mA][fA][fA][fU][fU][mA][mA][mA][mG][mU][mG][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1058
STAT3-1819	Modified 36 mer		[mUs][mG][mU][mG][mA][mA][mU][fU][fA][fU][fU][mC][mA][mG][mG][mG][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1059
STAT3-1908	Modified 36 mer		[mAs][mC][mA][mA][mU][mA][mU][fC][fA][fU][fU][mG][mA][mC][mC][mU][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1060
STAT3-1910	Modified 36 mer		[mAs][mA][mU][mA][mU][mC][mA][fU][fU][fG][fA][mC][mC][mU][mU][mG][mU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1061
STAT3-1913	Modified 36 mer		[mAs][mU][mC][mA][mU][mU][mG][fA][fC][fC][fU][mU][mG][mU][mG][mA][mA][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ade	1062

			mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
STAT3-2154	Modified 36 mer		[mUs][mG][mU][mC][mA][mU][mU][fU][fG][fC][fU][mG][mA][mA][mA][mU][mC][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1063
STAT3-2327	Modified 36 mer		[mCs][mU][mG][mA][mA][mG][mA][fC][fC][fA][fA][mG][mU][mU][mU][mA][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1064
STAT3-2335	Modified 36 mer		[mCs][mA][mA][mG][mU][mU][mU][fA][fU][fC][fU][mG][mU][mG][mU][mG][mA][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1065
STAT3-2418	Modified 36 mer		[mAs][mG][mU][mU][mU][mG][mG][fA][fA][fA][fU][mA][mA][mU][mG][mG][mU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1066
STAT3-2692	Modified 36 mer		[mAs][mA][mA][mU][mA][mG][mA][fG][fA][fA][fA][mU][mG][mA][mG][mU][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1067
STAT3-2693	Modified 36 mer		[mAs][mA][mU][mA][mG][mA][mG][fA][fA][fA][fU][mG][mA][mG][mU][mG][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1068
STAT3-2627	Modified 36 mer	Hs-Mf-Mm	[mUs][mU][mG][mU][mG][mG][mU][fU][fC][fC][fA][mG][mA][mU][mU][mU][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1069

STAT3-2626	Modified 36 mer	Hs-Mf-Mm	[mUs][mU][mU][mG][mU][mG][mG][fU][fU][fC][fC][mA][mG][mA][mU][mU][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1070
STAT3-2407	Modified 36 mer	Hs-Mf-Mm	[mUs][mU][mC][mA][mU][mU][mG][fA][fU][fG][fC][mA][mG][mU][mU][mU][mG][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1071
STAT3-2412	Modified 36 mer	Hs-Mf-Mm	[mUs][mG][mA][mU][mG][mC][mA][fG][fU][fU][fU][mG][mG][mA][mA][mA][mU][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1072
STAT3-2151	Modified 36 mer	Hs-Mf-Mm	[mAs][mC][mA][mU][mG][mU][mC][fA][fU][fU][fU][mG][mC][mU][mG][mA][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1073
STAT3-2625	Modified 36 mer	Hs-Mf-Mm	[mCs][mU][mU][mU][mG][mU][mG][fG][fU][fU][fC][mC][mA][mG][mA][mU][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1074
STAT3-4836	Modified 36 mer	Hs-Mf-Mm	[mUs][mA][mA][mA][mA][mA][mU][fU][fU][fA][fU][mA][mU][mU][mA][mU][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1075
STAT3-2408	Modified 36 mer	Hs-Mf-Mm	[mUs][mC][mA][mU][mU][mG][mA][fU][fG][fC][fA][mG][mU][mU][mU][mG][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1076
STAT3-2159	Modified 36 mer	Hs-Mf-Mm	[mUs][mU][mU][mG][mC][mU][mG][fA][fA][fA][fU][mC][mA][mU][mC][mA][mU][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ade	1077

			mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
STAT3-2146	Modified 36 mer	Hs-Mf-Mm	[mGs][mA][mA][mC][mA][mA][mC][fA][fU][fG][fU][mC][mA][mU][mU][mU][mG][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1078
STAT3-2148	Modified 36 mer	Hs-Mf-Mm	[mAs][mC][mA][mA][mC][mA][mU][fG][fU][fC][fA][mU][mU][mU][mG][mC][mU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1079
STAT3-2147	Modified 36 mer	Hs-Mf-Mm	[mAs][mA][mC][mA][mA][mC][mA][fU][fG][fU][fC][mA][mU][mU][mU][mG][mC][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1080
STAT3-0461	Modified 36 mer	Hs-Mf-Mm	[mCs][mG][mA][mA][mG][mA][mA][fU][fC][fA][fA][mG][mC][mA][mG][mU][mU][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1081
STAT3-1584	Modified 36 mer	Hs-Mf-Mm	[mCs][mC][mU][mU][mG][mC][mC][fA][fG][fU][fU][mG][mU][mG][mG][mU][mG][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1082
STAT3-1047	Modified 36 mer	Hs-Mf-Mm	[mAs][mA][mC][mA][mA][mA][mU][fU][fA][fA][fG][mA][mA][mA][mC][mU][mG][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1083
STAT3-0773	Modified 36 mer	Hs-Mf-Mm	[mCs][mU][mG][mA][mA][mU][mG][fG][fA][fA][fA][mC][mA][mA][mC][mC][mA][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1084

STAT3-0492	Modified 36 mer	Hs-Mf-Mm	[mAs][mU][mC][mU][mU][mG][mA][fG][fA][fA][fG][mC][mC][mA][mA][mU][mG][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1085
STAT3-0462	Modified 36 mer	Hs-Mf-Mm	[mGs][mA][mA][mG][mA][mA][mU][fC][fA][fA][fG][mC][mA][mG][mU][mU][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1086
STAT3-1586	Modified 36 mer	Hs-Mf-Mm	[mUs][mU][mG][mC][mC][mA][mG][fU][fU][fG][fU][mG][mG][mU][mG][mA][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1087
STAT3-0771	Modified 36 mer	Hs-Mf-Mm	[mAs][mU][mC][mU][mG][mA][mA][fU][fG][fG][fA][mA][mA][mC][mA][mA][mC][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1088
STAT3-0681	Modified 36 mer	Hs-Mf-Mm	[mAs][mU][mC][mU][mA][mG][mA][fA][fC][fA][fG][mA][mA][mA][mA][mU][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1089
STAT3-0678	Modified 36 mer	Hs-Mf-Mm	[mAs][mG][mG][mA][mU][mC][mU][fA][fG][fA][fA][mC][mA][mG][mA][mA][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1090
STAT3-4837	Modified 36 mer	Hs-Mf-Mm	[mAs][mA][mA][mA][mA][mU][mU][fU][fA][fU][fA][mU][mU][mA][mU][mU][mG][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1091
STAT3-4833	Modified 36 mer	Hs-Mf-Mm	[mGs][mU][mG][mU][mA][mA][mA][fA][fA][fU][fU][mU][mA][mU][mA][mU][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ad	1092

			emA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
STAT3-1068	Modified 36 mer	Hs	[mAs][mG][mU][mU][mG][mC][mA][fG][fC][fA][fA][mA][mA][mA][mG][mU][mU][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1093
STAT3-1673	Modified 36 mer	Hs	[mAs][mA][mG][mA][mA][mU][mG][fU][fA][fA][fA][mC][mU][mU][mU][mU][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1094
STAT3-0426	Modified 36 mer	Hs	[mUs][mG][mC][mA][mA][mG][mA][fG][fU][fC][fG][mA][mA][mU][mG][mU][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1095
STAT3-2404	Modified 36 mer	Hs	[mAs][mG][mA][mU][mU][mC][mA][fU][fU][fG][fA][mU][mG][mC][mA][mG][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1096
STAT3-1067	Modified 36 mer	Hs	[mGs][mA][mG][mU][mU][mG][mC][fA][fG][fC][fA][mA][mA][mA][mA][mG][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1097
STAT3-0433	Modified 36 mer	Hs	[mGs][mU][mC][mG][mA][mA][mU][fG][fU][fU][fC][mU][mC][mU][mA][mU][mC][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1098
STAT3-1670	Modified 36 mer	Hs	[mCs][mC][mC][mA][mA][mG][mA][fA][fU][fG][fU][mA][mA][mA][mC][mU][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1099

STAT3-1388	Modified 36 mer	Hs	[mGs][mU][mG][mA][mU][mG][mA][fA][fC][fA][fU][mG][mG][mA][mA][mG][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1100
STAT3-0429	Modified 36 mer	Hs	[mAs][mA][mG][mA][mG][mU][mC][fG][fA][fA][fU][mG][mU][mU][mC][mU][mC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1101
STAT3-2405	Modified 36 mer	Hs	[mGs][mA][mU][mU][mC][mA][mU][fU][fG][fA][fU][mG][mC][mA][mG][mU][mU][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1102
STAT3-0430	Modified 36 mer	Hs	[mAs][mG][mA][mG][mU][mC][mG][fA][fA][fU][fG][mU][mU][mC][mU][mC][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1103
STAT3-0432	Modified 36 mer	Hs	[mAs][mG][mU][mC][mG][mA][mA][fU][fG][fU][fU][mC][mU][mC][mU][mA][mU][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1104
STAT3-1815	Modified 36 mer	Hs	[mCs][mU][mG][mG][mU][mG][mU][fG][fA][fA][fU][mU][mA][mU][mU][mC][mA][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1105
STAT3-0424	Modified 36 mer	Hs	[mCs][mC][mU][mG][mC][mA][mA][fG][fA][fG][fU][mC][mG][mA][mA][mU][mG][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1106
STAT3-2024	Modified 36 mer	Hs	[mAs][mC][mC][mU][mU][mC][mC][fU][fG][fC][fU][mA][mA][mG][mA][mU][mU][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ade	1107

			mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
STAT3-1813	Modified 36 mer	Hs	[mAs][mC][mC][mU][mG][mG][mU][fG][fU][fG][fA][mA][mU][mU][mA][mU][mU][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1108
STAT3-1674	Modified 36 mer	Hs	[mAs][mG][mA][mA][mU][mG][mU][fA][fA][fA][fC][mU][mU][mU][mU][mU][mU][mA][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1109
STAT3-1241	Modified 36 mer	Hs	[mCs][mA][mG][mU][mU][mC][mA][fC][fU][fA][fC][mU][mA][mA][mA][mG][mU][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1110
STAT3-1672	Modified 36 mer	Hs	[mCs][mA][mA][mG][mA][mA][mU][fG][fU][fA][fA][mA][mC][mU][mU][mU][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1111
STAT3-0425	Modified 36 mer	Hs	[mCs][mU][mG][mC][mA][mA][mG][fA][fG][fU][fC][mG][mA][mA][mU][mG][mU][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1112
STAT3-1817	Modified 36 mer	Hs	[mGs][mG][mU][mG][mU][mG][mA][fA][fU][fU][fA][mU][mU][mC][mA][mG][mG][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1113
STAT3-1671	Modified 36 mer	Hs	[mCs][mC][mA][mA][mG][mA][mA][fU][fG][fU][fA][mA][mA][mC][mU][mU][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1114

STAT3-2136	Modified 36 mer	Hs-Mm	[mAs][mG][mC][mA][mG][mC][mA][fG][fC][fU][fG][mA][mA][mC][mA][mA][mC][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1115
STAT3-2143	Modified 36 mer	Hs-Mm	[mGs][mC][mU][mG][mA][mA][mC][fA][fA][fC][fA][mU][mG][mU][mC][mA][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1116
STAT3-2144	Modified 36 mer	Hs-Mm	[mCs][mU][mG][mA][mA][mC][mA][fA][fC][fA][fU][mG][mU][mC][mA][mU][mU][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1117
STAT3-2138	Modified 36 mer	Hs-Mm	[mCs][mA][mG][mC][mA][mG][mC][fU][fG][fA][fA][mC][mA][mA][mC][mA][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1118
STAT3-4909	Modified 36 mer	Hs-Mm	[mUs][mU][mU][mA][mA][mC][mU][fU][fC][fC][fA][mG][mA][mA][mA][mU][mA][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1119
STAT3-2139	Modified 36 mer	Hs-Mm	[mAs][mG][mC][mA][mG][mC][mU][fG][fA][fA][fC][mA][mA][mC][mA][mU][mG][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1120
STAT3-2411	Modified 36 mer	Hs-Mm	[mUs][mU][mG][mA][mU][mG][mC][fA][fG][fU][fU][mU][mG][mG][mA][mA][mA][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1121
STAT3-2145	Modified 36 mer	Hs-Mm	[mUs][mG][mA][mA][mC][mA][mA][fC][fA][fU][fG][mU][mC][mA][mU][mU][mU][mG][mC][mA][mG][mC][mA][mG][mC][mC][mG][ade	1122

			mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
STAT3-4831	Modified 36 mer	Hs-Mm	[mUs][mA][mG][mU][mG][mU][mA][fA][fA][fA][fA][mU][mU][mU][mA][mU][mA][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1123
STAT3-2622	Modified 36 mer	Hs-Mm	[mUs][mA][mA][mC][mU][mU][mU][fG][fU][fG][fG][mU][mU][mC][mC][mA][mG][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1124
STAT3-2135	Modified 36 mer	Hs-Mm	[mAs][mA][mG][mC][mA][mG][mC][fA][fG][fC][fU][mG][mA][mA][mC][mA][mA][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1125
STAT3-1383	Modified 36 mer	Hs-Mm	[mCs][mA][mA][mA][mA][mG][mU][fG][fA][fU][fG][mA][mA][mC][mA][mU][mG][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1126
STAT3-715	Modified 22 mer		[MePhosphonate-4O-mUs][fGs][fAs][fA][fA][mU][fC][mA][mA][fA][mG][mU][mC][fA][mU][mC][mC][mU][mG][mGs][mGs][mG]	1127
STAT3-716	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fGs][fA][fA][mA][fU][mC][mA][fA][mA][mG][mU][fC][mA][mU][mC][mC][mU][mGs][mGs][mG]	1128
STAT3-717	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fUs][fG][fA][mA][fA][mU][mC][fA][mA][mA][mG][fU][mC][mA][mU][mC][mC][mUs][mGs][mG]	1129
STAT3-720	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fAs][fG][fU][mU][fG][mA][mA][fA][mU][mC][mA][fA][mA][mG][mU][mC][mA][mUs][mGs][mG]	1130

STAT3-372	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fGs][fA][fU][mU][fA][mU][mG][fA][mA][mA][mC][fA][mC][mC][mA][mA][mA][mGs][mGs][mG]	1131
STAT3-721	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fUs][fA][fG][mU][fU][mG][mA][fA][mA][mU][mC][fA][mA][mA][mG][mU][mC][mAs][mGs][mG]	1132
STAT3-722	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fAs][fU][fA][mG][fU][mU][mG][fA][mA][mA][mU][fC][mA][mA][mA][mG][mU][mCs][mGs][mG]	1133
STAT3-768	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fUs][fG][fU][mU][fU][mC][mC][fA][mU][mU][mC][fA][mG][mA][mU][mC][mU][mUs][mGs][mG]	1134
STAT3-1001	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fUs][fG][fA][mC][fG][mU][mU][fA][mU][mC][mC][fA][mG][mU][mU][mU][mU][mCs][mGs][mG]	1135
STAT3-1006	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fGs][fC][fU][mA][fA][mU][mG][fA][mC][mG][mU][fU][mA][mU][mC][mC][mA][mGs][mGs][mG]	1136
STAT3-1145	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fCs][fA][fU][mU][fA][mA][mG][fU][mU][mU][mC][fU][mA][mA][mA][mC][mA][mGs][mGs][mG]	1137
STAT3-1151	Modified 22 mer		[MePhosphonate-4O-mUs][fCs][fAs][fC][fU][mU][fU][mU][mC][fA][mU][mU][mA][fA][mG][mU][mU][mU][mC][mUs][mGs][mG]	1138
STAT3-1268	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fCs][fA][fA][mC][fU][mC][mA][fG][mG][mG][mA][fA][mU][mU][mU][mG][mA][mCs][mGs][mG]	1139

STAT3-1273	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fUs][fA][fA][mU][fU][mC][mA][fA][mC][mU][mC][fA][mG][mG][mG][mA][mA][mUs][mGs][mG]	1140
STAT3-1279	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fAs][fG][fC][mU][fG][mA][mU][fA][mA][mU][mU][fC][mA][mA][mC][mU][mC][mAs][mGs][mG]	1141
STAT3-1280	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fAs][fA][fG][mC][fU][mG][mA][fU][mA][mA][mU][fU][mC][mA][mA][mC][mU][mCs][mGs][mG]	1142
STAT3-1281	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fUs][fA][fA][mG][fC][mU][mG][fA][mU][mA][mA][fU][mU][mC][mA][mA][mC][mUs][mGs][mG]	1143
STAT3-1284	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fUs][fU][fU][mU][fA][mA][mG][fC][mU][mG][mA][fU][mA][mA][mU][mU][mC][mAs][mGs][mG]	1144
STAT3-1286	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fAs][fA][fU][mU][fU][mU][mA][fA][mG][mC][mU][fG][mA][mU][mA][mA][mU][mUs][mGs][mG]	1145
STAT3-1287	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fUs][fA][fA][mU][fU][mU][mU][fA][mA][mG][mC][fU][mG][mA][mU][mA][mA][mUs][mGs][mG]	1146
STAT3-1292	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fCs][fA][fC][mU][fU][mU][mA][fA][mU][mU][mU][fU][mA][mA][mG][mC][mU][mGs][mGs][mG]	1147
STAT3-1293	Modified 22 mer		[MePhosphonate-4O-mUs][fCs][fAs][fC][fA][mC][fU][mU][mU][fA][mA][mU][mU][fU][mU][mA][mA][mG][mC][mUs][mGs][mG]	1148

STAT3-1819	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fCs][fA][fC][mC][fC][mU][mG][fA][mA][mU][mA][fA][mU][mU][mC][mA][mC][mAs][mGs][mG]	1149
STAT3-1908	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fCs][fA][fA][mG][fG][mU][mC][fA][mA][mU][mG][fA][mU][mA][mU][mU][mG][mUs][mGs][mG]	1150
STAT3-1910	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fCs][fA][fC][mA][fA][mG][mG][fU][mC][mA][mA][fU][mG][mA][mU][mA][mU][mUs][mGs][mG]	1151
STAT3-1913	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fUs][fU][fU][mC][fA][mC][mA][fA][mG][mG][mU][fC][mA][mA][mU][mG][mA][mUs][mGs][mG]	1152
STAT3-2154	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fUs][fG][fA][mU][fU][mU][mC][fA][mG][mC][mA][fA][mA][mU][mG][mA][mC][mAs][mGs][mG]	1153
STAT3-2327	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fGs][fA][fU][mA][fA][mA][mC][fU][mU][mG][mG][fU][mC][mU][mU][mC][mA][mGs][mGs][mG]	1154
STAT3-2335	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fGs][fU][fC][mA][fC][mA][mC][fA][mG][mA][mU][fA][mA][mA][mC][mU][mU][mGs][mGs][mG]	1155
STAT3-2418	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fCs][fA][fC][mC][fA][mU][mU][fA][mU][mU][mU][fC][mC][mA][mA][mA][mC][mUs][mGs][mG]	1156
STAT3-2692	Modified 22 mer		[MePhosphonate-4O-mUs][fUs][fUs][fC][fA][mC][fU][mC][mA][fU][mU][mU][mC][fU][mC][mU][mA][mU][mU][mUs][mGs][mG]	1157

STAT3-2693	Modified 22 mer		[MePhosphonate-4O-mUs][fAs][fUs][fU][fC][mA][fC][mU][mC][fA][mU][mU][mU][fC][mU][mC][mU][mA][mU][mUs][mGs][mG]	1158
STAT3-2627	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fA][fA][fA][mA][fA][mU][mC][fU][mG][mG][mA][fA][mC][mC][mA][mC][mA][mAs][mGs][mG]	1159
STAT3-2626	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fA][fA][fA][mA][fU][mC][mU][fG][mG][mA][mA][fC][mC][mA][mC][mA][mA][mAs][mGs][mG]	1160
STAT3-2407	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fUs][fC][fC][fA][mA][fA][mC][mU][fG][mC][mA][mU][fC][mA][mA][mU][mG][mA][mAs][mGs][mG]	1161
STAT3-2412	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fUs][fU][fA][fU][mU][fU][mC][mC][fA][mA][mA][mC][fU][mG][mC][mA][mU][mC][mAs][mGs][mG]	1162
STAT3-2151	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fU][fU][fU][mC][fA][mG][mC][fA][mA][mA][mU][fG][mA][mC][mA][mU][mG][mUs][mGs][mG]	1163
STAT3-2625	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fA][fA][fA][mU][fC][mU][mG][fG][mA][mA][mC][fC][mA][mC][mA][mA][mA][mGs][mGs][mG]	1164
STAT3-4836	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fC][fA][fA][mU][fA][mA][mU][fA][mU][mA][mA][fA][mU][mU][mU][mU][mU][mAs][mGs][mG]	1165
STAT3-2408	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fUs][fU][fC][fC][mA][fA][mA][mC][fU][mG][mC][mA][fU][mC][mA][mA][mU][mG][mAs][mGs][mG]	1166

STAT3-2159	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fCs][fC][fA][fU][mG][fA][mU][mG][fA][mU][mU][mU][fC][mA][mG][mC][mA][mA][mAs][mGs][mG]	1167
STAT3-2146	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fG][fC][fA][mA][fA][mU][mG][fA][mC][mA][mU][fG][mU][mU][mG][mU][mU][mCs][mGs][mG]	1168
STAT3-2148	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fUs][fC][fA][fG][mC][fA][mA][mA][fU][mG][mA][mC][fA][mU][mG][mU][mU][mG][mUs][mGs][mG]	1169
STAT3-2147	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fCs][fA][fG][fC][mA][fA][mA][mU][fG][mA][mC][mA][fU][mG][mU][mU][mG][mU][mUs][mGs][mG]	1170
STAT3-0461	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fGs][fA][fA][fA][mC][fU][mG][mC][fU][mU][mG][mA][fU][mU][mC][mU][mU][mC][mGs][mGs][mG]	1171
STAT3-1584	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fU][fC][fA][mC][fC][mA][mC][fA][mA][mC][mU][fG][mG][mC][mA][mA][mG][mGs][mGs][mG]	1172
STAT3-1047	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fUs][fC][fC][fA][mG][fU][mU][mU][fC][mU][mU][mA][fA][mU][mU][mU][mG][mU][mUs][mGs][mG]	1173
STAT3-0773	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fC][fU][fG][mG][fU][mU][mG][fU][mU][mU][mC][fC][mA][mU][mU][mC][mA][mGs][mGs][mG]	1174
STAT3-0492	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fUs][fC][fC][fA][mU][fU][mG][mG][fC][mU][mU][mC][fU][mC][mA][mA][mG][mA][mUs][mGs][mG]	1175

STAT3-0462	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fG][fA][fA][mA][fC][mU][mG][fC][mU][mU][mG][fA][mU][mU][mC][mU][mU][mCs][mGs][mG]	1176
STAT3-1586	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fG][fA][fU][mC][fA][mC][mC][fA][mC][mA][mA][fC][mU][mG][mG][mC][mA][mAs][mGs][mG]	1177
STAT3-0771	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fUs][fG][fG][fU][mU][fG][mU][mU][fU][mC][mC][mA][fU][mU][mC][mA][mG][mA][mUs][mGs][mG]	1178
STAT3-0681	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fUs][fU][fC][fA][mU][fU][mU][mU][fC][mU][mG][mU][fU][mC][mU][mA][mG][mA][mUs][mGs][mG]	1179
STAT3-0678	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fU][fU][fU][mU][fC][mU][mG][fU][mU][mC][mU][fA][mG][mA][mU][mC][mC][mUs][mGs][mG]	1180
STAT3-4837	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fCs][fA][fC][fA][mA][fU][mA][mA][fU][mA][mU][mA][fA][mA][mU][mU][mU][mU][mUs][mGs][mG]	1181
STAT3-4833	Modified 22 mer	Hs-Mf-Mm	[MePhosphonate-4O-mUs][fAs][fU][fA][fA][mU][fA][mU][mA][fA][mA][mU][mU][fU][mU][mU][mA][mC][mA][mCs][mGs][mG]	1182
STAT3-1068	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fGs][fA][fA][fA][mC][fU][mU][mU][fU][mU][mG][mC][fU][mG][mC][mA][mA][mC][mUs][mGs][mG]	1183
STAT3-1673	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fUs][fA][fA][fA][mA][fA][mA][mG][fU][mU][mU][mA][fC][mA][mU][mU][mC][mU][mUs][mGs][mG]	1184

STAT3-0426	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fAs][fG][fA][fA][mC][fA][mU][mU][fC][mG][mA][mC][fU][mC][mU][mU][mG][mC][mAs][mGs][mG]	1185
STAT3-2404	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fAs][fA][fA][fC][mU][fG][mC][mA][fU][mC][mA][mA][fU][mG][mA][mA][mU][mC][mUs][mGs][mG]	1186
STAT3-1067	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fAs][fA][fA][fC][mU][fU][mU][mU][fU][mG][mC][mU][fG][mC][mA][mA][mC][mU][mCs][mGs][mG]	1187
STAT3-0433	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fCs][fU][fG][fA][mU][fA][mG][mA][fG][mA][mA][mC][fA][mU][mU][mC][mG][mA][mCs][mGs][mG]	1188
STAT3-1670	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fAs][fA][fA][fA][mG][fU][mU][mU][fA][mC][mA][mU][fU][mC][mU][mU][mG][mG][mGs][mGs][mG]	1189
STAT3-1388	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fAs][fU][fU][fC][mU][fU][mC][mC][fA][mU][mG][mU][fU][mC][mA][mU][mC][mA][mCs][mGs][mG]	1190
STAT3-0429	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fUs][fA][fG][fA][mG][fA][mA][mC][fA][mU][mU][mC][fG][mA][mC][mU][mC][mU][mUs][mGs][mG]	1191
STAT3-2405	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fCs][fA][fA][fA][mC][fU][mG][mC][fA][mU][mC][mA][fA][mU][mG][mA][mA][mU][mCs][mGs][mG]	1192
STAT3-0430	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fAs][fU][fA][fG][mA][fG][mA][mA][fC][mA][mU][mU][fC][mG][mA][mC][mU][mC][mUs][mGs][mG]	1193

STAT3-0432	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fUs][fG][fA][fU][mA][fG][mA][mG][fA][mA][mC][mA][fU][mU][mC][mG][mA][mC][mUs][mGs][mG]	1194
STAT3-1815	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fCs][fC][fU][fG][mA][fA][mU][mA][fA][mU][mU][mC][fA][mC][mA][mC][mC][mA][mGs][mGs][mG]	1195
STAT3-0424	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fAs][fA][fC][fA][mU][fU][mC][mG][fA][mC][mU][mC][fU][mU][mG][mC][mA][mG][mGs][mGs][mG]	1196
STAT3-2024	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fUs][fG][fA][fA][mU][fC][mU][mU][fA][mG][mC][mA][fG][mG][mA][mA][mG][mG][mUs][mGs][mG]	1197
STAT3-1813	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fUs][fG][fA][fA][mU][fA][mA][mU][fU][mC][mA][mC][fA][mC][mC][mA][mG][mG][mUs][mGs][mG]	1198
STAT3-1674	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fGs][fU][fA][fA][mA][fA][mA][mA][fG][mU][mU][mU][fA][mC][mA][mU][mU][mC][mUs][mGs][mG]	1199
STAT3-1241	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fUs][fG][fA][fC][mU][fU][mU][mA][fG][mU][mA][mG][fU][mG][mA][mA][mC][mU][mGs][mGs][mG]	1200
STAT3-1672	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fUs][fG][fA][fC][mU][fU][mU][mA][fG][mU][mA][mG][fU][mG][mA][mA][mC][mU][mGs][mGs][mG]	1201
STAT3-0425	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fGs][fA][fA][fC][mA][fU][mU][mC][fG][mA][mC][mU][fC][mU][mU][mG][mC][mA][mGs][mGs][mG]	1202

STAT3-1817	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fAs][fC][fC][fC][mU][fG][mA][mA][fU][mA][mA][mU][fU][mC][mA][mC][mA][mC][mCs][mGs][mG]	1203
STAT3-1671	Modified 22 mer	Hs	[MePhosphonate-4O-mUs][fAs][fA][fA][fA][mA][fG][mU][mU][fU][mA][mC][mA][fU][mU][mC][mU][mU][mG][mGs][mGs][mG]	1204
STAT3-2136	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fAs][fU][fG][fU][mU][fG][mU][mU][fC][mA][mG][mC][fU][mG][mC][mU][mG][mC][mUs][mGs][mG]	1205
STAT3-2143	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fAs][fA][fA][fU][mG][fA][mC][mA][fU][mG][mU][mU][fG][mU][mU][mC][mA][mG][mCs][mGs][mG]	1206
STAT3-2144	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fCs][fA][fA][fA][mU][fG][mA][mC][fA][mU][mG][mU][fU][mG][mU][mU][mC][mA][mGs][mGs][mG]	1207
STAT3-2138	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fAs][fC][fA][fU][mG][fU][mU][mG][fU][mU][mC][mA][fG][mC][mU][mG][mC][mU][mGs][mGs][mG]	1208
STAT3-4909	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fUs][fU][fU][fA][mU][fU][mU][mC][fU][mG][mG][mA][fA][mG][mU][mU][mA][mA][mAs][mGs][mG]	1209
STAT3-2139	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fGs][fA][fC][fA][mU][fG][mU][mU][fG][mU][mU][mC][fA][mG][mC][mU][mG][mC][mUs][mGs][mG]	1210
STAT3-2411	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fUs][fA][fU][fU][mU][fC][mC][mA][fA][mA][mC][mU][fG][mC][mA][mU][mC][mA][mAs][mGs][mG]	1211

STAT3-2145	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fGs][fC][fA][fA][mA][fU][mG][mA][fC][mA][mU][mG][fU][mU][mG][mU][mU][mC][mAs][mGs][mG]	1212
STAT3-4831	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fAs][fA][fU][fA][mU][fA][mA][mA][fU][mU][mU][mU][fU][mA][mC][mA][mC][mU][mAs][mGs][mG]	1213
STAT3-2622	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fAs][fU][fC][fU][mG][fG][mA][mA][fC][mC][mA][mC][fA][mA][mA][mG][mU][mU][mAs][mGs][mG]	1214
STAT3-2135	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fUs][fG][fU][fU][mG][fU][mU][mC][fA][mG][mC][mU][fG][mC][mU][mG][mC][mU][mUs][mGs][mG]	1215
STAT3-1383	Modified 22 mer	Hs-Mm	[MePhosphonate-4O-mUs][fUs][fG][fU][fU][mG][fU][mU][mC][fA][mG][mC][mU][fG][mC][mU][mG][mC][mU][mUs][mGs][mG]	1216
NM_139276.3 human STAT3 nucleotide sequence			GTCGCAGCCGAGGGAACAAGCCCCAACCGGATCCTGGACAGGCACCCCGGCTTGGCGCTGTCTCTCCCCCTCGGCTCGGAGAGGCCCTTCGGCCTGAGGGAGCCTCGCCGCCCGTCCCCGGCACACGCGCAGCCCCGGCCTCTCGGCCTCTGCCGGAGAAACAGTTGGGACCCCTGATTTTAGCAGGATGGCCCAATGGAATCAGCTACAGCAGCTTGACACACGGTACCTGGAGCAGCTCCATCAGCTCTACAGTGACAGCTTCCCAATGGAGCTGCGGCAGTTTCTGGCCCCTTGGATTGAGAGTCAAGAATTGGGCATATGCGGCCAGCAAAGAATCACATGCCACTTTGGTGTTTCATAATCTCCTGGGAGAGATTGACCAGCAGTATAGCCGCTTCCTGCAAGAGTCGAATGTTCTCTATCAGCACAATCTACGAAGAATCAAGCAGTTTCTTCAGAGCAGGTATCTTGAGAAGCCAATGGAGATTGCCCGGATTGTGGCCCGGTGCCTGTGGGAAGAATCACGCCTTCTACAGACTGCAGCCACTGCGGCCCAGCAAGGGG	1217

			GCCAGGCCAACCACCCCACAGCAGCCGT GGTGACGGAGAAGCAGCAGATGCTGGAG CAGCACCTTCAGGATGTCCGGAAGAGAG TGCAGGATCTAGAACAGAAAATGAAAGT GGTAGAGAATCTCCAGGATGACTTTGATT TCAACTATAAAACCCTCAAGAGTCAAGG AGACATGCAAGATCTGAATGGAAACAAC CAGTCAGTGACCAGGCAGAAGATGCAGC AGCTGGAACAGATGCTCACTGCGCTGGA CCAGATGCGGAGAAGCATCGTGAGTGAG CTGGCGGGGCTTTTGTCAGCGATGGAGT ACGTGCAGAAAACTCTCACGGACGAGGA GCTGGCTGACTGGAAGAGGCGGCAACAG ATTGCCTGCATTGGAGGCCCGCCCAACAT CTGCCTAGATCGGCTAGAAAACTGGATA ACGTCATTAGCAGAATCTCAACTTCAGAC CCGTCAACAAATTAAGAAACTGGAGGAG TTGCAGCAAAAAGTTTCCTACAAAGGGG ACCCCATTGTACAGCACCGGCCGATGCT GGAGGAGAGAATCGTGGAGCTGTTTAGA AACTTAATGAAAAGTGCCTTTGTGGTGG AGCGGCAGCCCTGCATGCCCATGCATCCT GACCGGCCCCTCGTCATCAAGACCGGCG TCCAGTTCACTACTAAAGTCAGGTTGCTG GTCAAATTCCCTGAGTTGAATTATCAGCT TAAAATTAAAGTGTGCATTGACAAAGAC TCTGGGGACGTTGCAGCTCTCAGAGGAT CCCGGAAATTTAACATTCTGGGCACAAA CACAAAAGTGATGAACATGGAAGAATCC AACAACGGCAGCCTCTCTGCAGAATTCA AACACTTGACCCTGAGGGAGCAGAGATG TGGGAATGGGGGCCGAGCCAATTGTGAT GCTTCCCTGATTGTGACTGAGGAGCTGCA CCTGATCACCTTTGAGACCGAGGTGTATC ACCAAGGCCTCAAGATTGACCTAGAGAC CCACTCCTTGCCAGTTGTGGTGATCTCCA ACATCTGTCAGATGCCAAATGCCTGGGC GTCCATCCTGTGGTACAACATGCTGACCA ACAATCCCAAGAATGTAAACTTTTTTACC AAGCCCCCAATTGGAACCTGGGATCAAG TGGCCGAGGTCCTGAGCTGGCAGTTCTCC TCCACCACCAAGCGAGGACTGAGCATCG AGCAGCTGACTACACTGGCAGAGAAACT CTTGGGACCTGGTGTGAATTATTCAGGGT GTCAGATCACATGGGCTAAATTTTGCAA AGAAAACATGGCTGGCAAGGGCTTCTCC	

			TTCTGGGTCTGGCTGGACAATATCATTGA CCTTGTGAAAAAGTACATCCTGGCCCTTT GGAACGAAGGGTACATCATGGGCTTTAT CAGTAAGGAGCGGGAGCGGGCCATCTTG AGCACTAAGCCTCCAGGCACCTTCCTGCT AAGATTCAGTGAAAGCAGCAAAGAAGGA GGCGTCACTTTCACTTGGGTGGAGAAGG ACATCAGCGGTAAGACCCAGATCCAGTC CGTGGAACCATACACAAAGCAGCAGCTG AACAACATGTCATTTGCTGAAATCATCAT GGGCTATAAGATCATGGATGCTACCAAT ATCCTGGTGTCTCCACTGGTCTATCTCTA TCCTGACATTCCCAAGGAGGAGGCATTC GGAAAGTATTGTCGGCCAGAGAGCCAGG AGCATCCTGAAGCTGACCCAGGTAGCGC TGCCCCATACCTGAAGACCAAGTTTATCT GTGTGACACCAACGACCTGCAGCAATAC CATTGACCTGCCGATGTCCCCCCGCACTT TAGATTCATTGATGCAGTTTGGAAATAAT GGTGAAGGTGCTGAACCCTCAGCAGGAG GGCAGTTTGAGTCCCTCACCTTTGACATG GAGTTGACCTCGGAGTGCGCTACCTCCCC CATGTGAGGAGCTGAGAACGGAAGCTGC AGAAAGATACGACTGAGGCGCCTACCTG CATTCTGCCACCCCTCACACAGCCAAACC CCAGATCATCTGAAACTACTAACTTTGTG GTTCCAGATTTTTTTTAATCTCCTACTTCT GCTATCTTTGAGCAATCTGGGCACTTTTA AAAATAGAGAAATGAGTGAATGTGGGTG ATCTGCTTTTATCTAAATGCAAATAAGGA TGTGTTCTCTGAGACCCATGATCAGGGGA TGTGGCGGGGGGTGGCTAGAGGGAGAAA AAGGAAATGTCTTGTGTTGTTTTGTTCCC CTGCCCTCCTTTCTCAGCAGCTTTTTGTTA TTGTTGTTGTTGTTCTTAGACAAGTGCCT CCTGGTGCCTGCGGCATCCTTCTGCCTGT TTCTGTAAGCAAATGCCACAGGCCACCT ATAGCTACATACTCCTGGCATTGCACTTT TTAACCTTGCTGACATCCAAATAGAAGAT AGGACTATCTAAGCCCTAGGTTTCTTTTT AAATTAAGAAATAATAACAATTAAAGGG CAAAAAACACTGTATCAGCATAGCCTTTC TGTATTTAAGAAACTTAAGCAGCCGGGC ATGGTGGCTCACGCCTGTAATCCCAGCAC TTTGGGAGGCCGAGGCGGATCATAAGGT CAGGAGATCAAGACCATCCTGGCTAACA	

			CGGTGAAACCCCGTCTCTACTAAAAGTA CAAAAAATTAGCTGGGTGTGGTGGTGGG CGCCTGTAGTCCCAGCTACTCGGGAGGCT GAGGCAGGAGAATCGCTTGAACCTGAGA GGCGGAGGTTGCAGTGAGCCAAAATTGC ACCACTGCACACTGCACTCCATCCTGGGC GACAGTCTGAGACTCTGTCTCAAAAAAA AAAAAAAAAAAAAGAAACTTCAGTTAAC AGCCTCCTTGGTGCTTTAAGCATTCAGCT TCCTTCAGGCTGGTAATTTATATAATCCC TGAAACGGGCTTCAGGTCAAACCCTTAA GACATCTGAAGCTGCAACCTGGCCTTTGG TGTTGAAATAGGAAGGTTTAAGGAGAAT CTAAGCATTTTAGACTTTTTTTTATAAAT AGACTTATTTTCCTTTGTAATGTATTGGC CTTTTAGTGAGTAAGGCTGGGCAGAGGG TGCTTACAACCTTGACTCCCTTTCTCCCT GGACTTGATCTGCTGTTTCAGAGGCTAGG TTGTTTCTGTGGGTGCCTTATCAGGGCTG GGATACTTCTGATTCTGGCTTCCTTCCTG CCCCACCCTCCCGACCCCAGTCCCCCTGA TCCTGCTAGAGGCATGTCTCCTTGCGTGT CTAAAGGTCCCTCATCCTGTTTGTTTTAG GAATCCTGGTCTCAGGACCTCATGGAAG AAGAGGGGGAGAGAGTTACAGGTTGGAC ATGATGCACACTATGGGGCCCCAGCGAC GTGTCTGGTTGAGCTCAGGGAATATGGTT CTTAGCCAGTTTCTTGGTGATATCCAGTG GCACTTGTAATGGCGTCTTCATTCAGTTC ATGCAGGGCAAAGGCTTACTGATAAACT TGAGTCTGCCCTCGTATGAGGGTGTATAC CTGGCCTCCCTCTGAGGCTGGTGACTCCT CCCTGCTGGGGCCCCACAGGTGAGGCAG AACAGCTAGAGGGCCTCCCCGCCTGCCC GCCTTGGCTGGCTAGCTCGCCTCTCCTGT GCGTATGGGAACACCTAGCACGTGCTGG ATGGGCTGCCTCTGACTCAGAGGCATGG CCGGATTTGGCAACTCAAAACCACCTTGC CTCAGCTGATCAGAGTTTCTGTGGAATTC TGTTTGTTAAATCAAATTAGCTGGTCTCT GAATTAAGGGGGAGACGACCTTCTCTAA GATGAACAGGGTTCGCCCCAGTCCTCCTG CCTGGAGACAGTTGATGTGTCATGCAGA GCTCTTACTTCTCCAGCAACACTCTTCAG TACATAATAAGCTTAACTGATAAACAGA ATATTTAGAAAGGTGAGACTTGGGCTTA	

			CCATTGGGTTTAAATCATAGGGACCTAG GGCGAGGGTTCAGGGCTTCTCTGGAGCA GATATTGTCAAGTTCATGGCCTTAGGTAG CATGTATCTGGTCTTAACTCTGATTGTAG CAAAAGTTCTGAGAGGAGCTGAGCCCTG TTGTGGCCCATTAAAGAACAGGGTCCTC AGGCCCTGCCCGCTTCCTGTCCACTGCCC CCTCCCCATCCCCAGCCCAGCCGAGGGA ATCCCGTGGGTTGCTTACCTACCTATAAG GTGGTTTATAAGCTGCTGTCCTGGCCACT GCATTCAAATTCCAATGTGTACTTCATAG TGTAAAAATTTATATTATTGTGAGGTTTT TTGTCTTTTTTTTTTTTTTTTTTTTTGGTA TATTGCTGTATCTACTTTAACTTCCAGAA ATAAACGTTATATAGGAACCGTC	
XM_005584240.2 Non-human primate STAT3 nucleotide sequence			TGCATGACGGCGTGCCTCGGCCAGGCTG GGGCTGGGCGGGGATTGGCTGAAGGGGC TGTAATTCAGCGGTTTCCGGAGCTGCGGC GGCGTAGACCGGGAGGGGGAGCCGGGG GTTCCGACGTAGCAGCCGAGGGAACAAG CCCCAACCGGATCCTGGACAGGCACCCC GGCTCGGCGCTGTCTCTCCCCCTCGGCTC GGATAAGCCCTCCGGCCTGAGGGAGCCC CGTCGCCCGCCCCCGGCGCACGCGCAGC CCCGGCCTCTCGGCCTCTGCTGGAGAAAC AGCAGGATGGCCCAATGGAATCAGCTAC AGCAGCTTGACACACGGTACCTGGAGCA GCTCCATCAGCTCTACAGTGACAGCTTCC CAATGGAGTTGCGGCAGTTTCTGGCCCCT TGGATTGAGAGTCAAGATTGGGCATATG CGGCCAGCAAAGAATCACATGCCACTTT GGTGTTTCATAATCTCCTGGGCGAGATTG ACCAGCAGTATAGCCGCTTCCTGCAAGA ATCGAATGTTCTCTATCAGCACAATCTAC GAAGAATCAAGCAGTTTCTTCAGAGCAG GTATCTTGAGAAGCCAATGGAGATTGCC CGGATTGTGGCCCGGTGCCTGTGGGAAG AGTCACGCCTCCTACAGACTGCAGCCACT GCGGCCCAGCAAGGGGGCCAGGCCAACC ACCCCACAGCAGCTGTGGTGACGGAGAA GCAGCAGATGCTGGAGCAGCACCTTCAG GATGTCCGGAAGAGAGTACAGGATCTAG AACAGAAAATGAAAGTGGTAGAGAATCT CCAGGATGACTTTGATTTCAACTATAAAA CCCTCAAGAGTCAAGGAGACATGCAAGA TCTGAATGGAAACAACCAGTCAGTGACC	1218

			AGGCAGAAGATGCAGCAGCTGGAACAGA TGCTCACTGCGCTGGACCAGATGCGGAG AAGCATCGTGAGTGAGCTGGCGGGGCTT TTGTCAGCGATGGAGTACGTGCAGAAAA CTCTCACAGACGAGGAGCTGGCTGACTG GAAGAGGCGGCAACAGATTGCCTGCATT GGAGGTCCGCCCAACATCTGCCTAGATC GGCTAGAAAACTGGATAACGTCATTAGC AGAATCTCAACTTCAGACCCGTCAACAA ATTAAGAAACTGGAGGAGTTGCAGCAAA AAGTGTCCTACAAAGGGGACCCCATTGT ACAGCACCGGCCGATGCTGGAGGAGAGA ATCGTGGAGCTGTTCAGAAACTTAATGA AAAGTGCCTTTGTGGTGGAGCGGCAGCC CTGCATGCCCATGCATCCCGACCGGCCCC TTGTCATCAAGACCGGCGTCCAGTTCACT ACCAAAGTCAGGTTGCTGGTCAAATTCCC TGAGTTAAATTATCAACTTAAAATTAAAG TGTGCATTGACAAAGACTCTGGGGATGTT GCAGCTCTCAGAGGATCCCGGAAATTTA ACATTCTGGGCACAAACACCAAAGTGAT GAACATGGAAGAGTCCAACAACGGCAGC CTCTCTGCAGAATTCAAACACTTGACCCT GAGGGAGCAGAGATGTGGGAATGGGGG CCGAGCCAATTGTGATGCTTCCCTGATTG TGACTGAGGAGCTGCACCTGATCACCTTT GAGACAGAGGTATATCACCAAGGCCTCA AGATTGACCTAGAGACCCACTCCTTGCCA GTTGTGGTGATCTCCAACATCTGTCAGAT GCCAAATGCCTGGGCGTCCATCCTGTGGT ACAACATGCTGACCAACAACCCCAAGAA CGTAAACTTTTTTACCAAGCCCCCAATCG GAACCTGGGATCAAGTGGCCGAGGTCCT GAGCTGGCAGTTCTCCTCCACCACCAAGC GAGGACTGAGCATCGAGCAGCTGACTAC ACTGGCGGAGAAACTCTTGGGACCTGGC GTGAATTATTCAGGGTGTCAGATCACATG GGCTAAATTTTGCAAAGAAAACATGGCT GGCAAGGGCTTCTCCTTCTGGGTCTGGCT GGACAATATCATTGACCTTGTGAAAAAG TACATCCTGGCCCTTTGGAATGAAGGGTA CATCATGGGCTTTATCAGTAAGGAGCGG GAGCGGGCCATCTTGAGCACCAAGCCTC CAGGCACCTTTCTGCTAAGATTCAGTGAA AGCAGCAAAGAAGGCGGCGTCACTTTCA CTTGGGTGGAGAAGGACATCAGTGGTAA	

			GACCCAGATCCAGTCCGTGGAACCATAC ACCAAGCAGCAGTTGAACAACATGTCAT TTGCTGAAATCATCATGGGCTATAAGATC ATGGATGCTACCAATATTCTGGTGTCTCC GCTGGTCTATCTCTACCCTGACATTCCCA AGGAGGAGGCATTCGGAAAGTATTGTCG GCCAGAGAGCCAGGAGCATCCTGAAGCT GACCCAGGCGCCGCCCCATACCTGAAGA CCAAGTTTATCTGTGTGACACCATTCATT GATGCAGTTTGGAAATAATGGTGAAGGT GCTGAACCCTCAGCAGGAGGGCAGTTTG AGTCCCTCACCTTTGACATGGAGTTGACC TCGGAGTGTGCTACCTCCCCCATGTGAGG AGCTGAGAACGGAAGCTGCAAAAGATAC GACTGAGGCGCCTACCTGTGTTCCGCCAC CCCTCACACAGCCAAACCCCAGATCATC TGAAACTACTAACTTTGTGGTTCCAGATT TTTTTTAATCTCCTACTTCTGCTATCTTTG AGCAATCTGGGCACTTTTAAAAATAAGA GAAATGAGTGAATGTGGGTGATCTGCTTT TATCTAAATGCAAATAAGGATGTGTTCTC TGAGACCCGTGATGGGGGGATGTGGCGG GGGGTGGCTAGAGGGAGAAAAAGGAAA TGTCTTGTGTTGTTTTGTTCCCCTGCCCTC CTTTCTCAGCAGCTTTTTGTTATTGTTGTT GTTGTTCTTAGACAAGTGCCTCCTGGTGC CCGCGGCATCCTTCTGCCTGTTTCTGTAA GCAAATGCCACAGGCCACCTGTAGCTAC ATACTCCTGGCATTGCACTTTTTAACCTT GCTGACATCCAAATAGAAGATAGGACTA TCTGAGCCCTAGGTTTCTTTTTAAATTAA GAAATAAGAACAATTAAAGGGCAAAAA ACACTGTTTCAGCATAGCCTTTCTGTATT TAAGAAACTTCAGCAGCCGGCCGCAGGG ACTCACGCCTGTAATCCCAGCACTTTGGG AGGCCGAGGTGGGTGGATCATGAGGTTA GGAGATCAAGACTGTCCTGGCTAACATG GTGAAACCCCGTCTCTACTAACAGTACA AAAAATTAGCCGGGCGTGGTGGTGGGTG CCTGTAGTCCCAGCTACTCGGGAGGCTG AGGCAGGAGAATGGCATGAACCCAAGAG GCGGAGGTTGCAGTGAGCCAAAATCACA CCACTGCACTCCAACTCAGGCAACAGTG TGAGACTCCATCTCAAAAAAAAAAGAAA AGAAAAAGAAACTTCAGTTAACAGCCTC CTTGGTGCTTTAAGCATTCAGCTTCCTTC	

			AGGTTGATAATTTATATAACCCCTGAAAC AGGCTTCAGGTCAAACCCTTAAAAGACG TCTGAAGCTGCAGCCTGGCCTTTGATGTT GAAATAGGAAGGTTTAAGGAGAATCTAA GCATTTTAGACTTTTTTTTATAAATAGAC TTCTATTTTCCTTTGTAATGTATTGGTCTT TTAGTGGGTAAGGCTGGGCAGAGGGTGC TTACAACCTTGACTCCCTTTCTCCCTGGA CTTGATCTGCTGTTTCAGAGGCTAGGTTG TTTCTGTGGGTGCCTTATCAGGGCTGGGA TACTTCTGATTTGGGCTTCCTTCTTGCCCC ACCCTCCCGACCCCAGTTCCCCTGACCCT GCTAGTGGCATGTCTCCTCCCATGTCTGA AGGTCCCTCGTCCTGTTTGTTTTAGGAAT CCTGGTCTCAGGACCTCATGGAAGAAGA GGGGGAGAAAGTTACCAGTTGGATATGA TGCAGACTATGGGGCCCCAGCGACGTGT CTGGTTGAGCTCAGGGAATATGGTTCTTA GCCCAGTTTCTTGGTGATTTCCAGCGGTC AGTTCAGGCAGGGCAAAGGCTTACTGAT AAACTTGAGTCTGCCCTCGTATGAGGGTT ATAGCTGGCCTCCCTCTGAGGCTGGTGAC TCTTCCCTGCTGGGGCCCCACAGGTGAGA CAGAACAGGTAGAGGGCCTCCCTGTCTG CCCGCCTTGGCCAGCTAGCTTGCCTCTCC TGTGCGTATGGGAACACCTAGCACGTGC TGGGTGGGCTGCCTCTGACCCAGAGGCA TGGCCGAATTTGGCGACTCAAAACCACC TTGCCTCAGCTGATCAGAGTTTCTGTGGA ATTCTGATTGTTAGATCAAATTAGCTGGC CTCTGAATTAAGTGGGAGAGGACCTTCTC TAAGATGAACCGGGTTCGCCCCAGTCCTC CTGCCTGGAGACAGTTGATGTGTCTTGCA GAGCTCTCGCTTCCCCAGCAACACTCTTC AGTACATAATAAGCTTAACTGATAAACA GAGAGAATATTTAGGAAGGTGAGTCTTG GGCTTACCATTGGGTTTAAATCATAGGGA CCTCGGGAAAGGGTTCGGGCTTCTCTGG AGCAGATATTATGAAGTTCATGGCCTTAG GTAGCATGTGTATCTGGTCTTAACTCTGA TTGTAGCAAAAGTTCTGAGAGGAGCTGA GCCTTGTTCTGGCCCCTTAAAGAACAGGG TCCTCAGGCCCTGCCCGCTTCCTGTCCAC TGCCCTCCTGCCCGTCCCCAGCCCAGCTG AGGGAATCCCGTGGGTTGCTTACCTACCT ATAAGGTGGTTTATAAGCTGCTGTCCTGG	

			CCACTGCATTCAAATTCCAATGTGTACTT CATAGTGTAAAAATTTATATTATTGTGGG GTTTTTTGTCTTTTTTTTTTTTTTTTTTG GTATATTGCTGTATCTACTTTAACTTCCA GAAATAAACGTTATATAGGAACCGTC	
Forward 1			TTGTGTTTGTGCCCAGAATG	1219
Reverse 1			TCCCTGAGTTGAATTATCAGCTT	1220
Probe 1			/56-FAM/ACGTCCCCA/ZEN/GAGTCTTTGTCA ATGC/3IABkFQ/	1221
Forward 2			GATGATTTCAGCAAATGACATGTTG	1222
Reverse 2			CAGTGAAAGCAGCAAAGAAGG	1223
Probe 2			/56-FAM/AGGACATCA/ZEN/GCGGTAAGACCC AGA/3IABkFQ/	1224
STAT3-721	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fU][fA][fG][mU][fU][mG][mA][fA][mA][mU][mC][fA][mA][mA][mG][mU][mC][mAs][mGs][mG]	1225
STAT3-1286	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fA][fA][fU][mU][fU][mU][mA][fA][mG][mC][mU][fG][mA][mU][mA][mA][mU][mUs][mGs][mG]	1226
STAT3-1287	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fU][fA][fA][mU][fU][mU][mU][fA][mA][mG][mC][fU][mG][mA][mU][mA][mA][mUs][mGs][mG]	1227
STAT3-1388	Modified 22mer		[MePhosphonate-4O-mUs][fAs][fUs][fU][fC][mU][fU][mC][mC][fA][mU][mG][mU][fU][mC][mA][mU][mC][mA][mCs][mGs][mG]	1228
NM_213659.3 Mus musculus STAT3 nucleotid			AATTATGCATGGAGGCGTGTCTTGGCCA GTGGCGGCTGGGTGGGGATTGGCTGGAG GGGCTGTAATTCAGCGGTTTCCGGAGCTG CAGTGTAGACAGGGAGGGGGAACCTGGG GTTCCGACGTCGCGGCGGAGGGAACGAG CCCTAACCGGATCGCTGAGGTACAACCC CGCTCGGTGTCGCCTGACCGCGTCGGCTA	1229

e sequence			GGAGAGGCCAGGCGGCCCTCGGGAGCCC AGCAGCTCGCGCCTGGAGTCAGCGCAGG CCGGCCAGTCGGGCCTCAGCCCCGGAGA CAGTCGAGACCCCTGACTGCAGCAGGAT GGCTCAGTGGAACCAGCTGCAGCAGCTG GACACACGCTACCTGGAGCAGCTGCACC AGCTGTACAGCGACAGCTTCCCCATGGA GCTGCGGCAGTTCCTGGCACCTTGGATTG AGAGTCAAGACTGGGCATATGCAGCCAG CAAAGAGTCACATGCCACGTTGGTGTTTC ATAATCTCTTGGGTGAAATTGACCAGCA ATATAGCCGATTCCTGCAAGAGTCCAAT GTCCTCTATCAGCACAACCTTCGAAGAAT CAAGCAGTTTCTGCAGAGCAGGTATCTTG AGAAGCCAATGGAAATTGCCCGGATCGT GGCCCGATGCCTGTGGGAAGAGTCTCGC CTCCTCCAGACGGCAGCCACGGCAGCCC AGCAAGGGGGCCAGGCCAACCACCCAAC AGCCGCCGTAGTGACAGAGAAGCAGCAG ATGTTGGAGCAGCATCTTCAGGATGTCCG GAAGCGAGTGCAGGATCTAGAACAGAAA ATGAAGGTGGTGGAGAACCTCCAGGACG ACTTTGATTTCAACTACAAAACCCTCAAG AGCCAAGGAGACATGCAGGATCTGAATG GAAACAACCAGTCTGTGACCAGACAGAA GATGCAGCAGCTGGAACAGATGCTCACA GCCCTGGACCAGATGCGGAGAAGCATTG TGAGTGAGCTGGCGGGGCTCTTGTCAGC AATGGAGTACGTGCAGAAGACACTGACT GATGAAGAGCTGGCTGACTGGAAGAGGC GGCAGCAGATCGCGTGCATCGGAGGCCC TCCCAACATCTGCCTGGACCGTCTGGAAA ACTGGATAACTTCATTAGCAGAATCTCAA CTTCAGACCCGCCAACAAATTAAGAAAC TGGAGGAGCTGCAGCAGAAAGTGTCCTA CAAGGGCGACCCTATCGTGCAGCACCGG CCCATGCTGGAGGAGAGGATCGTGGAGC TGTTCAGAAACTTAATGAAGAGTGCCTTC GTGGTGGAGCGGCAGCCCTGCATGCCCA TGCACCCGGACCGGCCCTTAGTCATCAA GACTGGTGTCCAGTTTACCACGAAAGTC AGGTTGCTGGTCAAATTTCCTGAGTTGAA TTATCAGCTTAAAATTAAAGTGTGCATTG ATAAAGACTCTGGGGATGTTGCTGCCCTC AGAGGGTCTCGGAAATTTAACATTCTGG GCACGAACACAAAAGTGATGAACATGGA	

			GGAGTCTAACAACGGCAGCCTGTCTGCA GAGTTCAAGCACCTGACCCTTAGGGAGC AGAGATGTGGGAATGGAGGCCGTGCCAA TTGTGATGCCTCCTTGATCGTGACTGAGG AGCTGCACCTGATCACCTTCGAGACTGA GGTGTACCACCAAGGCCTCAAGATTGAC CTAGAGACCCACTCCTTGCCAGTTGTGGT GATCTCCAACATCTGTCAGATGCCAAATG CTTGGGCATCAATCCTGTGGTATAACATG CTGACCAATAACCCCAAGAACGTGAACT TCTTCACTAAGCCGCCAATTGGAACCTGG GACCAAGTGGCCGAGGTGCTCAGCTGGC AGTTCTCGTCCACCACCAAGCGGGGGCT GAGCATCGAGCAGCTGACAACGCTGGCT GAGAAGCTCCTAGGGCCTGGTGTGAACT ACTCAGGGTGTCAGATCACATGGGCTAA ATTCTGCAAAGAAAACATGGCTGGCAAG GGCTTCTCCTTCTGGGTCTGGCTAGACAA TATCATCGACCTTGTGAAAAAGTATATCT TGGCCCTTTGGAATGAAGGGTACATCAT GGGTTTCATCAGCAAGGAGCGGGAGCGG GCCATCCTAAGCACAAAGCCCCCGGGCA CCTTCCTACTGCGCTTCAGCGAGAGCAGC AAAGAAGGAGGGGTCACTTTCACTTGGG TGGAAAAGGACATCAGTGGCAAGACCCA GATCCAGTCTGTAGAGCCATACACCAAG CAGCAGCTGAACAACATGTCATTTGCTG AAATCATCATGGGCTATAAGATCATGGA TGCGACCAACATCCTGGTGTCTCCACTTG TCTACCTCTACCCCGACATTCCCAAGGAG GAGGCATTTGGAAAGTACTGTAGGCCCG AGAGCCAGGAGCACCCCGAAGCCGACCC AGGTAGTGCTGCCCCGTACCTGAAGACC AAGTTCATCTGTGTGACACCAACGACCTG CAGCAATACCATTGACCTGCCGATGTCCC CCCGCACTTTAGATTCATTGATGCAGTTT GGAAATAACGGTGAAGGTGCTGAGCCCT CAGCAGGAGGGCAGTTTGAGTCGCTCAC GTTTGACATGGATCTGACCTCGGAGTGTG CTACCTCCCCCATGTGAGGAGCTGAAAC CAGAAGCTGCAGAGACGTGACTTGAGAC ACCTGCCCCGTGCTCCACCCCTAAGCAGC CGAACCCCATATCGTCTGAAACTCCTAAC TTTGTGGTTCCAGATTTTTTTTTTTAATTT CCTACTTCTGCTATCTTTGGGCAATCTGG GCACTTTTTAAAATAGAGAAATGAGTGA	

			GTGTGGGTGATAAACTGTTATGTAAAGA GGAGAGCACCTCTGAGTCTGGGGATGGG GCTGAGAGCAGAAGGGAGCAAGGGGAA CACCTCCTGTCCTGCCCGCCTGCCCTCCT TTTTCAGCAGCTCGGGGTTGGTTGTTAGA CAAGTGCCTCCTGGTGCCCATGGCATCCT GTTGCCCCACTCTGTGAGCTGATACCCCA GGCTGGGAACTCCTGGCTCTGCACTTTCA ACCTTGCTAATATCCACATAGAAGCTAG GACTAAGCCCAGAGGTTCCTCTTTAAATT AAAAAAAAAAAAAAATAAGAATTAAAGG GCAAAACACACTGACACAGCATAGCCTT TCCATATCAAGGAATACTCAGTTAACAG CCTCTCCAGCGCTGTCTTCAGGCTGATCA TCTATATAAACCCTGGAATGGTTGCAGAT CAAATCTGTAAAAGAGATCCGAGAGCTG TGGCTTGGCCTCTGGTTCAAACACAAAG GCTAGAGAGAACCTAGATATCCCTGGGT TTTGTTTACCCAGTATGCTTGTCGGTTGG AGGTGTGAGGTAGGCCAAGGGCACTGGA AAGCCTTTGTCATCACCCTACTCCCTCCC CAACCCAGACTCCAGACCCTGTTTCAGG GTCAGCCTGCCCTGTGGGTGCCTTACTGG GCCTAGGGTCAACCTGCCTTCCTTTCCCA CTTGACCTTGCTGGTAGTATGTCCCCTTC CCATGTCCAAAGGCCCTCTGTCCTGCTTC TATTGGGAATCCCTGCCTCAGGACCTTGT GTCGAGAGGGATTGCCTTACAGGTTTGA ACCTGCCTCAGACTACAGGCCCTCAGCA AAGCTCAGGGAGTATGGTCCTTATTCTAT GCGCTTGGTTCCCAGGGATATCTGTAACC ACAGGGCAAAAGCTGACATATACTCCAG GTCTGCCCTCATATGAGTGGTGTATTCTT GGCCTCCCCTGAGACTGGCAACTGTCTGC TCCCCATTGGGTCTCCCAGGTGAGGTGGA ACACAGTTCCTGCACCTACTGTGGCCTCC ATGTCGCTTGCTTGCTTCGCTCACTCAGC TTACTGGAACACTGAGTGTTCAAGGCAA GCCTTTCCTGACAGAGGCATGGCTAGATT CAGTGACTCAAAGCCACCTCATTCAGCTG ATCAGTGTCTGTGGAATTGTTTCCTTCCA GTTAACCAGTGTCTGAATTAAGGGCAGT GAGGACATTGTCTCCAAGACGAACTGCT TGCCTTGACCACCCCAGCCTTCTGCTTCG AGACAGTTACTGCTCTCCCACCCCATCAA TGTTCTTTAGTTATACAATAAGCTGAACT	

			TATAAACTGAAAGGGTATTTAGGAAGGC AAGGCTTGGGCATTTTTATGGCTTTCAAT CCTGGGGACCCAGGAACAAGGTGAGGGC TTCTCTGGGGCTGGTGTTGTACCTCAGGG GCTCTGGGAAGTCTGTGTGCCTGGGTTAA CCACCCATAGTGAGCCCCTGGAACTGCC CACTTTCCCTCTCCTTGGCCCCACTTGGC CCCAGCCTCACCCAGCCTGCAGACTGCTT AGCCTTTCAGTGCAGTGGCTTGTGTTCTG GCCACTGCACTCAGATTCCAATGTAAACT TTCTAGTGTAAAAATTTATATTATTGTGG GTTGTTTTTTGTTGTTGTTTGTTTTTGTAT ATTGCTGTAACTACTTTAACTTCCAGAAA TAAAGATTATATAGGAACTGTCTGGC	

Claims

1. An oligonucleotide for reducing STAT3 expression, the oligonucleotide comprising an antisense strand of 15 to 30 nucleotides in length and a sense strand of 15 to 40 nucleotides in length, wherein the sense strand and antisense strand form a duplex region, wherein the antisense strand has a region of complementarity to a target sequence of *STAT3* as set forth in SEQ ID NO: 85 or SEQ ID NO: 1217, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides.

2. The oligonucleotide of claim 1, wherein the region of complementarity is fully complementary to the target sequence of *STAT3*.

3. The oligonucleotide of claim 1 or 2, wherein the target sequence comprises any one of SEQ ID NOs: 89-280.

4. The oligonucleotide of any one of claims 1-3, wherein the antisense strand is 19 to 27 nucleotides in length.

5. The oligonucleotide of any one of claims 1-4, wherein the antisense strand is 21 to 27 nucleotides in length, optionally wherein the antisense strand is 22 nucleotides in length.

6. The oligonucleotide of any one of claims 1-5, wherein the sense strand is 19 to 40 nucleotides in length, optionally wherein the sense strand is 36 nucleotides in length.

7. The oligonucleotide of any one of claims 1-6, wherein the duplex region is at least 19 nucleotides in length.

8. The oligonucleotide of any one of claims 1-7, wherein the duplex region is at least 21 nucleotides in length, optionally wherein the duplex region is 20 nucleotides in length.

9. The oligonucleotide of any one of claims 1-8, wherein the region of complementarity to *STAT3* is at least 19 contiguous nucleotides in length.

10. The oligonucleotide of any one of claims 1-9, wherein the region of complementarity to *STAT3* is at least 21 contiguous nucleotides in length.

11. The oligonucleotide of any one of claims 1-2 and 4-10, wherein the antisense strand comprises a sequence as set forth in any one of SEQ ID NOs: 10, 38, 66, or 70.

12. The oligonucleotide of any one of claims 1-2 and 4-11, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 9, 37, 65, or 69 .

13. The oligonucleotide of any one of claims 1 to 12, wherein the sense strand comprises at its 3′ end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.

14. An oligonucleotide for reducing STAT3 expression, the oligonucleotide comprising an antisense strand and a sense strand, wherein the antisense strand is 21 to 27 nucleotides in length and has a region of complementarity to a target sequence of *STAT3* as set forth in SEQ ID NO: 85 or SEQ ID NO: 1217, wherein the sense strand comprises at its 3′ end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, and wherein the antisense strand and the sense strand form a duplex structure of at least 19 nucleotides in length.

15. An oligonucleotide for reducing STAT3 expression, the oligonucleotide comprising an antisense strand and a sense strand, wherein the antisense strand is 21 to 27 nucleotides in length and has a region of complementarity to a target sequence of *STAT3* as set forth in any one of SEQ ID NOs: 89-280, wherein the sense strand comprises at its 3′ end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, and wherein the antisense strand and the sense strand form a duplex structure of at least 19 nucleotides in length.

16. A double stranded oligonucleotide for reducing STAT3 expression, the oligonucleotide comprising:

(i) an antisense strand of 19-30 nucleotides in length, wherein the antisense strand comprises a nucleotide sequence comprising a region of complementarity to a *STAT3* mRNA target sequence, wherein the region of complementarity is selected from SEQ ID NOs: 89-280, and

(ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the antisense and sense strands are separate strands which form an asymmetric duplex region having an overhang of 1-4 nucleotides at the 3' terminus of the antisense strand.

17. The oligonucleotide of claims 14-16, wherein the region of complementarity is fully complementary to at least 19 contiguous nucleotides of *STAT3* mRNA.

18. The oligonucleotide of claims 14-16, wherein the region of complementarity is fully complementary to at least 19 contiguous nucleotides of the *STAT3* mRNA target sequence.

19. The oligonucleotide of any one of claims 13-18, wherein L is a tetraloop, optionally wherein L is 4 nucleotides in length.

20. The oligonucleotide of any one of claims 13-19, wherein L comprises a sequence set forth as GAAA.

21. The oligonucleotide of any one of claims 1-20, wherein the antisense strand is 27 nucleotides in length and the sense strand is 25 nucleotides in length, optionally wherein the antisense strand is 22 nucleotides in length and the sense strand is 36 nucleotides in length.

22. The oligonucleotide of claim 21, wherein the antisense strand and sense strand form a duplex region of 25 nucleotides in length, optionally wherein the duplex is 20 nucleotides in length.

23. The oligonucleotide of any one of claims 1-22, wherein the antisense strand comprises a 3’ overhang sequence of one or more nucleotides in length, optionally wherein the 3’ overhang sequence is 2 nucleotides in length, optionally wherein the 3’ overhang sequence is GG.

24. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleotide.

25. The oligonucleotide of claim 24, wherein the modified nucleotide comprises a 2′-modification.

26. The oligonucleotide of claim 25, wherein the 2′-modification is a modification selected from 2′-aminoethyl, 2′-fluoro, 2′-O-methyl, 2′-O-methoxyethyl, and 2′-deoxy-2′-fluoro-β-d-arabinonucleic acid.

27. The oligonucleotide of any one of claims 24-26, wherein about 10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprise a 2’-fluoro modification.

28. The oligonucleotide of any one of claims 24-27, wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the antisense strand comprise a 2’-fluoro modification.

29. The oligonucleotide of any one of claims 24-26, wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the oligonucleotide comprise a 2’-fluoro modification.

30. The oligonucleotide of any one of claims 24-29, wherein the sense strand comprises 36 nucleotides with positions 1-36 from 5’ to 3 ’, wherein positions 8-11 comprise a 2’-fluoro modification.

31. The oligonucleotide of any one of claims 24-30, wherein the antisense strand comprises 22 nucleotides with positions 1-22 from 3' to 5', and wherein positions 2, 3, 4, 5, 7, 10 and 14 comprise a 2'-fluoro modification.

32. The oligonucleotide of any one of claims 27-31, wherein the remaining nucleotides comprise a 2'-O-methyl modification.

33. The oligonucleotide of any one of claims 24-32, wherein all of the nucleotides of the oligonucleotide are modified.

34. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified internucleotide linkage.

35. The oligonucleotide of claim 31, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

36. The oligonucleotide of any one of the preceding claims, wherein the 4′-carbon of the sugar of the 5′-nucleotide of the antisense strand comprises a phosphate analog.

37. The oligonucleotide of claim 36, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate.

38. The oligonucleotide of any one of the preceding claims, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands.

39. The oligonucleotide of claim 38, wherein the nucleotide is conjugated to more than one targeting ligands, wherein the targeting ligands are the same or are different.

40. The oligonucleotide of claim 38 or 39, wherein the one or more targeting ligands is selected from carbohydrate, amino sugar, cholesterol, polypeptide, or lipid.

41. The oligonucleotide of claim 38 or 39, wherein the one or more targeting ligands is a saturated or unsaturated fatty acid moiety.

42. The oligonucleotide of claim 38 or 39, wherein the targeting ligand is a saturated fatty acid moiety that ranges in size from C10 to C24 long.

43. The oligonucleotide of claim 42, wherein the targeting ligand is a C16 saturated fatty acid moiety.

44. The oligonucleotide of claim 42, wherein the targeting ligand is a C18 saturated fatty acid moiety.

45. The oligonucleotide of claim 42, wherein the targeting ligand is a C22 saturated fatty acid moiety.

46. The oligonucleotide of 38 or 39, wherein the targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety.

47. The oligonucleotide of claim 46, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety.

48. The oligonucleotide of any one of claims 13-47, wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

49. The oligonucleotide of any one of claims 1-10 and 13-48, wherein the sense strand comprises a sequence as set forth in SEQ ID NOs: 857-946.

50. The oligonucleotide of any one of claims 1-10 and 13-49, wherein the antisense strand comprises a sequence as set for in SEQ ID NOs: 947-1036.

51. The oligonucleotide of any one of claims 1-2, 4-14, and 17-48, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 9 and 10, respectively;

(b) SEQ ID NOs: 37 and 38, respectively;

(c) SEQ ID NOs: 65 and 66, respectively; and

(d) SEQ ID NOs: 69 and 70, respectively.

52. The oligonucleotide of any one of claims 1-10, and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 861 and 951, respectively;

(b) SEQ ID NOs: 857 and 947, respectively;

(c) SEQ ID NOs: 858 and 948, respectively;

(d) SEQ ID NOs: 859 and 949, respectively;

(e) SEQ ID NOs: 860 and 950, respectively;

(f) SEQ ID NOs: 862 and 952, respectively;

(g) SEQ ID NOs: 863 and 953, respectively;

(h) SEQ ID NOs: 864 and 954, respectively;

(i) SEQ ID NOs: 865 and 955, respectively;

(j) SEQ ID NOs: 866 and 956, respectively;

(k) SEQ ID NOs: 867 and 957, respectively;

(l) SEQ ID NOs: 868 and 958, respectively;

(m) SEQ ID NOs: 869 and 959, respectively;

(n) SEQ ID NOs: 870 and 960, respectively;

(o) SEQ ID NOs: 871 and 961, respectively;

(p) SEQ ID NOs: 872 and 962, respectively;

(q) SEQ ID NOs: 873 and 963, respectively;

(r) SEQ ID NOs: 874 and 964, respectively;

(s) SEQ ID NOs: 875 and 965, respectively;

(t) SEQ ID NOs: 876 and 966, respectively;

(u) SEQ ID NOs: 877 and 967, respectively;

(v) SEQ ID NOs: 878 and 968, respectively;
(w) SEQ ID NOs: 879 and 969, respectively;
(x) SEQ ID NOs: 880 and 970, respectively;
(y) SEQ ID NOs: 881and 971, respectively;
(z) SEQ ID NOs: 882 and 972, respectively;
(aa) SEQ ID NOs: 883 and 973, respectively;
(bb) SEQ ID NOs: 884 and 974, respectively;
(cc) SEQ ID NOs: 885 and 975, respectively;
(dd) SEQ ID NOs: 886 and 976, respectively;
(ee) SEQ ID NOs: 887 and 977, respectively;
(ff) SEQ ID NOs: 888 and 978, respectively;
(gg) SEQ ID NOs: 940 and 1030, respectively;
(hh) SEQ ID NOs: 896 and 986, respectively; and
(ii) SEQ ID NOs: 920 and 1010, respectively.

53. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 862 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 952.

54. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 875 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 965.

55. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 876 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 966.

56. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 920 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 1010.

57. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively.

58. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively.

59. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;

(c) SEQ ID NOs: 913 and 1003, respectively; and

(d) SEQ ID NOs: 920 and 1010, respectively.

60. The oligonucleotide of any one of claims, 1-2, 4-14, and 17-48, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 11, 39, 67 and 71.

61. The oligonucleotide of any one of claims 1-2, 4-14, 17-48, and 60, wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 12, 40, 68 and 72.

62. The oligonucleotide of any one of claims 1-2, 4-14, 17-48, and 60-61, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 11 and 12, respectively;

(b) SEQ ID NOs: 39 and 40, respectively;

(c) SEQ ID NOs: 67 and 68, respectively; and

(d) SEQ ID NOs: 71 and 72, respectively.

63. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises a nucleotide sequence selected from SEQ ID NOs: 1042, 1055, 1056, and 1100.

64. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the antisense strand comprises a nucleotide sequence selected from SEQ ID NOs: 1132, 1145, 1146, and 1190.

65. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 1041 and 1131, respectively;

(b) SEQ ID NOs: 1037 and 1127, respectively;

(c) SEQ ID NOs: 1038 and 1128, respectively;

(d) SEQ ID NOs: 1039 and 1129, respectively;

(e) SEQ ID NOs: 1040 and 1130, respectively;

(f) SEQ ID NOs: 1042 and 1132, respectively;

(g) SEQ ID NOs: 1043 and 1133, respectively;

(h) SEQ ID NOs: 1044 and 1134, respectively;

(i) SEQ ID NOs: 1045 and 1135, respectively;

(j) SEQ ID NOs: 1046 and 1136, respectively;

(k) SEQ ID NOs: 1047 and 1137, respectively;

(l) SEQ ID NOs: 1048 and 1138, respectively;

(m) SEQ ID NOs: 1049 and 1139, respectively;

(n) SEQ ID NOs: 1050 and 1140, respectively;

(o) SEQ ID NOs: 1051 and 1141, respectively;
(p) SEQ ID NOs: 1052 and 1142, respectively;
(q) SEQ ID NOs: 1053 and 1143, respectively;
(r) SEQ ID NOs: 1054 and 1144, respectively;
(s) SEQ ID NOs: 1055 and 1145, respectively;
(t) SEQ ID NOs: 1056 and 1146, respectively;
(u) SEQ ID NOs: 1057 and 1147, respectively;
(v) SEQ ID NOs: 1058 and 1148, respectively;
(w) SEQ ID NOs: 1059 and 1149, respectively;
(x) SEQ ID NOs: 1060 and 1150, respectively;
(y) SEQ ID NOs: 1061 and 1151, respectively;
(z) SEQ ID NOs: 1062 and 1152, respectively;
(aa) SEQ ID NOs: 1063 and 1153, respectively;
(bb) SEQ ID NOs: 1064 and 1154, respectively;
(cc) SEQ ID NOs: 1065 and 1155, respectively;
(dd) SEQ ID NOs: 1066 and 1156, respectively;
(ee) SEQ ID NOs: 1067 and 1157, respectively;
(ff) SEQ ID NOs: 1068 and 1158, respectively;
(gg) SEQ ID NOs: 1120 and 1210, respectively;
(hh) SEQ ID NOs: 1076 and 1166, respectively; and
(ii) SEQ ID NOs: 1100 and 1190, respectively.

66. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 1042 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 1132.

67. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 1055 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 1145.

68. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 1056 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 1146.

69. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 1100 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 1190.

70. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 1081 and 1171, respectively;

(b) SEQ ID NOs: 1090 and 1180, respectively;

(c) SEQ ID NOs: 1079 and 1169, respectively;

(d) SEQ ID NOs: 1076 and 1166, respectively;

(e) SEQ ID NOs: 1072 and 1162, respectively;

(f) SEQ ID NOs: 1070 and 1160, respectively; and

(g) SEQ ID NOs: 1069 and 1159, respectively.

71. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 1120 and 1210, respectively;

(b) SEQ ID NOs: 1117 and 1207, respectively; and

(c) SEQ ID NOs: 1119 and 1209, respectively.

72. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

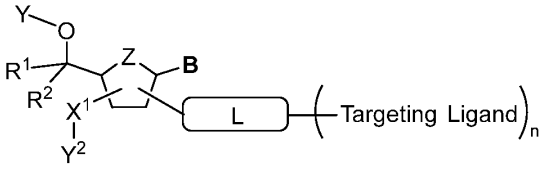
(a) SEQ ID NOs: 1095 and 1185, respectively;

(b) SEQ ID NOs: 1104 and 1194, respectively;

(c) SEQ ID NOs: 1093 and 1183, respectively; and

(d) SEQ ID NOs: 1100 and 1190, respectively.

73. An oligonucleotide-ligand conjugate comprising a nucleotide sequence that reduces expression of *STAT3* mRNA in an immune cell associated with a tumor microenvironment and one or more targeting ligands, wherein one or more nucleosides of the nucleotide sequence conjugated with one or more targeting ligands is represented by formula **I-a:**



I-a;

or a pharmaceutically acceptable salt thereof, wherein:

B is a nucleobase or hydrogen;

R^1 and R^2 are independently hydrogen, halogen, R^A, -CN, -S(O)R, -$S(O)_2$R, -$Si(OR)_2$R, -$Si(OR)R_2$, or -SiR_3; or

R^1 and R^2 on the same carbon are taken together with their intervening atoms to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, a suitable protecting group, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

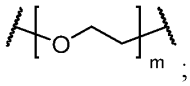
two R groups on the same atom are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, silicon, and sulfur;

each targeting ligand is selected from a lipid conjugate moiety (LC), carbohydrate, amino sugar or GalNAc; and wherein LC is independently a lipid conjugate moiety comprising a saturated or

unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -Cy-, -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, -P(S)OR-;

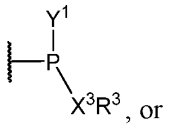
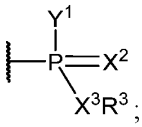
each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

n is 1-10;

L is a covalent bond or a bivalent saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -Cy-, -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, -P(S)OR-, -$V^1CR^2W^1$-, or  ;

m is 1-50;

X^1, V^1 and W^1 are independently -$C(R)_2$-, -OR, -O-, -S-, -Se-, or -NR-;

Y is hydrogen, a suitable hydroxyl protecting group,  , or  ;

R^3 is hydrogen, a suitable protecting group, a suitable prodrug, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

X^2 is O, S, or NR;

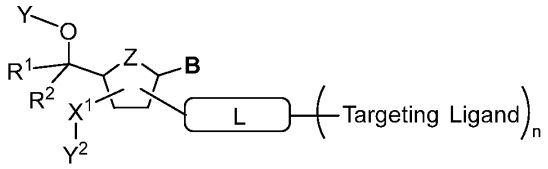
X^3 is -O-, -S-, -BH_2-, or a covalent bond;

Y^1 is a linking group attaching to the 2′- or 3′-terminal of a nucleoside, a nucleotide, or an oligonucleotide;

Y^2 is hydrogen, a suitable protecting group, a phosphoramidite analogue, an internucleotide linking group attaching to the 5′-terminal of a nucleoside, a nucleotide, or an oligonucleotide, or a linking group attaching to a solid support; and

Z is -O-, -S-, -NR-, or -CR_2-.

74. An oligonucleotide-ligand conjugate comprising a nucleotide sequence that reduces expression of a target mRNA in an immune cell associated with a tumor microenvironment and one or more targeting ligands, wherein one or more nucleosides of the nucleotide sequence conjugated with one or more targeting ligands is represented by formula **I-a**:



I-a;

or a pharmaceutically acceptable salt thereof, wherein:

B is a nucleobase or hydrogen;

R^1 and R^2 are independently hydrogen, halogen, R^A, -CN, -S(O)R, -$S(O)_2$R, -$Si(OR)_2$R, -$Si(OR)R_2$, or -SiR_3; or

R^1 and R^2 on the same carbon are taken together with their intervening atoms to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R is independently hydrogen, a suitable protecting group, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated

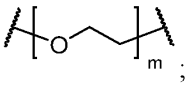
heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same atom are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, silicon, and sulfur;

each targeting ligand is selected from lipid conjugate moiety (LC), carbohydrate, amino sugar or GalNAc; and wherein LC is independently a lipid conjugate moiety comprising a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -Cy-, -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, $-S(O)_2-$, -P(O)OR-, -P(S)OR-;

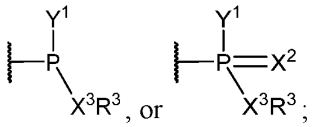
each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

n is 1-10;

L is a covalent bond or a bivalent saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -Cy-, -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, $-S(O)_2-$, -P(O)OR-, -P(S)OR-, $-V^1CR^2W^1-$, or  ;

m is 1-50;

X^1, V^1 and W^1 are independently $-C(R)_2-$, -OR, -O-, -S-, -Se-, or -NR-;

Y is hydrogen, a suitable hydroxyl protecting group,  , or ;

R^3 is hydrogen, a suitable protecting group, a suitable prodrug, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

X^2 is O, S, or NR;

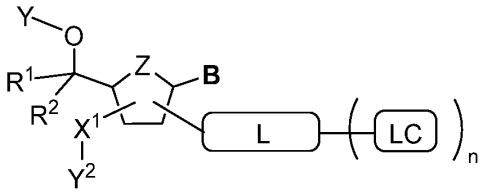
X^3 is -O-, -S-, $-BH_2-$, or a covalent bond;

Y^1 is a linking group attaching to the 2′- or 3′-terminal of a nucleoside, a nucleotide, or an oligonucleotide;

Y^2 is hydrogen, a suitable protecting group, a phosphoramidite analogue, an internucleotide linking group attaching to the 5′-terminal of a nucleoside, a nucleotide, or an oligonucleotide, or a linking group attaching to a solid support; and

Z is -O-, -S-, -NR-, or $-CR_2-$.

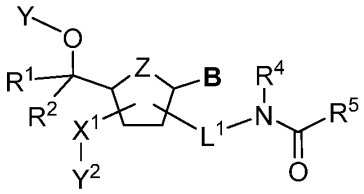
75. The oligonucleotide-ligand conjugate of claim 73 or 74, wherein the one or more nucleosides is represented by formula **II-a**:



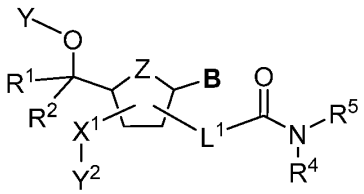
II-a.

or a pharmaceutically acceptable salt thereof.

76. The oligonucleotide-ligand conjugate of any one of claims 73-76, wherein the one or more nucleosides is represented by formula **II-b** or **II-c**:

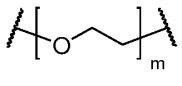


II-b



II-c

or a pharmaceutically acceptable salt thereof, wherein:

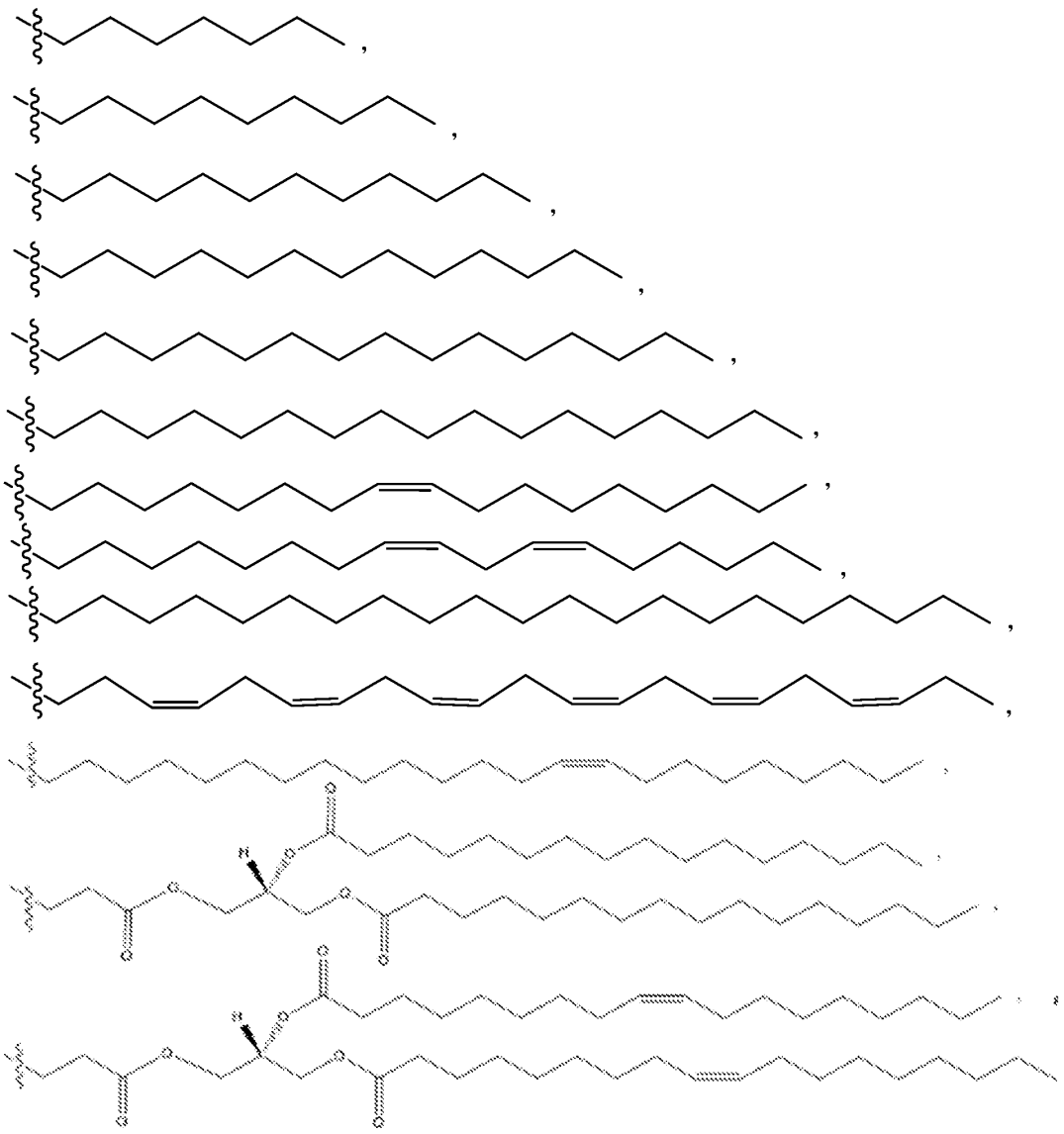
L^1 is a covalent bond, a monovalent or a bivalent saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -Cy-, -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, -P(S)OR-, or  ;

R^4 is hydrogen, R^A, or a suitable amine protection group; and

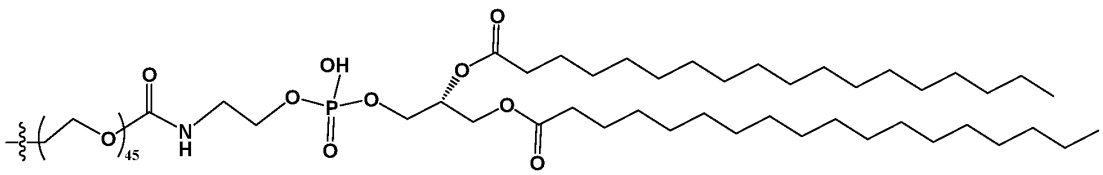
R^5 is adamantyl, or a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, or -P(S)OR.

77. The oligonucleotide-ligand conjugate of claim 76, wherein:

R^5 is selected from

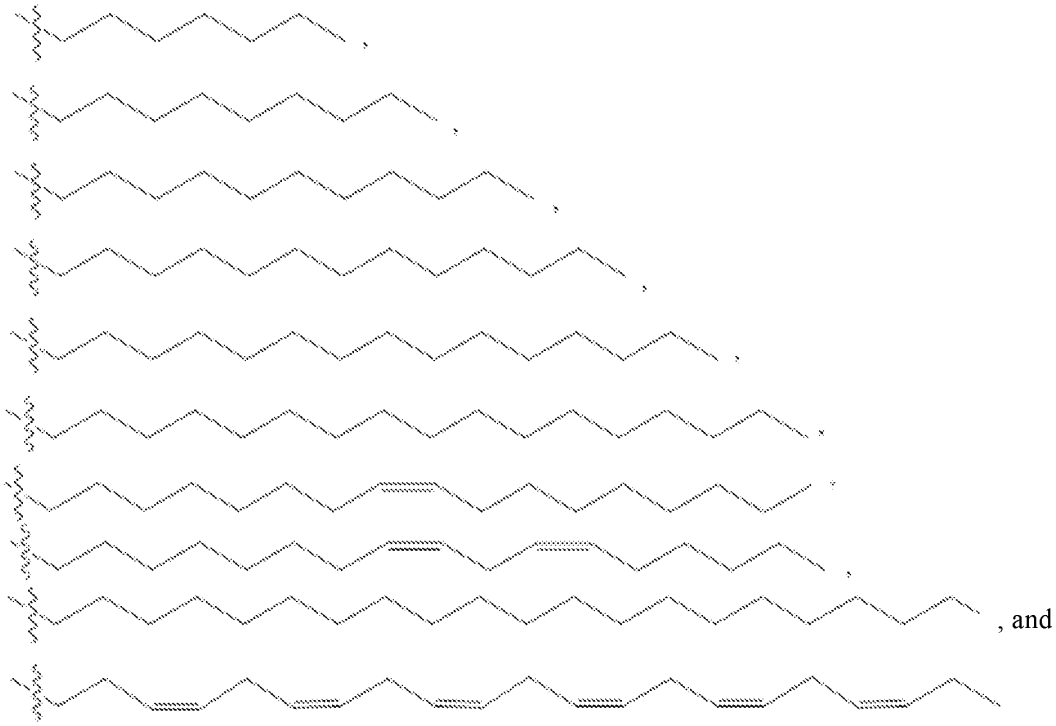


and,



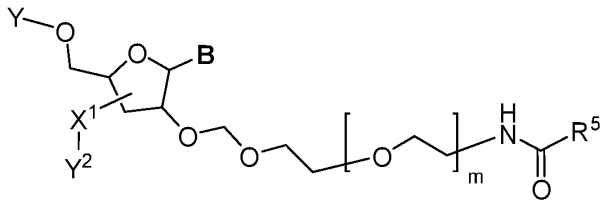
78. The oligonucleotide-ligand conjugate of claim 75, wherein:

R^5 is selected from

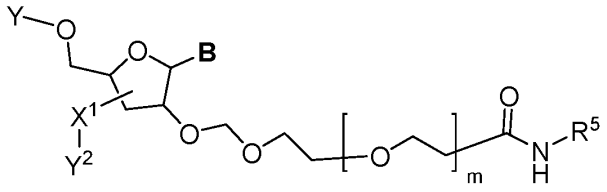


, and

79. An oligonucleotide-ligand conjugate comprising a nucleotide sequence that reduces expression of *STAT3* mRNA in an immune cell associated with a tumor microenvironment and one or more targeting ligands, wherein one or more nucleosides of the nucleotide sequence conjugated with one or more targeting ligands is represented by formula **II-Ib** or **II-Ic**:



II-Ib



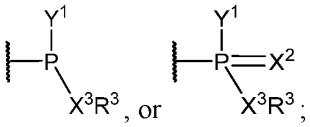
II-Ic

or a pharmaceutically acceptable salt thereof; wherein

B is a nucleobase or hydrogen;

m is 1-50;

X^1 is -O-, or -S-;

Y is hydrogen,  ;

R^3 is hydrogen, or a suitable protecting group;

X^2 is O, or S;

X^3 is -O-, -S-, or a covalent bond;

Y^1 is a linking group attaching to the 2′- or 3′-terminal of a nucleoside, a nucleotide, or an oligonucleotide;

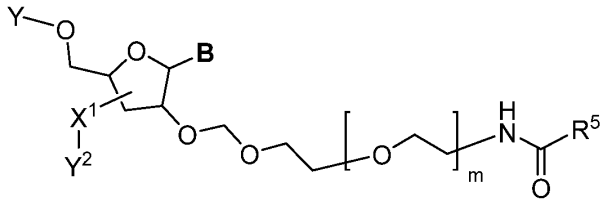
Y^2 is hydrogen, a phosphoramidite analogue, an internucleotide linking group attaching to the 5′-terminal of a nucleoside, a nucleotide, or an oligonucleotide, or a linking group attaching to a solid support;

R^5 is adamantyl, or a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, $-S(O)_2-$, -P(O)OR-, or -P(S)OR-; and

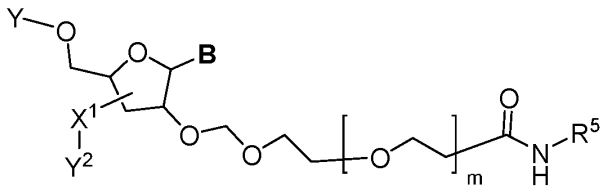
R is hydrogen, a suitable protecting group, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

80. An oligonucleotide-ligand conjugate comprising a nucleotide sequence that reduces expression of a target mRNA in an immune cell associated with a tumor microenvironment and

one or more targeting ligands, wherein one or more nucleosides of the nucleotide sequence conjugated with the targeting ligand is represented by formula **II-Ib** or **II-Ic**:



II-Ib



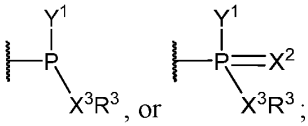
II-Ic

or a pharmaceutically acceptable salt thereof; wherein

B is a nucleobase or hydrogen;

m is 1-50;

X^1 is -O-, or -S-;

Y is hydrogen,  ;

R^3 is hydrogen, or a suitable protecting group;

X^2 is O, or S;

X^3 is -O-, -S-, or a covalent bond;

Y^1 is a linking group attaching to the 2′- or 3′-terminal of a nucleoside, a nucleotide, or an oligonucleotide;

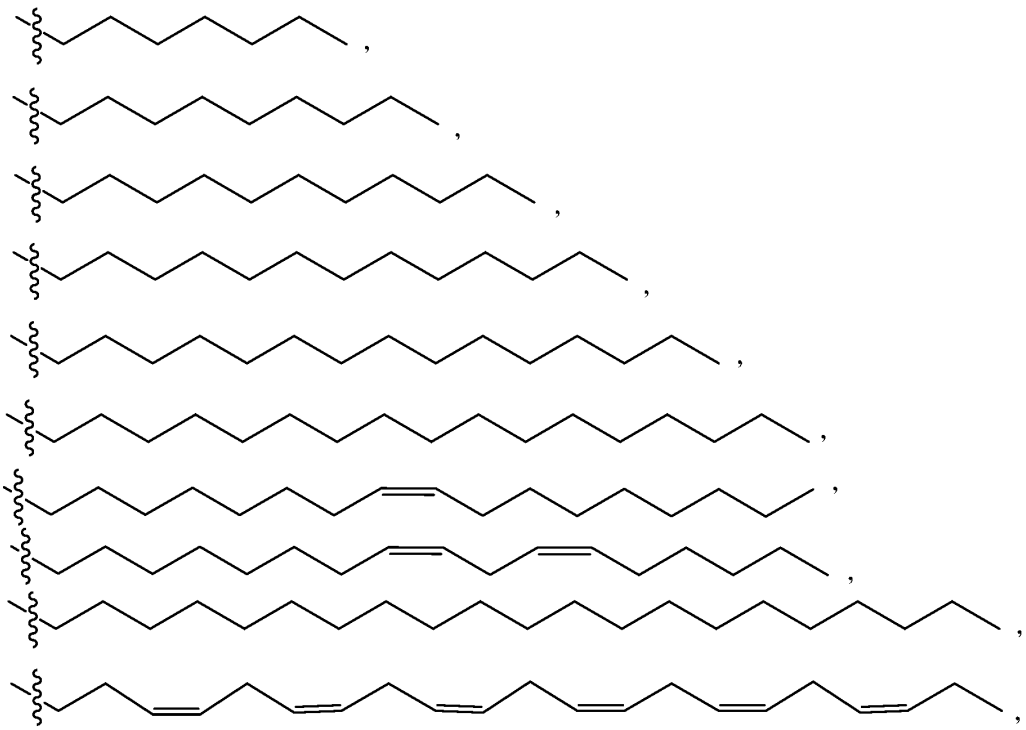
Y^2 is hydrogen, a phosphoramidite analogue, an internucleotide linking group attaching to the 5′-terminal of a nucleoside, a nucleotide, or an oligonucleotide, or a linking group attaching to a solid support;

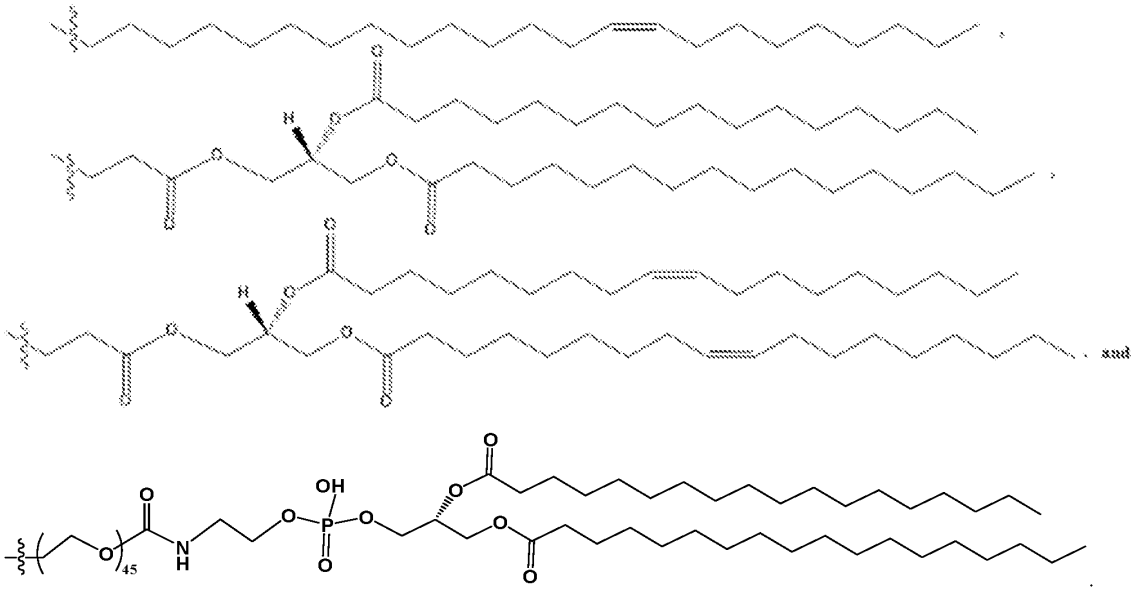
R^5 is adamantyl, or a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, or -P(S)OR-; and

R is hydrogen, a suitable protecting group, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

81. The oligonucleotide-ligand conjugate of claim 79 or 80, wherein:

R^5 is selected from





82. The oligonucleotide-ligand conjugate of any one of claims 73-81, wherein the nucleotide sequence comprises 1-10 targeting ligands.

83. The oligonucleotide-ligand conjugate of any one of claims 73-82, wherein the nucleotide sequence comprises 1, 2 or 3 targeting ligands.

84. The oligonucleotide-ligand conjugate of any one of claims 73, 75-79 and 81-83, wherein the oligonucleotide comprises a sense strand of 10-53 nucleotides in length and an antisense strand of 15-53 nucleotides in length, wherein the antisense strand has a region of complementarity to the *STAT3* mRNA, wherein the region of complementarity is at least 15 nucleotides in length differing by no more than 3 nucleotides from the *STAT3* mRNA.

85. The oligonucleotide of claim 84, wherein the region of complementarity is selected from SEQ ID NOs: 89-280.

86. The oligonucleotide-ligand conjugate of any one of claims 74-78 and 80-83, wherein the oligonucleotide comprises a sense strand of 10-53 nucleotides in length and an antisense strand of 15-53 nucleotides in length, wherein the antisense strand has a region of complementarity to

the *STAT3* mRNA, wherein the region of complementarity is at least 15 nucleotides in length differing by no more than 3 nucleotides from the *STAT3* mRNA.

87. The oligonucleotide-ligand conjugate of any one of claims 74-78, 80-83 and 86, wherein the target mRNA encodes a regulator of immune suppression.

88. The oligonucleotide-ligand conjugate of claim 87, wherein the regulator of immune suppression is a transcription factor.

89. The oligonucleotide-ligand conjugate of any one of claims 73-88, wherein the immune cell associated with the tumor microenvironment is a myeloid cell

90. The oligonucleotide conjugate of any one of claims 73-88, wherein the immune cell associated with the tumor microenvironment is a T cell.

91. The oligonucleotide-ligand conjugate of any one of claims 73-88, wherein the nucleotide sequence reduces expression of the target mRNA or *STAT3* mRNA in more than one immune cell associated with the tumor microenvironment.

92. The oligonucleotide-ligand conjugate of claim 91, wherein the immune cell is a myeloid cell.

93. The oligonucleotide-ligand conjugate of claim 91, wherein the immune cell is a T cell.

94. The oligonucleotide-ligand conjugate of claim 90 or 93, wherein the myeloid cell is a myeloid derived suppressor cell (MDSC).

95. The oligonucleotide-ligand conjugate of claim 94, wherein the MDSC is a granulocytic MDSC (G-MDSC) or monocytic MDSC (M-MDSC).

96. The oligonucleotide-ligand conjugate of claim 95, wherein the nucleotide sequence reduces expression of the target mRNA in G-MDSCs and M-MDSCs.

97. The oligonucleotide-ligand conjugate of any one of claims 91 and 93-96, wherein the T cell is a CD8+T cell or Treg cell.

98. The oligonucleotide-ligand conjugate of any one of claims 73-83 and 87-97, wherein the oligonucleotide is single stranded, optionally wherein the single stranded oligonucleotide is 15-30 nucleotides in length.

99. The oligonucleotide-ligand conjugate of any one of claims 73-83 and 87-97, wherein the oligonucleotide is double stranded.

100. The oligonucleotide-ligand conjugate of claim 99, wherein the oligonucleotide comprises an antisense strand of 15 to 30 nucleotides in length and a sense strand of 15 to 40 nucleotides in length, wherein the sense strand and antisense strand form a duplex region, wherein the antisense strand has a region of complementarity to the target mRNA or *STAT3* mRNA, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the target mRNA or *STAT3* mRNA.

101. The oligonucleotide-ligand conjugate of claim 100, wherein the antisense strand is 19 to 27 nucleotides in length.

102. The oligonucleotide-ligand conjugate of claim 100 or 101, wherein the antisense strand is 21 to 27 nucleotides in length, optionally wherein the antisense strand is 22 nucleotides in length.

103. The oligonucleotide-ligand conjugate of claim 100 or 102, wherein the sense strand is 19 to 40 nucleotides in length, optionally wherein the sense strand is 36 nucleotides in length.

104. The oligonucleotide-ligand conjugate of any one of claims 100-103, wherein the duplex region is at least 19 nucleotides in length.

105. The oligonucleotide-ligand conjugate of any one of claims 100-104, wherein the duplex region is at least 21 nucleotides in length, optionally wherein the duplex region is 20 nucleotides in length.

106. The oligonucleotide-ligand conjugate of any one of claims 100-105, wherein the region of complementarity to the target mRNA is at least 19 contiguous nucleotides in length.

107. The oligonucleotide-ligand conjugate of any one of claims 100-106, wherein the region of complementarity to the target mRNA is at least 21 contiguous nucleotides in length.

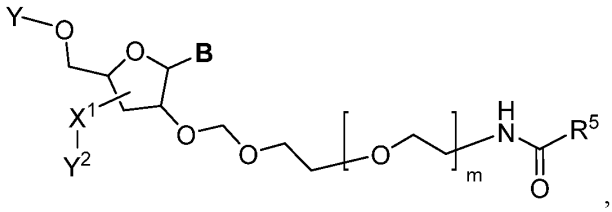
108. The oligonucleotide-ligand conjugate of any one of claims 100-107, wherein the sense strand comprises at its 3′ end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.

109. The oligonucleotide-ligand conjugate of claim 108, wherein L is a tetraloop.

110. The oligonucleotide-ligand conjugate of any one of claims 108-109, wherein L comprises a sequence set forth as GAAA.

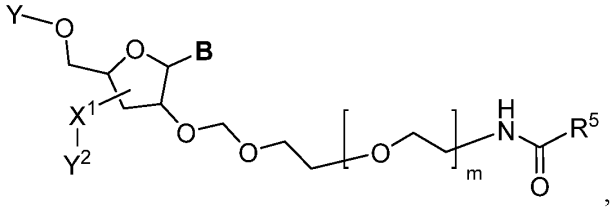
111. The oligonucleotide-ligand conjugate of any one of claims 100-110, wherein the antisense strand comprises a 3’ overhang sequence of one or more nucleotides in length, optionally wherein the 3’ overhang sequence is 2 nucleotides in length, optionally wherein the 3’ overhang sequence is GG.

112. An oligonucleotide-ligand conjugate comprising an antisense strand of 15 to 30 nucleotides and a sense strand of 15 to 40 nucleotide, wherein the sense and antisense strands form a duplex region, wherein the antisense strand comprises a region of complementarity to a human *STAT3* mRNA target sequence expressed in an immune cell associated with a tumor microenvironment, wherein the sense strand comprises at its 3’ end a stem-loop comprising a tetraloop comprising 4 nucleosides, wherein one or more of the 4 nucleosides conjugated with one or more targeting ligands is represented by formula II-Ib:



wherein B is selected from an adenine and a guanine nucleobase, and wherein R^5 is a hydrocarbon chain.

113. An oligonucleotide-ligand conjugate comprising an antisense strand of 15 to 30 nucleotides and a sense strand of 15 to 40 nucleotide, wherein the sense and antisense strands form a duplex region, wherein the antisense strand comprises a region of complementarity to a target sequence expressed in an immune cell associated with a tumor microenvironment, wherein the sense strand comprises at its 3' end a stem-loop comprising a tetraloop comprising 4 nucleosides, wherein one or more of the 4 nucleosides conjugated with the targeting ligand is represented by formula II-Ib:

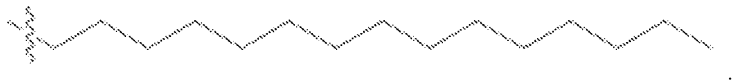


wherein B is selected from an adenine and a guanine nucleobase, and wherein R^5 is a hydrocarbon chain.

114. The oligonucleotide-ligand conjugate of claim 112 or 113, wherein the hydrocarbon chain is a C8-C30 hydrocarbon chain.

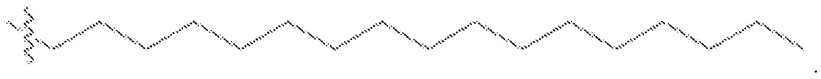
115. The oligonucleotide-ligand conjugate of any one of claims 112-114, wherein the hydrocarbon chain is a C16 hydrocarbon chain.

116. The oligonucleotide-ligand conjugate of claim 115, wherein the C16 hydrocarbon chain is represented by



117. The oligonucleotide-ligand conjugate of any one of claims 112-114, wherein the hydrocarbon chain is a C18 hydrocarbon chain.

118. The oligonucleotide-ligand conjugate of claim 117, wherein the C18 hydrocarbon chain is represented by



119. The oligonucleotide-ligand conjugate of any one of claims 112-118, wherein the 4 nucleosides of the tetraloop are numbered 1-4 from 5' to 3', and wherein position 1 is represented by formula II-Ib.

120. The oligonucleotide-ligand conjugate of any one of claims 112-118, wherein the 4 nucleosides of the tetraloop are numbered 1-4 from 5' to 3', and wherein position 2 is represented by formula II-Ib.

121. The oligonucleotide-ligand conjugate of any one of claims 112-118, wherein the 4 nucleosides of the tetraloop are numbered 1-4 from 5' to 3', and wherein position 3 is represented by formula II-Ib.

122. The oligonucleotide-ligand conjugate of any one of claims 112-118, wherein the 4 nucleosides of the tetraloop are numbered 1-4 from 5' to 3', and wherein position is represented by formula II-Ib.

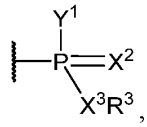
123. The oligonucleotide-ligand conjugate of any one of claims 112-122, wherein the sense strand is 36 nucleotides with positions numbered 1-36 from 5' to 3', wherein the stem-loop comprises nucleotides at positions 21-36, and wherein one or more nucleosides at positions 27-30 are represented by formula II-Ib.

124. The oligonucleotide-ligand conjugate of any one of claims 112-123, wherein

m is 1,

X1 is O,

Y2 is an internucleotide linking group attaching to the 5' terminal of a nucleoside,

Y is represented by  , Y1 is a linking group attaching to the 2' or 3' terminal of a nucleotide,

X2 is O,

X3 is O, and

R3 is H.

125. The oligonucleotide-ligand conjugate of any one of claims 112-124, wherein the antisense strand is 22 nucleotides.

126. The oligonucleotide-ligand conjugate of claims 73-125, wherein the oligonucleotide comprises at least one modified nucleotide.

127. The oligonucleotide-ligand conjugate of claim 126, wherein the modified nucleotide comprises a 2′-modification.

128. The oligonucleotide-ligand conjugate of claim 126, wherein the 2′-modification is a modification selected from 2′-aminoethyl, 2′-fluoro, 2′-O-methyl, 2′-O-methoxyethyl, and 2′-deoxy-2′-fluoro-β-d-arabinonucleic acid.

129. The oligonucleotide-ligand conjugate of any one of claims 126-128, wherein about 10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprise a 2'-fluoro modification.

130. The oligonucleotide-ligand conjugate of any one of claims 126-129, wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the antisense strand comprise a 2'-fluoro modification.

131. The oligonucleotide-ligand conjugate of any one of claims 126-130, wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the oligonucleotide comprise a 2'-fluoro modification.

132. The oligonucleotide-ligand conjugate of any one of claims 126-131, wherein the sense strand comprises 36 nucleotides with positions 1-36 from 5' to 3 ', wherein positions 8-11 comprise a 2'-fluoro modification.

133. The oligonucleotide-ligand conjugate of any one of claims 126-132, wherein the antisense strand comprises 22 nucleotides with positions 1-22 from 5' to 3', and wherein positions 2, 3, 4, 5, 7, 10 and 14 comprise a 2'-fluoro modification.

134. The oligonucleotide-ligand conjugate of any one of claims 129-133, wherein the remaining nucleotides comprise a 2'-O-methyl modification .

135. The oligonucleotide-ligand of any one of claims 129-133, wherein all of the nucleotides of the oligonucleotide are modified.

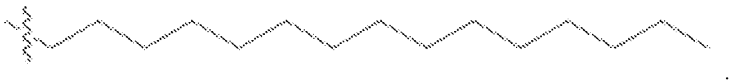
136. The oligonucleotide-ligand conjugate of any one of claims 73-135, wherein the oligonucleotide comprises at least one modified internucleotide linkage.

137. The oligonucleotide-ligand conjugate of claim 136, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

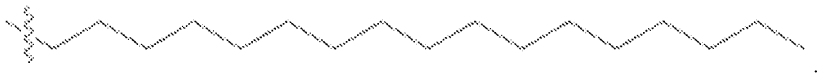
138. The oligonucleotide-ligand conjugate of any one of claims 100-137, wherein the 4′-carbon of the sugar of the 5′-nucleotide of the antisense strand comprises a phosphate analog.

139. The oligonucleotide-ligand conjugate of claim 138, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate.

140. The oligonucleotide-ligand conjugate of any one of claims 76-113 and 119-139, wherein R5 is



141. The oligonucleotide-ligand conjugate of any one of claims 76-113 and 119-139, wherein R5 is



142. The oligonucleotide-ligand conjugate of any one of claims 100-141, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 9 and 10, respectively;

(b) SEQ ID NOs: 37 and 38, respectively;

(c) SEQ ID NOs: 65 and 66, respectively; and

(d) SEQ ID NOs: 69 and 70, respectively.

143. The oligonucleotide of any one of claims 100-141, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 861 and 951, respectively;

(b) SEQ ID NOs: 857 and 947, respectively;

(c) SEQ ID NOs: 858 and 948, respectively;

(d) SEQ ID NOs: 859 and 949, respectively;

(e) SEQ ID NOs: 860 and 950, respectively;

(f) SEQ ID NOs: 862 and 952, respectively;

(g) SEQ ID NOs: 863 and 953, respectively;

(h) SEQ ID NOs: 864 and 954, respectively;

(i) SEQ ID NOs: 865 and 955, respectively;

(j) SEQ ID NOs: 866 and 956, respectively;
(k) SEQ ID NOs: 867 and 957, respectively;
(l) SEQ ID NOs: 868 and 958, respectively;
(m) SEQ ID NOs: 869 and 959, respectively;
(n) SEQ ID NOs: 870 and 960, respectively;
(o) SEQ ID NOs: 871 and 961, respectively;
(p) SEQ ID NOs: 872 and 962, respectively;
(q) SEQ ID NOs: 873 and 963, respectively;
(r) SEQ ID NOs: 874 and 964, respectively;
(s) SEQ ID NOs: 875 and 965, respectively;
(t) SEQ ID NOs: 876 and 966, respectively;
(u) SEQ ID NOs: 877 and 967, respectively;
(v) SEQ ID NOs: 878 and 968, respectively;
(w) SEQ ID NOs: 879 and 969, respectively;
(x) SEQ ID NOs: 880 and 970, respectively;
(y) SEQ ID NOs: 881and 971, respectively;
(z) SEQ ID NOs: 882 and 972, respectively;
(aa) SEQ ID NOs: 883 and 973, respectively;
(bb) SEQ ID NOs: 884 and 974, respectively;
(cc) SEQ ID NOs: 885 and 975, respectively;
(dd) SEQ ID NOs: 886 and 976, respectively;
(ee) SEQ ID NOs: 887 and 977, respectively;
(ff) SEQ ID NOs: 888 and 978, respectively;
(gg) SEQ ID NOs: 940 and 1030, respectively;
(hh) SEQ ID NOs: 896 and 986, respectively; and
(ii) SEQ ID NOs: 920 and 1010, respectively.

144. The oligonucleotide of any one of claims 100-141, wherein the sense strand comprises a nucleotide sequence of SEQ ID NO: 862 and the antisense strand comprises a nucleotide sequence of SEQ ID NO: 952.

145. The oligonucleotide of any one of claims 100-141, wherein the sense strand comprises a nucleotide sequence of SEQ ID NO: 875 and the antisense strand comprises a nucleotide sequence of SEQ ID NO: 965.

146. The oligonucleotide of any one of claims 100-141, wherein the sense strand comprises a nucleotide sequence of SEQ ID NO: 876 and the antisense strand comprises a nucleotide sequence of SEQ ID NO: 966.

147. The oligonucleotide of any one of claims 100-141, wherein the sense strand comprises a nucleotide sequence of SEQ ID NO: 920 and the antisense strand comprises a nucleotide sequence of SEQ ID NO: 1010.

148. The oligonucleotide of any one of claims 100-141, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 901 and 991, respectively;

(b) SEQ ID NOs: 910 and 1000, respectively;

(c) SEQ ID NOs: 899 and 989, respectively;

(d) SEQ ID NOs: 896 and 986, respectively;

(e) SEQ ID NOs: 892 and 982, respectively;

(f) SEQ ID NOs: 890 and 980, respectively; and

(g) SEQ ID NOs: 889 and 979, respectively.

149. The oligonucleotide of any one of claims 100-141, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 940 and 1030, respectively;

(b) SEQ ID NOs: 937 and 1027, respectively; and

(c) SEQ ID NOs: 939 and 1029, respectively.

150. The oligonucleotide of any one of claims 100-141, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOs: 915 and 1005, respectively;

(b) SEQ ID NOs: 924 and 1014, respectively;
(c) SEQ ID NOs: 913 and 1003, respectively; and
(d) SEQ ID NOs: 920 and 1010, respectively.

151. A pharmaceutical composition comprising the oligonucleotide or oligonucleotide-ligand conjugate of any one of the preceding claims and a pharmaceutically acceptable carrier, delivery agent or excipient.

152. A method for delivering an oligonucleotide to an immune cell associated with a tumor microenvironment, comprising administering the oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150, or the composition of claim 151, thereby delivering the oligonucleotide to the immune cell.

153. A method of reducing expression of a target mRNA in an immune cell associated with a tumor microenvironment in a subject, comprising administering the oligonucleotide-ligand conjugate of any one of claims 1-150, or the composition of claim 151, thereby reducing expression of the target mRNA in the subject.

154. The method of claim 152 or 153, wherein the immune cell is a myeloid cell and/or a T cell.

155. The method of claim 154, wherein the myeloid cell is a myeloid derived suppressor cell (MDSC).

156. The method of claim 155, wherein the MDSC is a granulocytic MDSC (G-MDSC) or monocytic MDSC (M-MDSC).

157. The method of any one of claims 154-156, wherein the T cell is a CD8+T cell or Treg cell.

158. A method for increasing an immune response in a subject in need thereof, comprising administering the oligonucleotide-ligand conjugate of any one of claims 1-150, or the composition of claim 151, thereby increasing the immune response in the subject.

159. The method of claim 158, wherein the subject has cancer.

160. The method of any one of claims 158-159, comprising administering a second composition or therapeutic agent.

161. The method of claim 160, wherein the second composition or therapeutic agent is selected from the group consisting of: a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy, or a combination thereof.

162. Use of the oligonucleotide-ligand conjugate of any one of claims 1-150, or the composition of claim 151, for delivering an oligonucleotide to an immune cells associated with a tumor microenvironment in a subject, comprising administering the oligonucleotide-ligand conjugate to the subject.

163. Use of the oligonucleotide-ligand conjugate of any one of claims 1-150, or the composition of claim 151, for reducing expression of a target mRNA in an immune cell associated with a tumor microenvironment in a subject, comprising administering the oligonucleotide-ligand conjugate to the subject.

164. Use of the oligonucleotide-ligand conjugate of any one of claims 1-150, or the composition of claim 151, for increasing an immune response in a subject in need thereof, comprising administering the oligonucleotide-ligand conjugate to the subject.

165. The use of the oligonucleotide-ligand conjugate of any one of claims 162-164, wherein the subject has cancer.

166. A kit comprising the oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with STAT3 expression.

167. A method for treating a subject having a disease, disorder or condition associated with STAT3 expression, the method comprising administering to the subject a therapeutically effective amount of the oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1 to 150 or the pharmaceutical composition of claim 151.

168. The method of claim 167, wherein the disease, disorder or condition associated with STAT3 expression is selected from the group consisting of cancer, carcinoma, sarcoma, melanoma, lymphoma, and leukemia, prostate cancer, breast cancer, hepatocellular carcinoma (HCC), colorectal cancer, pancreatic cancer and glioblastoma.

169. The method of claim 167, wherein the disease, disorder or condition associated with STAT3 expression is prostate cancer, breast cancer, hepatocellular carcinoma (HCC), colorectal cancer, and glioblastoma.

170. The method of any one of claims 167-169, wherein the oligonucleotide, or pharmaceutical composition, is administered in combination with a second composition or therapeutic agent.

171. The method of claim 170 wherein the second composition or therapeutic agent is selected from the group consisting of: a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy, or a combination thereof.

172. The method of any one of claims 167-169 wherein the oligonucleotide, or pharmaceutical composition, is administered in combination with at least 2 additional therapeutic agents.

173. A method of inhibiting tumor growth in a subject, comprising administering to the subject the oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150 or the pharmaceutical composition of claim 151.

174. A method of treating cancer, or preventing metastasis of cancer, in a subject, comprising administering to the subject the oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150 or the pharmaceutical composition of claim 151, wherein tumor associated cells express STAT3.

175. A pharmaceutical composition comprising a therapeutically effective amount of the oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150, wherein the oligonucleotide decreases the expression, production, or activity of STAT3.

176. Use of the oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150, or the pharmaceutical composition of claim 151, for reducing STAT3 expression in an immune cell associated with a tumor microenvironment in a subject.

177. The oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150, for use in reducing STAT3 expression in an immune cell associated with a tumor microenvironment in a subject.

178. Use of the oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150, or the pharmaceutical composition of claim 151, for reducing STAT3 expression in a subject having a disease, disorder or condition associated with STAT3 expression.

179. The use of claim 178, wherein the disease, disorder or condition associated with STAT3 expression is selected from the group consisting of cancer, carcinoma, sarcoma,

melanoma, lymphoma, and leukemia, prostate cancer, breast cancer, hepatocellular carcinoma (HCC), colorectal cancer, pancreatic cancer and glioblastoma.

180. The use of claim 178-179, wherein tumor growth is reduced or inhibited.

181. The oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150, for use in reducing STAT3 expression in a subject having a disease, disorder or condition associated with STAT3 expression.

182. The oligonucleotide or oligonucleotide-ligand conjugate of claim 181, wherein the disease, disorder or condition associated with STAT3 expression is selected from the group consisting of cancer, carcinoma, sarcoma, melanoma, lymphoma, and leukemia, prostate cancer, breast cancer, hepatocellular carcinoma (HCC), colorectal cancer, pancreatic cancer and glioblastoma.

183. The oligonucleotide or oligonucleotide-ligand conjugate of claim 181 or 182, wherein tumor growth is reduced or inhibited.