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(71) Applicant: **DICERNA PHARMACEUTICALS, INC.** [US/US]; 75 Hayden Avenue, Lexington, Massachusetts 02421 (US).

(72) Inventors: **ABRAMS, Marc**; c/o Dicerna Pharmaceuticals, Inc., 75 Hayden Avenue, Lexington, Massachusetts 02421 (US). **DUDEK, Henryk T.**; c/o Dicerna Pharmaceuticals, Inc., 75 Hayden Avenue, Lexington, Massachusetts 02421 (US). **KRISHNAN, Harini Sivagurunatha**; c/o Dicerna Pharmaceuticals, Inc., 75 Hayden Avenue, Lexington, Massachusetts 02421 (US). **GANESH, Shanthi**; c/o Dicerna Pharmaceuticals, Inc., 75 Hayden Avenue, Lexington, Massachusetts 02421 (US).

(74) Agent: **MANDRAGOURAS, Amy** et al.; Foley Hoag LLP, 155 Seaport Boulevard, Boston, Massachusetts 02210-2600 (US).

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(54) Title: STAT3 TARGETING OLIGONUCLEOTIDES AND USES THEREOF

(57) Abstract: The subject matter disclosed herein is directed to modulating STAT3 gene expression using siRNA compositions and methods directed to affecting key cell populations supporting the growth and metastasis of cancer to affect the beneficial treatment, remission or removal of the underlying tumor in a patient.

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STAT3 TARGETING OLIGONUCLEOTIDES AND USES THEREOF

CROSS-RELATED APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Application Serial No. 63/425,861 filed November 16, 2022. The entire contents of which are incorporated herein by this reference.

BACKGROUND OF THE DISCLOSURE

[002] 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 tumor microenvironment 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). Novel therapies that target different facets of the TME that contribute to tumor growth are needed.

BRIEF SUMMARY OF THE DISCLOSURE

[003] The disclosure is based, in part, on the discovery of oligonucleotides that target STAT3 mRNA and reduce expression. The disclosure is further based on the discovery that a combination of a STAT3 oligonucleotide and a PD-L1 inhibitor provides synergistic anti-tumor efficacy for tumors of varying tumor microenvironments. Specifically, as demonstrated herein, a STAT3 oligonucleotide conjugated to a lipid, when delivered in combination with an anti-PD-L1 antibody, reduced tumor volume *in vivo* in immunosuppressive and inflamed tumor models. Further, as shown herein, the combination of a STAT3 oligonucleotide and PD-L1 inhibitor induced an anti-tumor memory response as when mice were re-challenged with cancer cells, no

tumors were established. In addition, the efficacy of the STAT3 oligonucleotide and PD-L1 inhibitor was dependent on the presence of CD8+ T cells.

[004] Accordingly, in some aspects, the disclosure provides 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: 140, wherein the sense strand comprises at least one lipid moiety conjugated to the 5'terminal nucleotide of the sense strand.

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

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

[007] In some or any of the foregoing or related aspects, the duplex region is at least 19 nucleotides in length. In some aspects, the duplex region is at least 20 nucleotides in length, optionally wherein the duplex region is 21 nucleotides in length. In some aspects, the region of complementarity to *STAT3* is at least 19 contiguous nucleotides in length. In some aspects, the region of complementarity to *STAT3* is at least 21 contiguous nucleotides in length.

[008] In some or any of the foregoing or related aspects the antisense strand comprises a sequence as set forth in SEQ ID NO: 965.

[009] In some or any of the foregoing or related aspects, the sense strand comprises a sequence as set forth in SEQ ID NO: 875.

[0010] In some or any of the foregoing or related aspects, 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.

[0011] In some aspects, the disclosure provides 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: 140, wherein the sense strand comprises at its 3′ end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, wherein L forms a

loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense strand and the sense strand form a duplex structure of at least 19 nucleotides in length, and wherein the sense strand comprises a lipid moiety conjugated to the 5' terminal nucleotide of the sense strand.

[0012] In some aspects, the disclosure provides 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 set forth in SEQ ID NO: 140, and

(ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the sense strand comprises a lipid moiety conjugated to the 5' terminal nucleotide of the sense 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.

[0013] In some or any of the foregoing or related aspects, L is a tetraloop, optionally wherein L is 4 nucleotides in length. In some aspects, L comprises a sequence set forth as GAAA.

[0014] In some or any of the foregoing or related aspects, 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. In some aspects, the antisense strand and sense strand form a duplex region of 25 nucleotides in length, optionally wherein the duplex is 20 nucleotides in length. In some aspects, 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.

[0015] In some or any of the foregoing or related aspects, the oligonucleotide comprises at least one modified nucleotide. In some aspects, the modified nucleotide comprises a 2′-modification. In some aspects, 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. In some aspects, about 10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprise a 2'-fluoro modification. In some aspects, 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 aspects, 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.

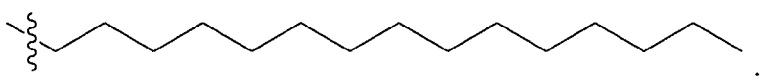
[0016] In some or any of the foregoing or related aspects, the sense strand comprises 36 nucleotides with positions 1-36 from 5' to 3', wherein positions 8-11 comprise a 2'-fluoro modification. In some aspects, the antisense strand comprises 22 nucleotides with positions 1-22 from 3' to 5', and wherein positions 2, 3, 4, 5, 7, 10 and 14 comprise a 2'-fluoro modification. In some aspects, the remaining nucleotides comprise a 2'-O-methyl modification.

[0017] In some or any of the foregoing or related aspects, the oligonucleotide comprises at least one modified internucleotide linkage. In some aspects, the at least one modified internucleotide linkage is a phosphorothioate linkage. In some aspects, the sense strand comprises a phosphorothioate linkage between positions 1 and 2 of the sense strand. In some aspects, the antisense strand comprises 22 nucleotides with positions 1-22 from 3' to 5', wherein the antisense strand comprises a phosphorothioate linkage between positions 1 and 2, 2 and 3, 3 and 4, 20 and 21, and 21 and 22. In some aspects, the sense strand comprises a phosphorothioate linkage between positions 1 and 2 of the sense strand and the antisense strand comprises 22 nucleotides with positions 1-22 from 3' to 5', wherein the antisense strand comprises a phosphorothioate linkage between positions 1 and 2, 2 and 3, 3 and 4, 20 and 21, and 21 and 22.

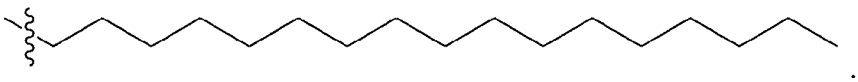
[0018] In some or any of the foregoing or related aspects, the 4′-carbon of the sugar of the 5′-nucleotide of the antisense strand comprises a phosphate analog. In some aspects, phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate.

[0019] In some or any of the foregoing or related aspects, the lipid moiety is a saturated or unsaturated fatty acid moiety. In some aspects, the lipid moiety is a saturated fatty acid moiety that ranges in size from C10 to C24 in length.

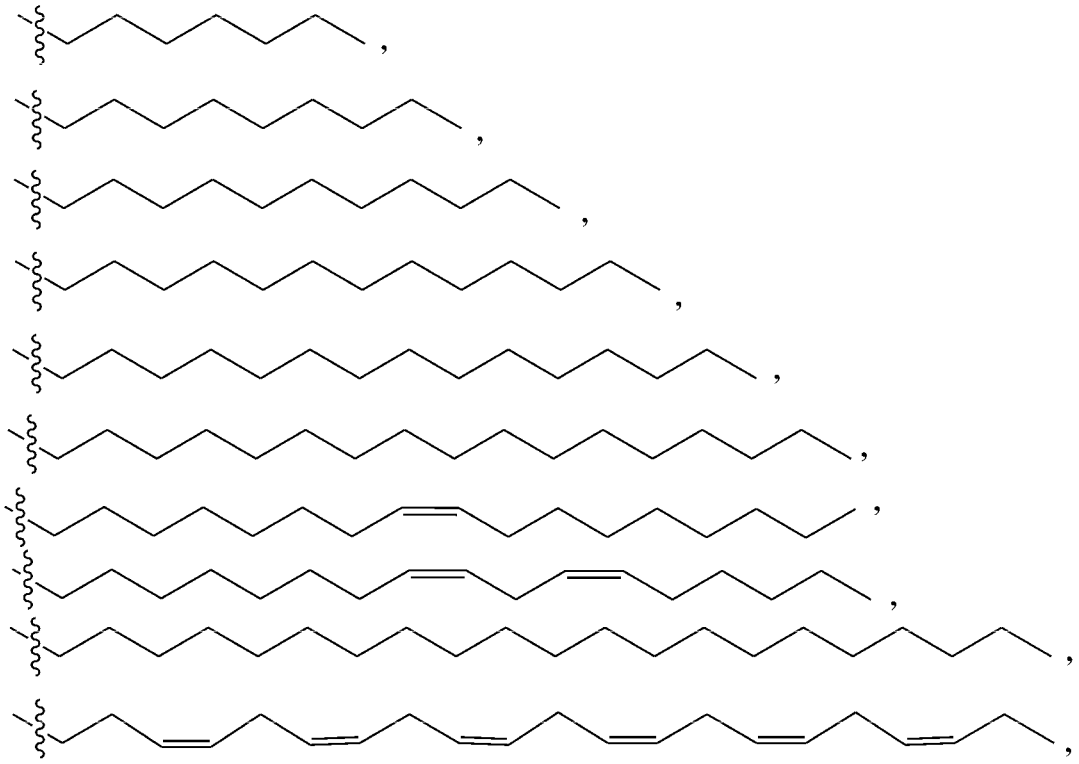
[0020] In some or any of the foregoing or related aspects, the lipid moiety is a C16 saturated fatty acid moiety. In some aspects, the C16 saturated fatty acid moiety is represented by:

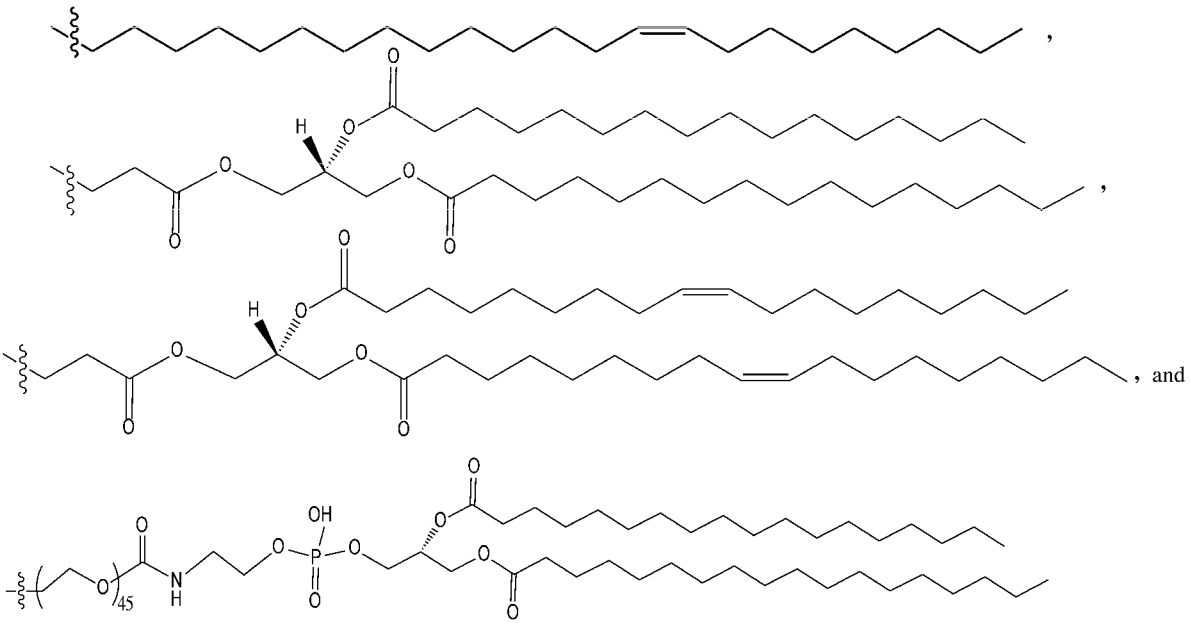


[0021] In some or any of the foregoing or related aspects, the lipid moiety is a C18 saturated fatty acid moiety. In some aspects, the C18 saturated fatty acid moiety is represented by:



[0022] In some or any of the foregoing or related aspects, the lipid moiety is selected from:





[0023] In some or any of the foregoing or related aspects, the lipid moiety is conjugated to the 2' carbon of the ribose ring of the 5' terminal nucleotide.

[0024] In some or any of the foregoing or related aspects, the sense strand comprises the sequence set forth in SEQ ID NO: 1222. In some aspects, the antisense strand comprises the sequence set forth in SEQ ID NO: 1145. In some or any of the foregoing or related aspects, the sense strand comprises the sequence set forth in SEQ ID NO: 1222, and wherein the antisense strand comprises the sequence set forth in SEQ ID NO: 1145.

[0025] In some aspects, the disclosure provides a double-stranded oligonucleotide for reducing STAT3 expression, wherein the oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 1222 and the antisense strand comprises the sequence set forth in SEQ ID NO: 1145, wherein the sense strand and antisense strand form an asymmetric duplex region of 20 nucleotides in length and having an overhang of 2 nucleotides at the 3' terminus of the antisense strand.

[0026] In some or any of the foregoing or related aspects, the region of complementary is fully complementary to the STAT3 target sequence. In some aspects, the region of complementary is partially complementary to the STAT3 target sequence. In some aspects, the region of complementary comprises no more than 4 mismatches to the STAT3 target sequence. In some aspects, the region of complementary is fully complementary to the STAT3 target sequence at nucleotide positions 2-8 or 2-11 of the antisense strand, wherein nucleotide positions are numbered 5' to 3'.

[0027] In some or any of the foregoing or related aspects, the oligonucleotide is a Dicer substrate that, upon endogenous Dicer processing, yields double-stranded nucleic acids of 19-21 nucleotides in length capable of reducing *STAT3* mRNA expression in a mammalian cell.

[0028] In some or any of the foregoing or related aspects, the oligonucleotide reduces expression of *STAT3* mRNA in one or more immune cells associated with a tumor microenvironment.

[0029] In some aspects, the disclosure provides a pharmaceutical composition comprising an oligonucleotide of any of the foregoing or related aspects, and a pharmaceutically acceptable carrier, delivery agent, or excipient.

[0030] 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 or pharmaceutical composition of any of the foregoing or related aspects.

[0031] In some or any of the foregoing or related aspects, the PD-L1 inhibitor is administered to the subject.

[0032] In some aspects, the disclosure provides a method of treating cancer in a subject that has received or is receiving a PD-L1 inhibitor, the method comprising administering an oligonucleotide or pharmaceutical composition of any of the foregoing or related aspects to the subject, thereby treating cancer in the subject.

[0033] In some aspects, the disclosure provides a method of treating cancer in a subject that has received or is receiving an oligonucleotide targeting *STAT3*, wherein the oligonucleotide targeting *STAT3* is an oligonucleotide or pharmaceutical composition of any of the foregoing or related aspects, the method comprising administering a PD-L1 inhibitor to the subject, thereby treating cancer in the subject.

[0034] In some aspects, the disclosure provides a method for treating a disease, disorder or condition associate with STAT3 expression in a subject, the method comprising administering to the subject an effective amount of an oligonucleotide or pharmaceutical composition of any of the foregoing or related aspects.

[0035] In some or any of the foregoing or related aspects, the PD-L1 inhibitor is administered to the subject.

[0036] In some aspects, the disclosure provides a method for treating a disease, disorder or condition associate with STAT3 expression in a subject that has received or is receiving a PD-L1 inhibitor, the method comprising administering an oligonucleotide or pharmaceutical composition of any of the foregoing or related aspects to the subject, thereby treating cancer in the subject.

[0037] In some aspects, the disclosure provides a method for treating a disease, disorder or condition associate with STAT3 expression in a subject that has received or is receiving an oligonucleotide targeting *STAT3*, wherein the oligonucleotide targeting *STAT3* is an oligonucleotide or pharmaceutical composition of any of the foregoing or related aspects, the method comprising administering a PD-L1 inhibitor to the subject, thereby treating cancer in the subject.

[0038] In some or any of the foregoing or related aspects, the disease, disorder or condition associated with STAT3 expression is a cancer. In some aspects, the cancer is selected from carcinoma, sarcoma, melanoma, lymphoma, and leukemia, prostate cancer, breast cancer,

hepatocellular carcinoma (HCC), colorectal cancer, pancreatic cancer and glioblastoma. In some aspects, the cancer comprises an immunosuppressive tumor microenvironment. In some aspects, the cancer comprises an inflamed tumor microenvironment. In some aspects, the inflamed tumor microenvironment comprises infiltrating T cells.

[0039] In some or any of the foregoing or related aspects, the PD-L1 inhibitor is an antibody. IN some aspects, the antibody is an anti-PD-L1 antibody. In some aspects, the anti-PDL1 antibody is selected from FAZ053, atezolizumab, avelumab, durvalumab, envafolimab, and BMS-936559.

[0040] In some or any of the foregoing or related aspects, the antibody is an anti-PD-1 antibody. In some aspects, the anti-PD-1 antibody is selected from nivolumab, pembrolizumab, and cemiplimab.

[0041] In some or any of the foregoing or related aspects, treating cancer comprises reducing or inhibiting tumor growth in the subject.

[0042] In some aspects, the disclosure provides a method of reducing expression of *STAT3* mRNA in a cell, comprising contacting the cell with an oligonucleotide of any of the foregoing or related aspects.

[0043] In some aspects, the disclosure provides a kit comprising a container comprising the oligonucleotide of any of the foregoing or related aspects, 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.

[0044] In some aspects, the disease, disorder or condition associated with STAT3 expression is a cancer.

[0045] In some aspects, the disclosure provides a kit comprising a container comprising the oligonucleotide of any of the foregoing or related aspects, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject with cancer that has received or is receiving a PD-L1 inhibitor.

[0046] In some aspects, the disclosure provides a kit comprising a container comprising a PD-L1 inhibitor, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject with cancer that has received or is receiving the oligonucleotide of any of the foregoing or related aspects.

[0047] In some aspects, the disclosure provides a kit comprising an oligonucleotide, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for

administering the oligonucleotide to a subject in need thereof that has received or is receiving a PD-L1 inhibitor, wherein the oligonucleotide is the oligonucleotide of any of the foregoing or related aspects.

[0048] In some aspects, the disclosure provides a kit comprising a PD-L1 inhibitor, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administering the inhibitor to a subject in need thereof that has received or is receiving an oligonucleotide, wherein the oligonucleotide is an oligonucleotide of any of the foregoing or related aspects.

[0049] In some or any of the foregoing or related aspects, the subject has a disease, disorder, or condition associated with activated *STAT3* expression. In some aspects, the subject has cancer.

[0050] In some aspects, the disclosure provides a method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of the subject, wherein the treatment is administration of an oligonucleotide targeting STAT3, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

[0051] In some aspects, the disclosure provides a method for determining responsiveness in a subject with cancer who has received or is receiving a treatment, comprising:

(i) obtaining a biological sample from the subject; and

(ii) detecting of the presence of MDSCs or a marker of MDSC activity in the biological sample, wherein the treatment is administration of an oligonucleotide targeting STAT3, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

[0052] In some or any of the foregoing or related aspects, detecting comprises determining an amount of MDSCs or an amount of a marker of MDSC activity.

[0053] In some aspects, reduction of MDSCs or marker of MDSC activity is relative to an amount or level of MDSCs or marker of MDSC activity prior to treatment of the subject.

[0054] In some aspects, the reduction of MDSCs or marker of MDSC activity is relative to an amount or level of MDSCs or marker of MDSC activity of a population of patients that did not receive the treatment. In some aspects, the reduction of MDSCs or marker of MDSC activity is

based on an amount or level of MDSCs or marker of MDSC activity of a population of patients that responded to the treatment.

[0055] In some aspects, the MDSCs are granulocytic-MDSCs (G-MDSCs). In some aspects, the MDSCs are monocytic-MDSCs (M-MDSCs). In some aspects, the MDSCs express Arg1.

[0056] In some aspects, the MDSCs express IDO. In some aspects, the presence of MDSCs or a marker of activity of MDSC is determined by flow cytometry.

[0057] In some aspects, the biological sample is a blood or serum sample.

[0058] In some aspects, responding to treatment comprises a reduction or inhibition of tumor growth and/or tumor size.

[0059] In some aspects, the oligonucleotide targeting STAT3 is the oligonucleotide of any of the foregoing or related aspects.

BRIEF DESCRIPTION OF THE DRAWINGS

[0060] **FIG. 1A** provides structures of RNAi oligonucleotide molecules having chemical modifications with GalNAc or lipid (*e.g.,* C18 hydrocarbon chain) conjugated to the oligonucleotide molecule to generate oligonucleotide-ligand conjugates.

[0061] **FIG. 1B** provides structures of lipid tails suitable for conjugation to RNAi oligonucleotide molecules.

[0062] **FIGs. 2A** and **2B** 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. 2A**) and or varying doses (0.3, 1.0, or 3.0 mg/kg) to determine dose responsiveness (**FIG. 2B**). Arrows indicate constructs selected for further study.

[0063] **FIGs. 3A** and **3B** are graphs showing mouse *Stat3* mRNA expression 3 days 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. 3A**) and 50 mg/kg (**FIG. 3B**).

[0064] **FIGs. 4A** and **4B** are graphs showing mouse *Stat3* mRNA expression after treatment of Pan02 xenograft mice with GalXC-STAT3-C18 conjugates in bulk tumor (TME) (**FIG. 4A**) and tumor draining lymph nodes TdLNs (**FIG. 4B**) at doses of 25 and 50 mg/kg.

[0065] **FIG. 5A** 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 3 days after a dose of 25 or 50 mg/kg of the conjugated oligonucleotide.

[0066] **FIG. 5B** provides graphs showing the effect of GalXC-STAT3-C18-4123 on *Stat3* and *Pdl1* mRNA levels in TdLN of Pan02 xenograft mice 7 days after a 25mg/kg dose of the conjugated oligonucleotide.

[0067] **FIGs. 6A** and **6B** are graphs showing the *in vivo* effect of subcutaneous treatment of a total dose of 50 mg/kg GalXC-STAT3-C18-4123 on tumor volume over time in immunocompetent mice bearing Pan02 murine pancreatic tumors. Mice were treated with either four 12.5 mg/kg (**FIG. 6A**) or two 25mg/kg (**FIG. 6B**) doses of the conjugated oligonucleotide. Lines show the average of all animals tested.

[0068] **FIG. 7** 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: 1, Reverse 2- SEQ ID NO: 2; Probe 2- SEQ ID NO: 3).

[0069] **FIGs. 8A** and **8B** 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 were assayed in **FIG. 8A** and 34 of those oligonucleotides were selected for further testing *in vivo* (**FIG. 8B**).

[0070] **FIGs. 9A** and **9B** 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.

[0071] **FIG. 10** 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 two different doses (0.3mg/kg or 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.

[0072] **FIG. 11** 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.

[0073] **FIG. 12** 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.

[0074] **FIGs. 13A** and **13B** 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.

[0075] **FIG. 14** 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.

[0076] **FIG. 15** 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.

[0077] **FIG. 16** 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.

[0078] **FIG. 17** 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.

[0079] **FIG. 18A** provides a graph depicting tumor volume after administration of a GalXC-STAT3-C18 oligonucleotide alone or in combination with an anti-PD-L1 mAb. Immunocompetent mice bearing Pan02 murine pancreatic tumors were dosed subcutaneously (s.c.) with 25 mg/kg of GalXC-STAT3-C18-4123 with intraperitoneal (i.p.) treatment of 10 mg/kg of anti-PD-L1 mAb. Controls included GalXC-Placebo (an HBV siRNA with identical

chemistry and lipid conjugation as GalXC-STAT3 oligonucleotides), GalXC-STAT3-C18-4123 at 25 mg/kg or GalXC-Placebo at 25 mg/kg in combination with anti-PD-L1 mAb at 10 mg/kg. Mice were first administered two doses three days apart, and two weeks later were administered two more doses three days apart [(q3dx2) x2]. Arrows indicate days doses were administered.

[0080] **FIG. 18B** provides a graph depicting tumor volume after administration of a GalXC-STAT3-C18 oligonucleotide in combination with an anti-PD-L1 mAb. Immunocompetent mice bearing Pan02 murine pancreatic tumors were dosed subcutaneously (s.c.) with 25 mg/kg of GalXC-STAT3-C18-4123 with intraperitoneal (i.p.) treatment of 10 mg/kg of anti-PD-L1 mAb. Mice were administered GalXC-Placebo 42 and 45 days after transplant then administered GalXC-STAT3 in combination with anti-PD-L1 mAb on days 60 and 63.

[0081] **FIGs. 19A-19C** provide graphs depicting tumor volume after administration of a GalXC-STAT3-C18 oligonucleotide alone or in combination with an anti-PD-L1 mAb or GalXC-Placebo alone or in combination with anti-PD-L1 mAb in tumors with different immunophenotypes., 4T1 (triple negative breast, checkpoint resistant) (**FIG. 19A**), MC-38 (Colon carcinoma, partially checkpoint sensitive) (**FIG. 19B**), or Hepa1-6 (Hepatocellular carcinoma, checkpoint sensitive) (**FIG. 19C**) cells were implanted into mice. Tumor bearing mice were dosed s.c. with 25 mg/kg of GalXC-STAT3-C18-4123 with i.p. treatment of 10 mg/kg of anti-PD-L1 mAb. Controls included GalXC-Placebo, GalXC-STAT3-C18-4123 at 25 mg/kg or GalXC-Placebo at 25 mg/kg in combination with anti-PD-L1 mAb at 10 mg/kg. Mice bearing MC-38 and Hepa1-6 tumors were administered two doses three days apart at 25 mg/kg and the same regimen was repeated the following week. Mice bearing 4T1 tumors were administered three doses each three days apart (q3d x 3). Arrow (5/5 CR) = All mice treated were complete responders.

[0082] **FIG. 20** provides a graph depicting the effect of Hepa1-6 re-challenge in the completely eradicated tumors. After tumors in all 5 mice were completely regressed with the treatment of GalXC-STAT3-C18 (25 mg/kg, s.c.) and anti-PD-L1 mAb (10 mg/kg, i.p.) in **FIG. 19C**, mice were rechallenged on day 51 with Hepa1-6 cells (2e6 cells/mouse) on the opposite flank of the mice and tumor volume was monitored (**FIG. 20**). Arrow (5/5 CR) = All mice remained tumor free even after the re-challenge.

[0083] **FIGs. 21A** and **21B** provide graphs depicting tumor volume after administration of GalXC-STAT3-C18 oligonucleotide alone or in combination with an anti-PD-L1 mAb in

immunocompetent mice with functional CD8+ T cells (**FIG. 21A**) and immunocompromised mice with no functional CD8+ T cells (**FIG. 21B**). Mice (immunocompetent or immunocompromised) bearing 4T1 tumors were dosed s.c. with GalXC-STAT3-C18-4123 (25 mg/kg, three times with each dose three days apart (q3d x 3)) and i.p. with anti-PD-L1 mAb (10 mg/kg, q3d x 3). Controls included GalXC-Placebo, GalXC-STAT3-C18-4123 at 25 mg/kg or GalXC-Placebo at 25 mg/kg in combination with anti-PD-L1 mAb at 10 mg/kg.

[0084] **FIG. 22** provides images showing the appearance of tumors (with cell death) from mice assayed in **FIG. 21A,** and perforin staining for positive cytotoxic CD8+ T cells in the tumors at the end of the study.

[0085] **FIG. 23** provides graphs depicting tumor volume and images showing lung tumor metastasis after administration of GalXC-STAT3-C18-4123 oligonucleotide alone or in combination with an anti-PD-L1 mAb. Mice (immunocompetent or immunocompromised) bearing 4T1 tumors were dosed s.c. with GalXC-STAT3-C18-4123 (50 mg/kg, q3d x 3) and i.p. with anti-PD-L1 mAb (10 mg/kg, q3d x 3). Controls included GalXC-Placebo, GalXC-STAT3-C18-4123 at 50 mg/kg or GalXC-Placebo at 50 mg/kg in combination with anti-PD-L1 mAb at 10 mg/kg.

[0086] **FIG. 24** provides a heat map showing the regulation of targets involved in immune modulation observed in CT26 tumors upon combination treatment of GalXC-STAT3-C18-4123 (s.c, 25 mg/kg, q3d x 3) and anti-PD-L1 mAb (i.p. at 10 mg/kg, q3d x 3) compared to controls including GalXC-Placebo, GalXC-STAT3-C18-4123 at 25 mg/kg or GalXC-Placebo at 25 mg/kg in combination with anti-PD-L1 mAb at 10 mg/kg.

[0087] **FIG. 25** provides the structure of an RNAi oligonucleotide molecule having chemical modifications with a C18 lipid conjugated to the 5' terminal nucleotide of the sense strand to generate an oligonucleotide-ligand conjugate.

[0088] **FIGS. 26A - 26C** provide graphs depicting tumor volume after administration of DCR-STAT3, (a human specific STAT3 sequence with C18 lipid conjugation at 5'end of the passenger strand corresponding to SEQ ID NOs: 1222 and 1145) or GalXC-Placebo (a chemically matched irrelevant sequence that does not bind *Stat3/STAT3* mRNA target sequence) alone or in combination with an anti-PD-L1 antibody. Immunocompetent mice bearing B16F10 (murine melanoma), Pan02 (murine pancreatic) and MC-38 (murine colorectal) tumors were treated with either three or four subcutaneous (s.c.) doses of 25 mg/kg of the conjugated

oligonucleotide either alone or in combination with 10 mg/kg intraperitoneal (i.p.) of anti-PD-L1 antibody. B16F10 tumor bearing mice were administered three doses three days apart, Pan02 tumor bearing mice were first administered 2 doses 3 days apart and a week later, were administered two more doses three days apart. MC-38 tumor bearing mice were first administered 2 doses 3 days apart and four days later, were administered two more doses three days apart. Arrows indicate days doses were administered.

DETAILED DESCRIPTION

[0089] 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.

Definitions

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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:

[0097] 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.

[0098] 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.

[0099] 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.

[00100] 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.

[00101] 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.

[00102] 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.

[00103] 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.

[00104] 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.

[00105] 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.

[00106] 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.

[00107] 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.

[00108] 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).

[00109] 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.*

[00110] 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.*

[00111] 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.

[00112] 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.

[00113] 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.

[00114] 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.

[00115] 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).

[00116] 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).

[00117] 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.

[00118] 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.

[00119] 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.

[00120] 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).

[00121] 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."

[00122] 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.

[00123] 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.

[00124] 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.

[00125] 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.

[00126] 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.

Methods of Use

Combination of STAT3 Oligonucleotide and PD-L1 Inhibitors

[00127] In some embodiments, the disclosure provides STAT3 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 has received or is receiving a PD-L1 inhibitor.

[00128] In some embodiments, methods described herein comprise selecting a subject having a disease, disorder or condition associated with STAT3 expression and/or PD-L1 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 and/or PD-L1 expression such as cancer or other chronic lymphoproliferative disorders.

[00129] Likewise, and as detailed herein, the methods also may include steps such as measuring or obtaining a baseline value for a marker of STAT3 expression and/or PD-L1 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.

[00130] In some embodiments, the disclosure provides methods of treating a subject having, suspected of having, or at risk of developing a disease, disorder, or condition with a STAT3 oligonucleotide herein, wherein the subject has received or is receiving a PD-L1 inhibitor. In some embodiments, the disclosure provides methods of treating a subject having, suspected of having, or at risk of developing a disease, disorder, or condition with a PD-L1 inhibitor described herein, wherein the subject has received or is receiving a STAT3 oligonucleotide described herein.

[00131] 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 a STAT3 oligonucleotide herein in combination with a PD-L1 inhibitor. 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 a STAT3 oligonucleotide herein in combination with a PD-L1 inhibitor. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of a STAT3 oligonucleotide herein in combination with a PD-L1 inhibitor. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of a STAT3 oligonucleotide herein to a subject that has received or is receiving a PD-L1 inhibitor. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of a PD-L1 inhibitor to a subject that has received or is receiving a STAT3 oligonucleotide herein. In some embodiments, the subject is treated therapeutically. In some embodiments, the subject is treated prophylactically.

[00132] 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 a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 875, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 965 in combination with a PD-L1 inhibitor. 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 a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 1222, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 1145 in combination with a PD-L1 inhibitor. 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 a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 875, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 965 in combination with a PD-L1 inhibitor. 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 a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 1222, and an antisense strand

which comprises the sequence set forth in SEQ ID NO: 1145 in combination with a PD-L1 inhibitor. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 875, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 965 in combination with a PD-L1 inhibitor. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 1222, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 1145 in combination with a PD-L1 inhibitor. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 875, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 965 to a subject that has received or is receiving a PD-L1 inhibitor. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 1222, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 1145 to a subject that has received or is receiving a PD-L1 inhibitor. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of a PD-L1 inhibitor to a subject that has received or is receiving a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 875, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 965. In some embodiments of the methods herein, the subject is treated by administering a therapeutically effective amount of a PD-L1 inhibitor to a subject that has received or is receiving a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 1222, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 1145. In some embodiments, the subject is treated therapeutically. In some embodiments, the subject is treated prophylactically.

[00133] In some embodiments of the methods herein, one or more STAT3 oligonucleotides herein, or a pharmaceutical composition comprising one or more STAT3 oligonucleotides, is administered to a subject having a disease, disorder or condition associated with STAT3 expression that has received or is receiving a PD-L1 inhibitor, such that STAT3

expression is reduced in the subject, thereby treating the subject. In some embodiments of the methods herein, a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 875, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 965, or a pharmaceutical composition comprising the STAT3 oligonucleotide, is administered to a subject having a disease, disorder or condition associated with STAT3 expression that has received or is receiving a PD-L1 inhibitor, such that STAT3 expression is reduced in the subject, thereby treating the subject. In some embodiments of the methods herein, a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 1222, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 1145, or a pharmaceutical composition comprising the STAT3 oligonucleotide, is administered to a subject having a disease, disorder or condition associated with STAT3 expression that has received or is receiving a PD-L1 inhibitor, 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. In some embodiments of the methods herein, one or more STAT3 oligonucleotides herein, or a pharmaceutical composition comprising one or more STAT3 oligonucleotides, is administered to a subject having a disease, disorder or condition associated with STAT3 expression that has received or is receiving a PD-L1 inhibitor such that STAT3 expression and PD-L1 signaling is reduced in the subject, thereby treating the subject. In some embodiments of the methods herein, a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 875, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 965, or a pharmaceutical composition comprising the STAT3 oligonucleotide, is administered to a subject having a disease, disorder or condition associated with STAT3 expression that has received or is receiving a PD-L1 inhibitor such that STAT3 expression and PD-L1 signaling is reduced in the subject, thereby treating the subject. In some embodiments of the methods herein, a STAT3 oligonucleotide comprising a sense strand which comprises the sequence set forth in SEQ ID NO: 1222, and an antisense strand which comprises the sequence set forth in SEQ ID NO: 1145, or a pharmaceutical composition comprising the STAT3 oligonucleotide, is administered to a subject having a disease, disorder or condition associated with STAT3 expression that has received or is receiving a PD-L1 inhibitor such that STAT3 expression and PD-L1 signaling is

reduced in the subject, thereby treating the subject. In some embodiments, an amount or level of *STAT3* mRNA and PD-L1 signaling is reduced in the subject. In some embodiments, an amount or level of STAT3 and/or protein is reduced in the subject and PD-L1 signaling is reduced in the subject.

[00134] In some embodiments, a therapeutically effective amount of a STAT3 oligonucleotide and/or PD-L1 inhibitor is administered to a subject. 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.

[00135] 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.

[00136] 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.

[00137] In some embodiments, a PD-L1 inhibitor (e.g., an anti-PD-L1 antibody) herein is administered quarterly (once every three months), bi-monthly (once every two months), monthly or weekly. For example, the inhibitor is administered every week or at intervals of two, or three weeks. Alternatively, the inhibitor is administered daily.

[00138] In some embodiments the oligonucleotides herein are administered in combination with a PD-L1 inhibitor. In some embodiments the oligonucleotide and inhibitor are

administered in combination concurrently, sequentially (in any order), or intermittently. For example, the oligonucleotide and inhibitor may be co-administered concurrently. Alternatively, the 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 the inhibitor, or vice versa.

[00139] 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.

Cancers

[00140] In some embodiments, the STAT3 oligonucleotide and PD-L1 inhibitor target are used to treat a cancer or 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

[00141] 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. In some embodiments, the cancer is resistant to immune checkpoint therapy. In some embodiments, the cancer is partially resistant to immune checkpoint therapy. In some embodiments, the cancer is sensitive to immune checkpoint therapy.

[00142] In some embodiments, the STAT3 oligonucleotide and PD-L1 inhibitor 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.

Treatment Response

[00143] In some embodiments, the disclosure provides a method of monitoring treatment response in a subject. In some embodiments, treatment comprises any of the STAT3 targeting oligonucleotides described herein. In some embodiments, treatment comprises any of the STAT3 targeting oligonucleotides described herein in combination with a PD-L1 inhibitor.

[00144] In some embodiments, the disclosure provides a method of monitoring treatment response in a subject having a tumor, the method comprising detecting an amount of myeloid-derived suppressor cells (MDSCs) in a biological sample of a subject that has received or is receiving treatment with an oligonucleotide targeting STAT3 for treating a tumor in the subject, wherein a reduced amount of MDSCs in the biological sample indicates the subject is responding to treatment with the oligonucleotide.

[00145] In some embodiments, the disclosure provides a method for monitoring treatment response in a subject having a tumor, comprising:

(i) obtaining a biological sample from a subject that has received or is receiving treatment with an oligonucleotide targeting STAT3;

(ii) detecting an amount of MDSCs in the biological sample; and

(iii) comparing the amount of MDSCs in the biological sample to a pre-determined amount of MDSCs, wherein a reduced amount of MDSCs in the biological sample indicates the subject is responding to treatment with the oligonucleotide.

[00146] In some embodiments, the disclosure provides a method of determining responsiveness to treatment in a subject with cancer. In some embodiments, treatment comprises any of the STAT3 targeting oligonucleotides described herein. In some embodiments, treatment comprises any of the STAT3 targeting oligonucleotides described herein in combination with a PD-L1 inhibitor.

[00147] In some embodiments, the disclosure provides a method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of a subject. In some embodiments, a method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of a subject, wherein the treatment is administration of an oligonucleotide targeting STAT3, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

[00148] In some embodiments, the disclosure provides a method for determining responsiveness in a subject with cancer who has received or is receiving a treatment, comprising:

(i) obtaining a biological sample from the subject; and

(ii) detecting of the presence of MDSCs or a marker of MDSC activity in the biological sample

wherein the treatment is administration of an oligonucleotide targeting STAT3, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

[00149] In some embodiments, the detecting comprising determining an amount of MDSCs or an amount of a marker of MDSC activity. In some embodiments, the reduction of MDSCs or marker of MDSC activity is relative to an amount or level of MDSCs or marker of MDSC activity prior to treatment of the subject. In some embodiments, the reduction of MDSCs or marker of MDSC activity is relative to an amount or level of MDSCs or marker of MDSC activity prior to treatment of the subject. In some embodiments, the reduction of MDSCs or marker of MDSC activity is relative to an amount of level of MDSCs or marker of MDSC activity of a population of patients that responded to the treatment.

[00150] In some embodiments, the pre-determined amount of MDSCs is an amount of MDSCs detected in a subject prior to treatment with an oligonucleotide. In some embodiments, the pre-determined amount of MDSCs is an average amount of MDSCs based on a population of patients that did not receive treatment with an oligonucleotide. In some embodiments, the population of patients is a healthy population of patients. In some embodiments, the population of patients is a population without cancer. In some embodiments, the population of patients is a population receiving treatment with a placebo oligonucleotide. In some embodiments, the population of patients is a population of patients that received treatment with an oligonucleotide and had a reduction or inhibition of tumor growth and/or tumor size.

[00151] In some embodiments, the MDSCs are granulocytic-MDSCs (G-MDSCs). In some embodiments, the MDSCs are monocytic-MDSCs (M-MDSCs). In some embodiments, the MDSCs express Arg1. In some embodiments, the MDSCs express IDO. In some embodiments, the MDSCs are Arg1+ M-MDSCs. In some embodiments, the MDSCs are Arg1+ G-MDSCs. In some embodiments, the MDSCs are IDO+ M-MDSCs. In some embodiments, the MDSCs are IDO+ G-MDSCs. In some embodiments, the MDSCs are G-MDSCs, M-MDSCs, Arg1+ M-MDSCs, Arg1+ G-MDSCs, IDO+ M-MDSCs, IDO+ G-MDSCs, or a combination thereof.

[00152] In some embodiments, the amount of MDSCs is determined using methods known to those of skill in the art. In some embodiments, the amount of MDSCs is determined using flow cytometry.

[00153] In some embodiments, the MDSCs are measured from a biological sample. In some embodiments, the biological sample is a blood sample. In some embodiments, the biological sample is a serum sample.

[00154] In some embodiments, responding to treatment comprises a reduction or inhibition in tumor growth and/or tumor size. In some embodiments, responding to treatment comprises a reduction or inhibition in tumor growth. In some embodiments, responding to treatment comprises a reduction or inhibition in tumor size.

[00155] In some embodiments, a method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of a subject, wherein the treatment is administration of an oligonucleotide targeting STAT3, wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in

the biological sample indicates the subject is responding to the treatment, and wherein the oligonucleotide targeting STAT3 comprises a sense strand comprising a sequence selected from SEQ ID NOs: 857-946 and an antisense strand comprising a sequence selected from SEQ ID NOs: 947-1036.

[00156] In some embodiments, a method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of a subject, wherein the treatment is administration of an oligonucleotide targeting STAT3, wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment, and wherein the oligonucleotide targeting STAT3 comprises a sense strand comprising a sequence selected from SEQ ID NOs: 1037-1126 and an antisense strand comprising a sequence selected from SEQ ID NOs: 1127-1216.

[00157] In some embodiments, a method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of a subject, wherein the treatment is administration of an oligonucleotide targeting STAT3, wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment, and wherein the oligonucleotide targeting STAT3 comprises a sense strand comprising a sequence selected from SEQ ID NOs: 9, 37, 65, and 69 and an antisense strand comprising a sequence selected from SEQ ID NOs: 10, 38, 66, and 70.

[00158] In some embodiments, a method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of a subject, wherein the treatment is administration of an oligonucleotide targeting STAT3, wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment, and wherein the oligonucleotide targeting STAT3 comprises a sense strand comprising a sequence selected from SEQ ID NOs: 11, 39, 67, and 71 and an antisense strand comprising a sequence selected from SEQ ID NOs: 12, 40, 68, and 72.

[00159] In some embodiments, a method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of a subject, wherein the treatment is administration of an oligonucleotide targeting STAT3, wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment, and wherein the oligonucleotide targeting STAT3 comprises a sense strand comprising a sequence selected from SEQ ID NOs: 9, 37, 65, and 69 and an antisense strand comprising a sequence selected from SEQ ID NOs: 10, 38, 66, 70.

[00160] In some embodiments, a method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of a subject, wherein the treatment is administration of an oligonucleotide targeting STAT3, wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment, and wherein the oligonucleotide targeting STAT3 comprises a sense strand comprising SEQ ID NO: 875 and an antisense strand comprising SEQ ID NO: 965.

[00161] In some embodiments, a method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of a subject, wherein the treatment is administration of an oligonucleotide targeting STAT3, wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment, and wherein the oligonucleotide targeting STAT3 comprises a sense strand comprising SEQ ID NO: 1145 and an antisense strand comprising SEQ ID NO: 1222.

[00162] In some embodiments, the disclosure provides a method for determining responsiveness in a subject with cancer who has received or is receiving a treatment, comprising:

(i) obtaining a biological sample from the subject; and

(ii) detecting of the presence of MDSCs or a marker of MDSC activity in the biological sample

wherein the treatment is administration of an oligonucleotide targeting STAT3 comprising a sense strand comprising a sequence selected from SEQ ID NOs: 857-946 and an antisense strand comprising a sequence selected from SEQ ID NOs: 947-1036, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

[00163] In some embodiments, the disclosure provides a method for determining responsiveness in a subject with cancer who has received or is receiving a treatment, comprising:

(i) obtaining a biological sample from the subject; and

(ii) detecting of the presence of MDSCs or a marker of MDSC activity in the biological sample

wherein the treatment is administration of an oligonucleotide targeting STAT3 comprising a sense strand comprising a sequence selected from SEQ ID NOs: 1037-1126 and an antisense strand comprising a sequence selected from SEQ ID NOs: 1127-1216, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

[00164] In some embodiments, the disclosure provides a method for determining responsiveness in a subject with cancer who has received or is receiving a treatment, comprising:

(i) obtaining a biological sample from the subject; and

(ii) detecting of the presence of MDSCs or a marker of MDSC activity in the biological sample

wherein the treatment is administration of an oligonucleotide targeting STAT3 comprising a sense strand comprising a sequence selected from SEQ ID NOs: 11, 39, 67, and 71 and an antisense strand comprising a sequence selected from SEQ ID NOs: 12, 40, 68, and 72, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

[00165] In some embodiments, the disclosure provides a method for determining responsiveness in a subject with cancer who has received or is receiving a treatment, comprising:

(i) obtaining a biological sample from the subject; and

(ii) detecting of the presence of MDSCs or a marker of MDSC activity in the biological sample

wherein the treatment is administration of an oligonucleotide targeting STAT3 comprising a sense strand comprising a sequence selected from SEQ ID NOs: 9, 37, 65, and 69 and an antisense strand comprising a sequence selected from SEQ ID NOs: 10, 38, 66, 70, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

[00166] In some embodiments, the disclosure provides a method for determining responsiveness in a subject with cancer who has received or is receiving a treatment, comprising:

(i) obtaining a biological sample from the subject; and

(ii) detecting of the presence of MDSCs or a marker of MDSC activity in the biological sample

wherein the treatment is administration of an oligonucleotide targeting STAT3 comprising a sense strand comprising SEQ ID NO: 875 and an antisense strand comprising SEQ ID NO: 965, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

[00167] In some embodiments, the disclosure provides a method for determining responsiveness in a subject with cancer who has received or is receiving a treatment, comprising:

(i) obtaining a biological sample from the subject; and

(ii) detecting of the presence of MDSCs or a marker of MDSC activity in the biological sample

wherein the treatment is administration of an oligonucleotide targeting STAT3 comprising a sense strand comprising SEQ ID NO: 1145 and an antisense strand comprising SEQ ID NO: 1222, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

Oligonucleotide Inhibitors of STAT3

[00168] 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.

[00169] 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).

[00170] 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.

[00171] 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.

[00172] 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.

STAT3 Target Sequences

[00173] 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.

[00174] 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 6) and as a result of *in vitro* and *in vivo* testing (*see*, *e.g.*, Example 7 and Example 8), 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, the sequence set forth in SEQ ID NO: 140.

STAT3 Targeting Sequences

[00175] 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 the sequence of SEQ ID NO: 140, 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 the sequence of SEQ ID NO: 140, 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 the sequence of SEQ ID NOs: 524, 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 the sequence of SEQ ID NO: 524, 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 the sequence of SEQ ID NO: 524, 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 the sequence of SEQ ID NO: 524, 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 the sequence of SEQ ID NO: 524 and the targeting sequence or region of complementarity is 24 nucleotides in length.

[00176] 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*.

[00177] In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to the sequence of SEQ ID NOs: 140. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to the sequence SEQ ID NO: 140.

[00178] 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.

[00179] 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 SEQ ID NO: 140, 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 SEQ ID NO: 524, wherein the contiguous sequence of nucleotides is 20 nucleotides in length.

[00180] 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*.

[00181] 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 SEQ ID NO: 140 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 NO: 140 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 SEQ ID NO: 524.

[00182] 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 SEQ ID NO: 140, 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 SEQ ID NO: 140, 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.

Types of Oligonucleotides

[00183] 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.

[00184] 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.

[00185] 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.

[00186] 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.

[00187] 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).

[00188] 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).

[00189] 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

[00190] 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).

[00191] 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.

[00192] 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.

[00193] 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.

[00194] 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 result 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).

[00195] 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.

[00196] 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.

[00197] 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

[00198] 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.

[00199] 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."

[00200] In some embodiments, an oligonucleotide disclosed herein for targeting *STAT3* comprises an antisense strand comprising or consisting of a sequence as set forth in SEQ ID NO: 333. In some embodiments, an oligonucleotide herein comprises an antisense strand comprising at least about 12 (*e.g.*, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in SEQ ID NO: 333. In some embodiments, an oligonucleotide disclosed herein (e.g., an RNAi oligonucleotide) for targeting *STAT3* comprises an antisense strand comprising or consisting of a sequence as set forth in SEQ ID NO: 716. In some embodiments, an oligonucleotide herein comprises an antisense strand comprising at least about 12 (*e.g.*, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in SEQ ID NO: 716. In some embodiments, an oligonucleotide disclosed herein for targeting *STAT3* comprises an antisense strand comprising or consisting of a sequence as set forth in SEQ ID NO: 965. In some embodiments, an oligonucleotide herein comprises an antisense strand comprising at least about 12 (*e.g.*, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in SEQ ID NO: 965. In some embodiments, an oligonucleotide disclosed herein for targeting *STAT3* comprises an antisense strand comprising or consisting of a sequence as set forth in SEQ ID NO: 333. In some embodiments, an oligonucleotide herein comprises an antisense strand comprising at least about 12 (*e.g.*, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in SEQ ID NO: 333.

b. Sense Strands

[00201] In some embodiments, an oligonucleotide disclosed herein (*e.g.,* and RNAi oligonucleotide) for targeting *STAT3* mRNA and inhibiting *STAT3* expression comprises a sense strand sequence as set forth in SEQ ID NO: 140. In some embodiments, an oligonucleotide herein has a sense strand that comprise at least about 12 (*e.g.*, at least 13, at least 14, at least 15,

at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in SEQ ID NOs: 140. In some embodiments, an oligonucleotide disclosed herein (e.g., an RNAi oligonucleotide) for targeting *STAT3* mRNA and inhibiting *STAT3* expression comprises a sense strand sequence a set forth in SEQ ID NO: 524. In some embodiments, an oligonucleotide herein has a sense strand that comprise at least about 12 (*e.g.*, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in SEQ ID NO: 524. In some embodiments, an oligonucleotide disclosed herein for targeting *STAT3* mRNA and inhibiting *STAT3* expression comprises a sense strand sequence as set forth in SEQ ID NO: 875. In some embodiments, an oligonucleotide herein has a sense strand comprised of least about 12 (*e.g.*, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22 or at least 23) contiguous nucleotides of a sequence as set forth in SEQ ID NO:875.

[00202] 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.

[00203] 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.

[00204] 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.

[00205] In some embodiments, an oligonucleotide provided 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 SEQ ID NO: 140, and the oligonucleotide 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 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 oligonucleotide comprises a targeting sequence or a region of complementary that is complementary to a contiguous sequence of nucleotides of SEQ ID NOs: 140, and the oligonucleotide 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 between S1 and S2 of 4 nucleotides in length.

[00206] 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).

[00207] 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.

[00208] 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.

[00209] 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

[00210] 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.

[00211] In some embodiments, a duplex between a sense and antisense strand spans the entire length of both the sense strand and the antisense strand. In some embodiments, the sense and antisense strands of an oligonucleotide comprise nucleotides sequences selected from the group consisting of:

(a) SEQ ID NOs: 875 and 965, respectively,

wherein 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).

Oligonucleotide Termini

[00212] 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.

[00213] 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.

[00214] 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.

[00215] 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.

[00216] 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.

[00217] 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.

[00218] 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

[00219] 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).

[00220] 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.

[00221] 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).

[00222] 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).

[00223] 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.

[00224] 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.

[00225] 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.

[00226] In some embodiments, the modified oligonucleotides comprise a sense strand sequence having a modification pattern as set forth in **FIG 1** or **Example 7** and an antisense

strand having a modification pattern as set forth in **FIG 1** or **Example 7.** 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.

[00227] 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.

[00228] 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.

[00229] 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.

[00230] In some embodiments, an oligonucleotide provided herein comprises an antisense strand having the sugar moiety at position 1, position 6, position 8, position 9, position 11, position 12, position 13, position 15, position 16, position 17, position 18, position 19, position 20, position 21, or position 22 modified with 2′-OMe.

[00231] 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).

[00232] 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 at positions 1-7 and 12-36 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).

[00233] 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.

[00234] 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.

[00235] 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).

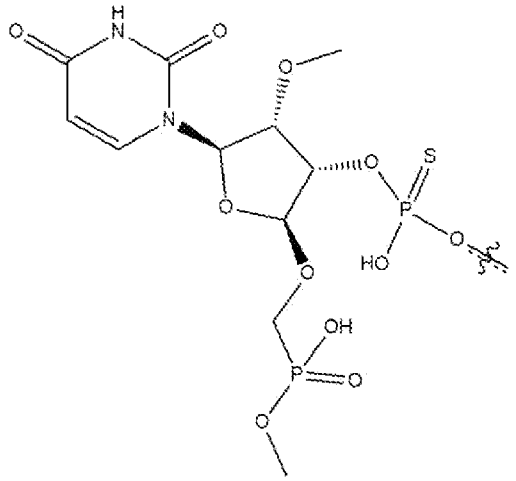
[00236] In some embodiments, an oligonucleotide provided herein comprises a sense strand having the sugar moiety at positions 8-11 modified with 2′-F and the sugar moiety at positions 1-7 and 12-36 modified with 2'OMe, and an antisense strand with the sugar moiety at each of the positions at positions 2, 3, 4, 5, 7, 10 and 14 modified with the 2′-F and the sugar moiety at positions 1, 6, 8, 9, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, and 22 modified with 2′-OMe.

b. 5′ Terminal Phosphates

[00237] 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").

[00238] 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.

[00239] 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

[00240] 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.

[00241] 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.

[00242] 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

[00243] 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).

[00244] 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.

[00245] 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

[00246] 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).

[00247] 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).

[00248] 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.

[00249] 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.

Targeting Ligands

[00250] 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).

[00251] 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.

[00252] 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.

[00253] 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

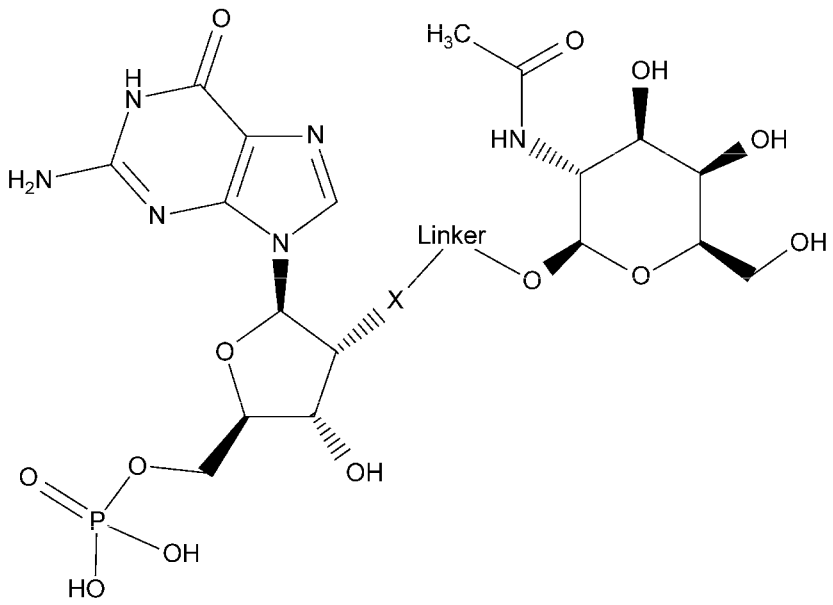
subsequent clearing circulating glycoproteins that contain terminal galactose or GalNAc residues (asialoglycoproteins). Conjugation (either indirect or direct) of GalNAc moieties to oligonucleotides of the instant disclosure can be used to target these oligonucleotides to the ASGPR expressed on cells. 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.

[00254] 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.

[00255] 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.

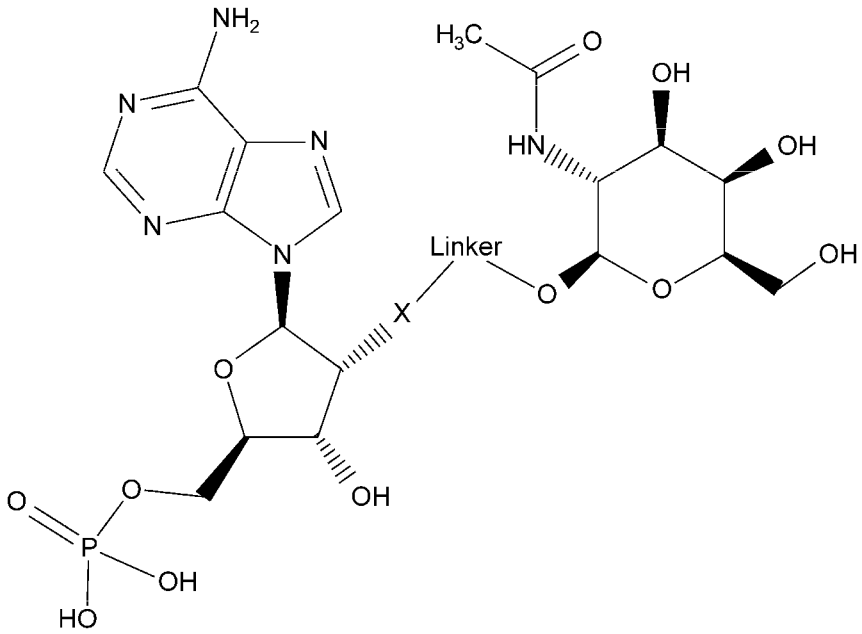
[00256] In some embodiments, the tetraloop is any combination of adenine and guanine nucleotides.

[00257] 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):



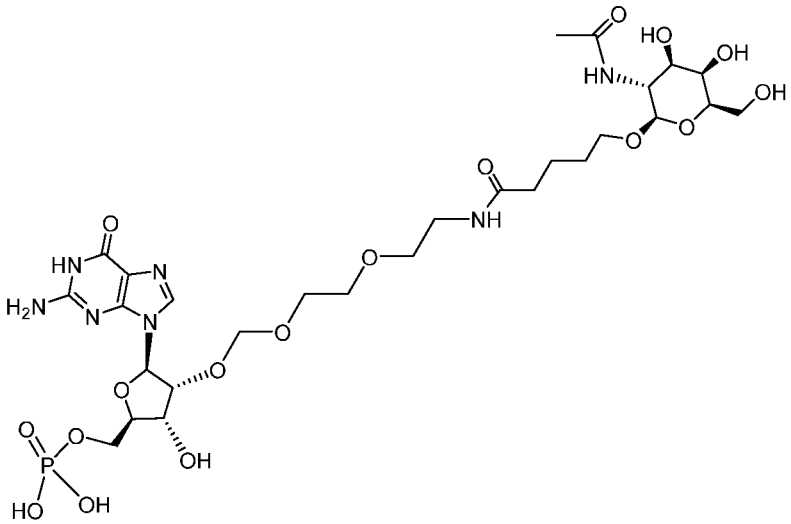
Chem 2

[00258] 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):



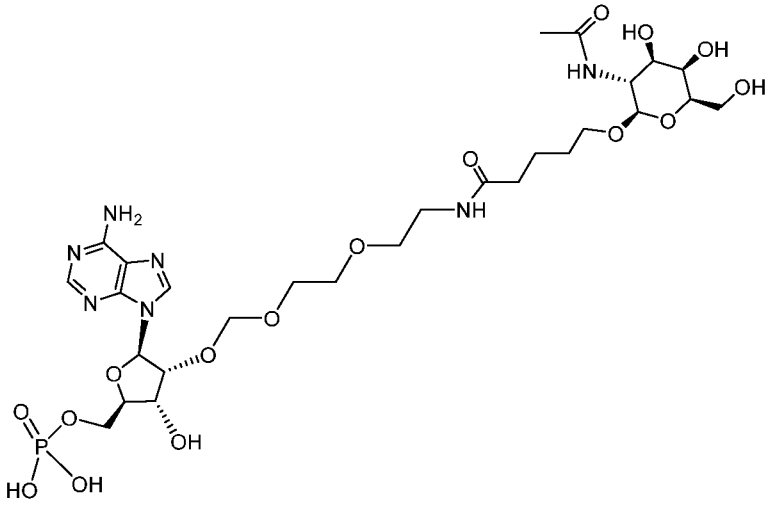
Chem 3

[00259] 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

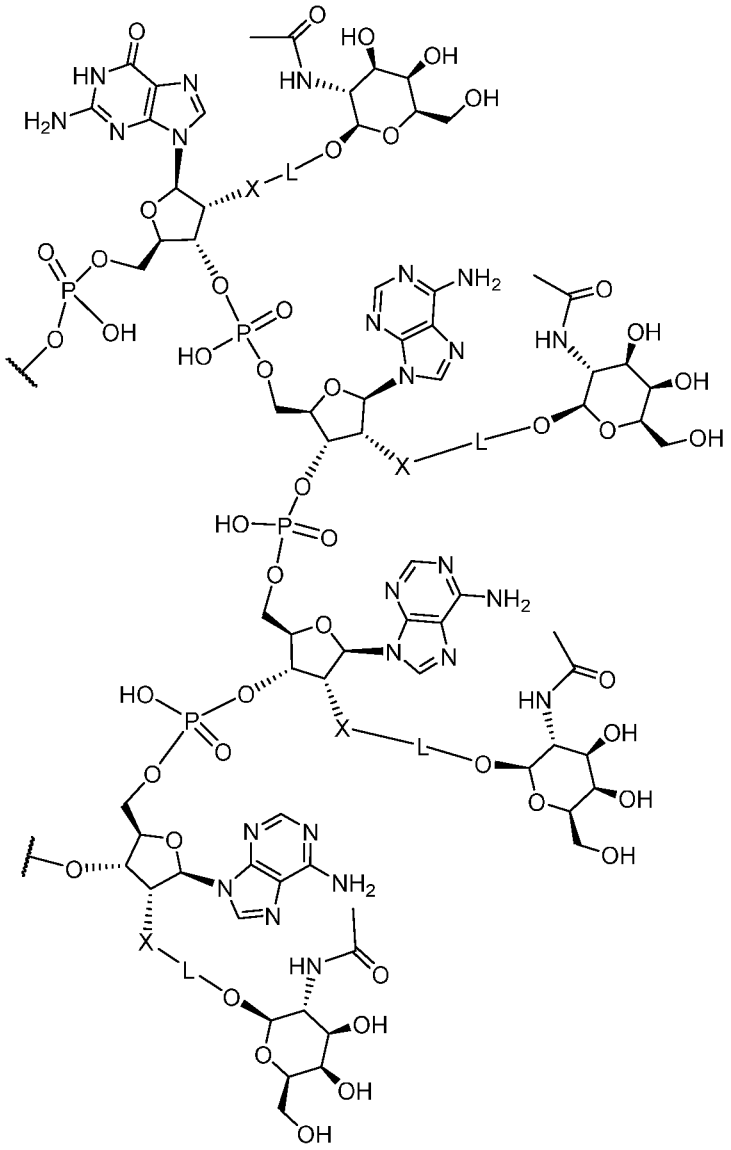
[00260] In some embodiments, an oligonucleotide herein comprises a monovalent GalNAc attached to an adenine nucleotide, referred to as [ademA-GalNAc] or 2′-aminodiethoxymethanol-Adenine-GalNAc, as depicted below in Chem 5:



Chem 5

[00261] 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

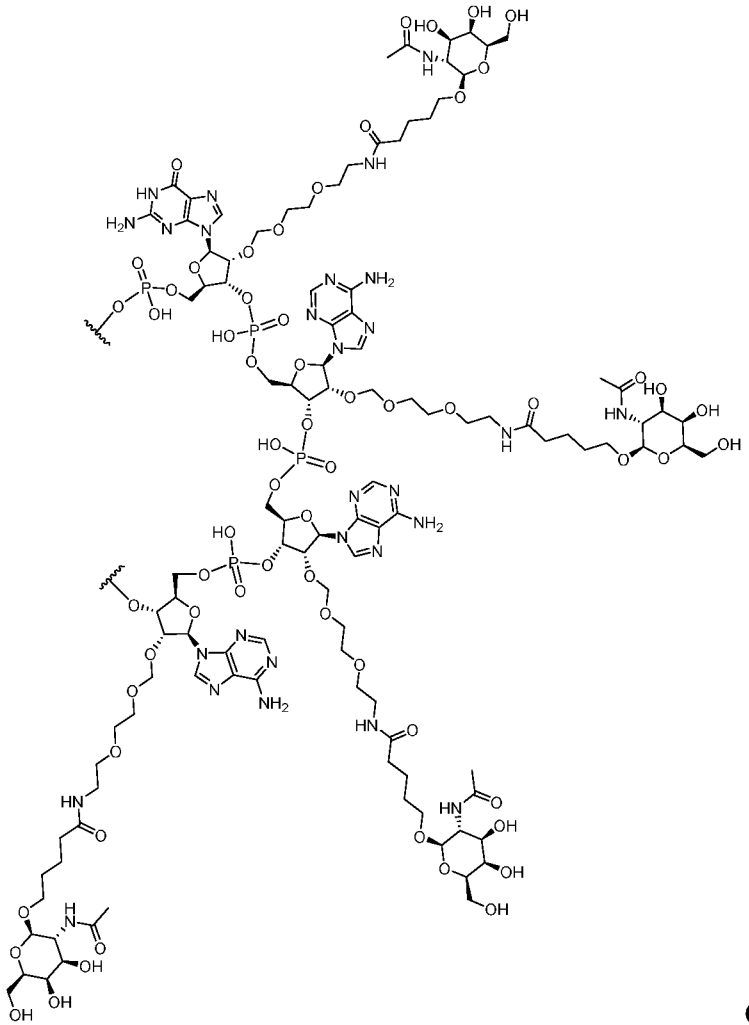
points are shown. Such a loop may be present, for example, at positions 27-30 of the sense strand as shown in **FIG. 1.** In the chemical formula, ≈ is used to describe an attachment point to the oligonucleotide strand (Chem 6).



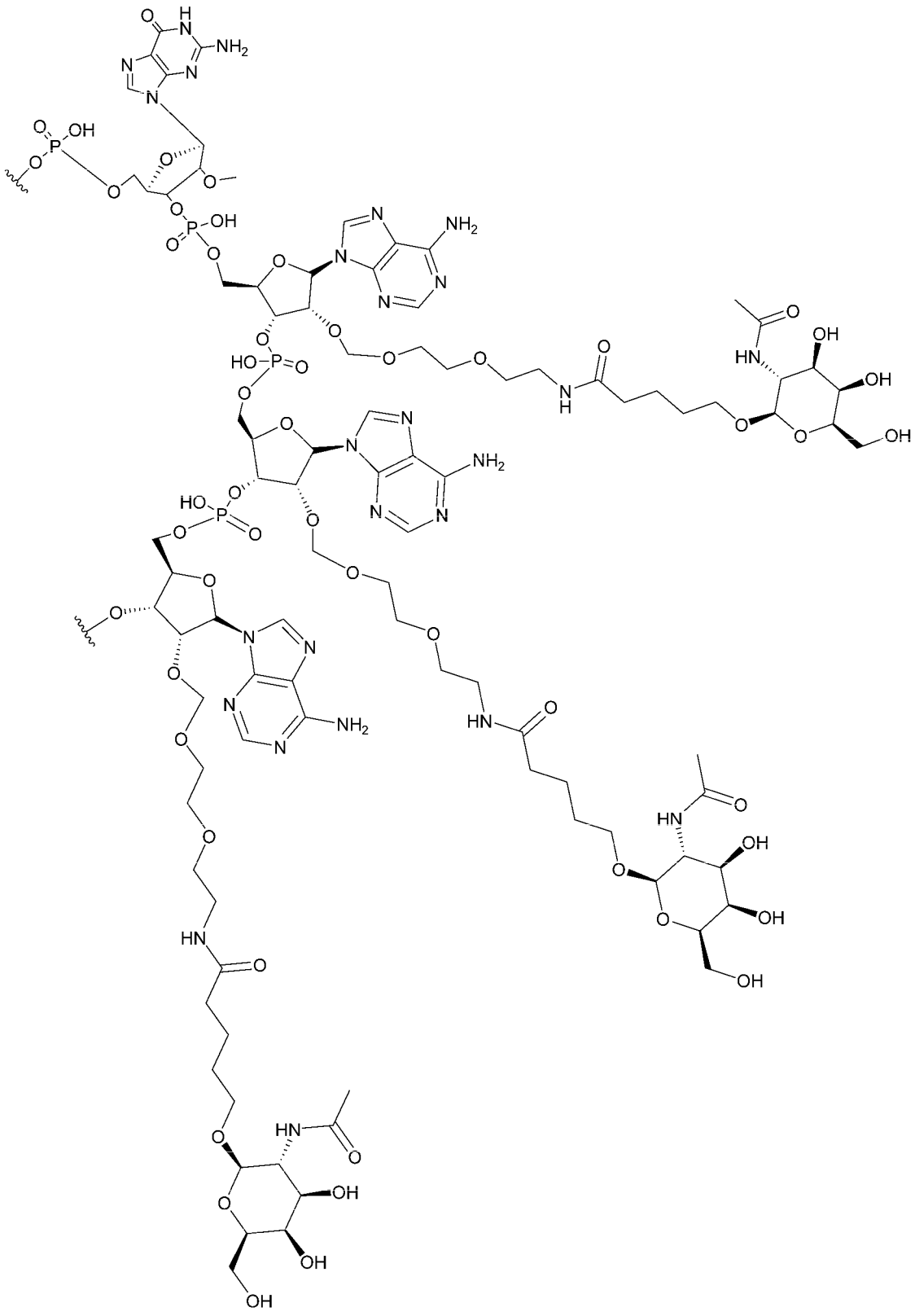
Chem 6

[00262] 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



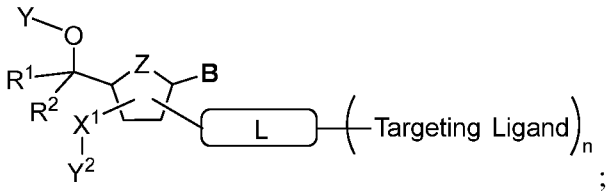
Chem 7.

[00263] 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.

[00264] 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

[00265] 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, $-S(O)_2R$, $-Si(OR)_2R$, $-Si(OR)R_2$, 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;

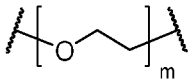
each R is independently hydrogen, a suitable protecting group, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered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

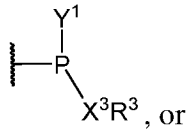
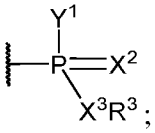
each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated 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;

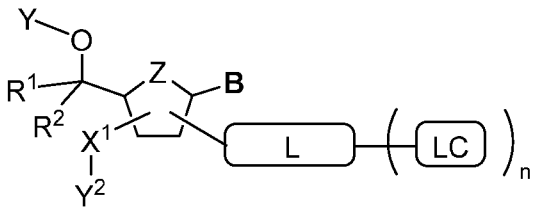
X^3 is -O-, -S-, -BH_2-, or a covalent bond;

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-.

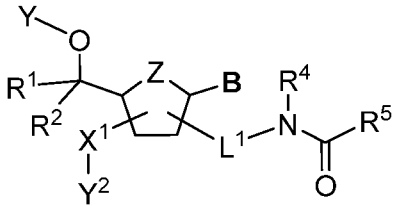
[00266] In some embodiments, the STAT3 targeting oligonucleotide comprises one or more nucleic acids conjugated with targeting ligands represented by formula **II-a**:



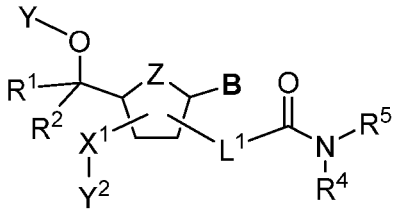
II-a.

or a pharmaceutically acceptable salt thereof.

[00267] 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**:

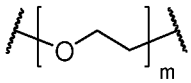


II-b



II-c

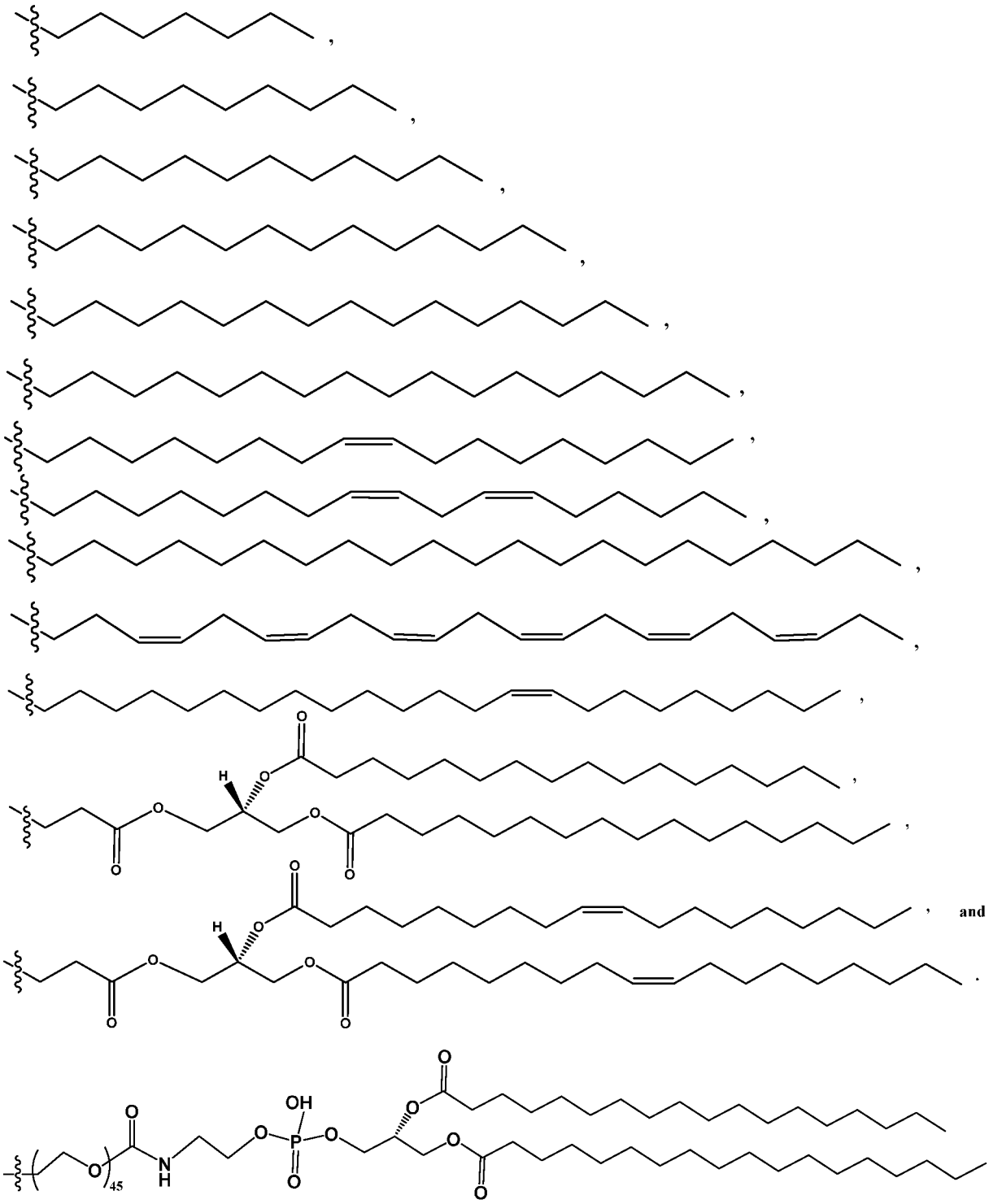
or a pharmaceutically acceptable salt thereof, wherein:

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  ;

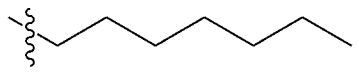
R^4 is hydrogen, R^A, or a suitable amine protection group; and

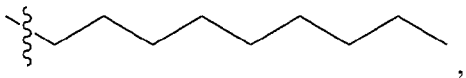
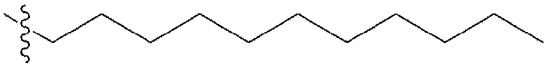
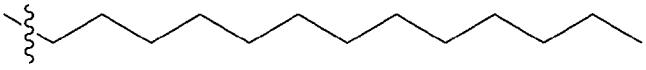
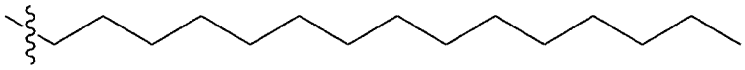
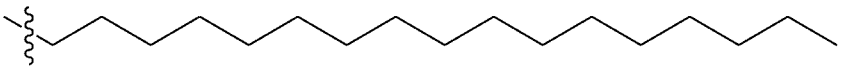
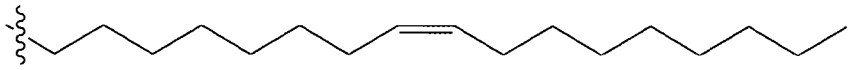
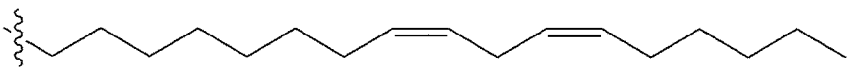
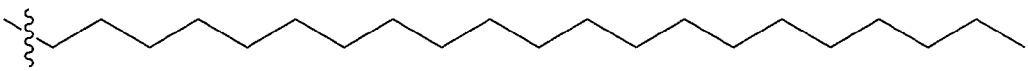
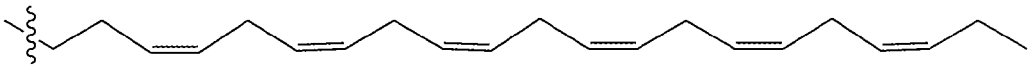
R^5 is adamantyl, or a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, or -P(S)OR.

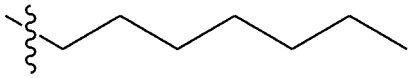
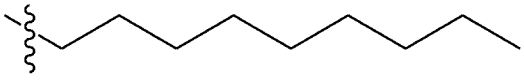
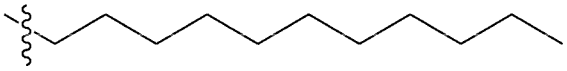
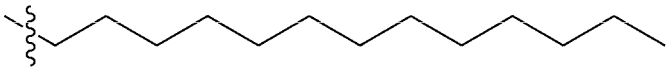
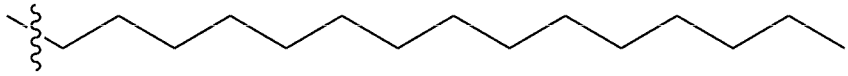
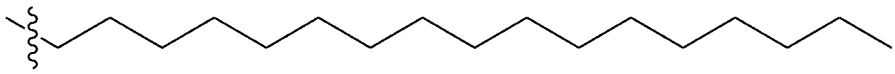
[00268] In some embodiments, R^5 is selected from

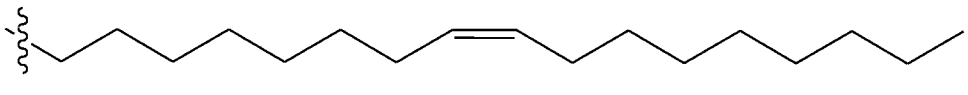


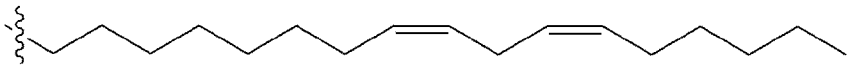
[00269] In some embodiments, R^5 is selected from:

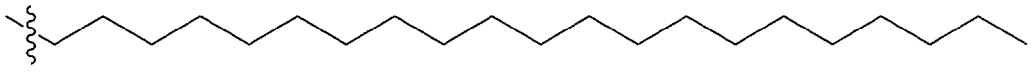


 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 .

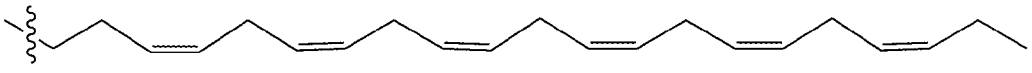
[00270] In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is  . In some embodiments, R^5 is



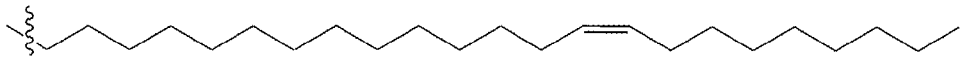
. In some embodiments, R^5 is  . In some embodiments, R^5 is



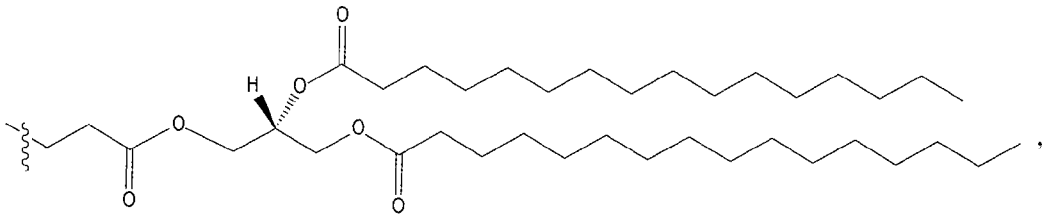
. In some embodiments, R^5 is



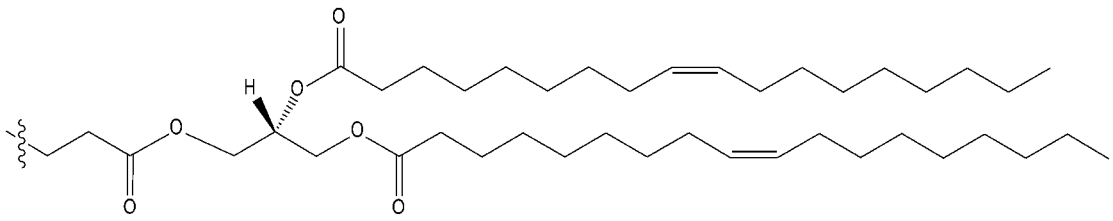
. In some embodiments, R^5 is



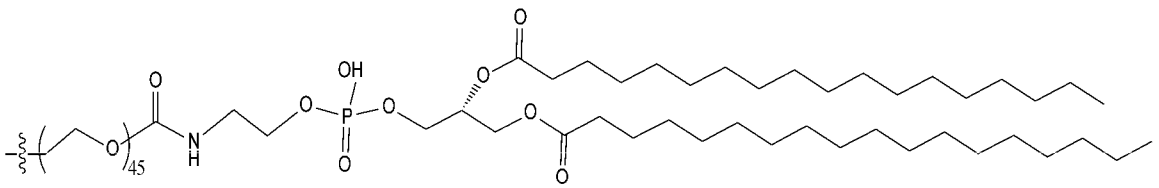
. In some embodiments, R^5 is



. In some embodiments, R^5 is

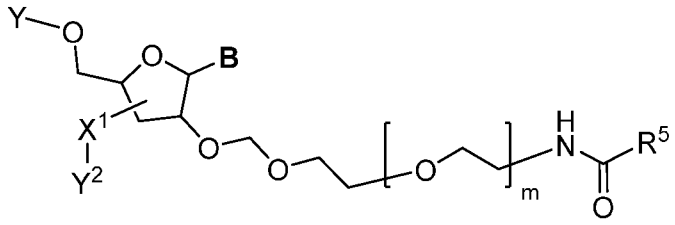


. In some embodiments, R^5 is

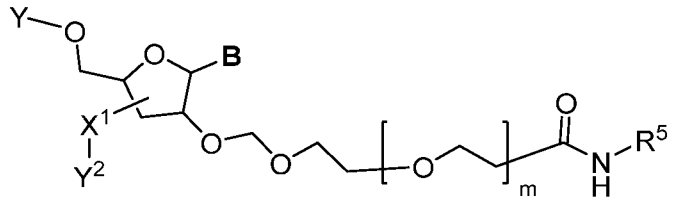


.

[00271] 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



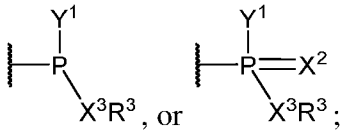
II-Ic

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,  ;

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;

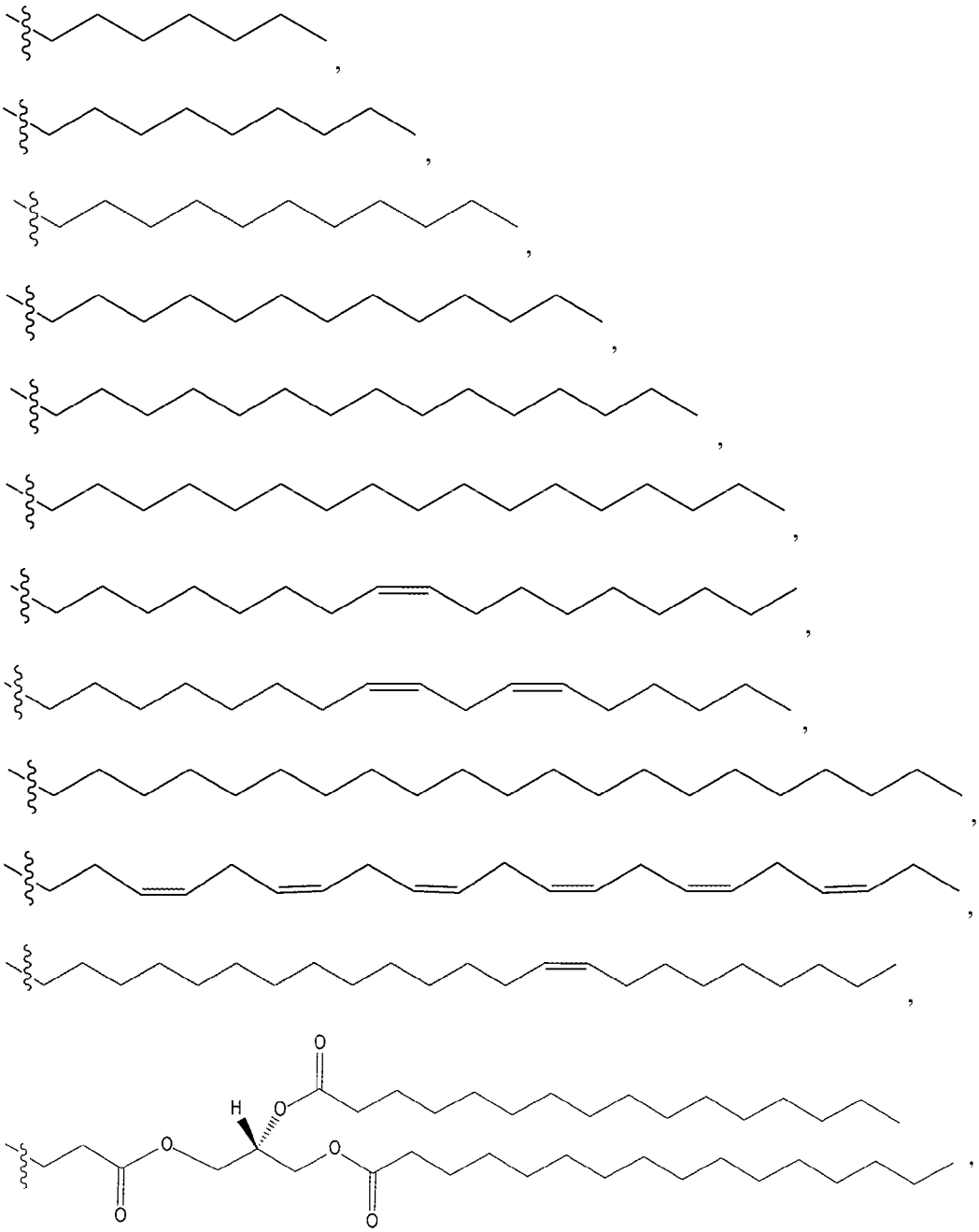
Y^2 is hydrogen, a phosphoramidite analogue, an internucleotide linking group attaching to the 5′-terminal of a nucleoside, a nucleotide, or an oligonucleotide, or a linking group attaching to a solid support;

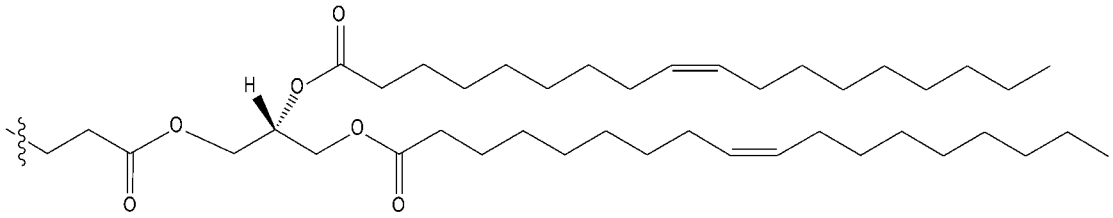
R^5 is adamantyl, or a saturated or unsaturated, straight, or branched C_{1-50} hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by -O-, -C(O)NR-, -NR-, -S-, -C(O)-, -C(O)O-, -S(O)-, -$S(O)_2$-, -P(O)OR-, or -P(S)OR-; and

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

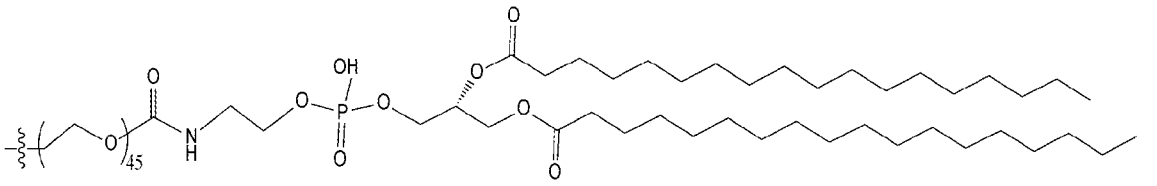
heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00272] In some embodiments, R^5 is selected from



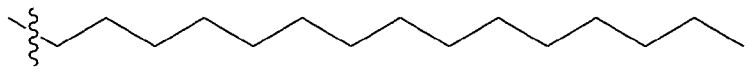


, and



.

[00273] In some embodiments, R^5 is



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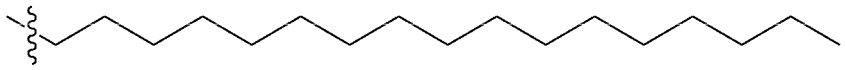
[00274] In some embodiments, R^5 is



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[00275] 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.

[00276] In some embodiments, the STAT3 targeting oligonucleotide is a double-stranded molecule. In some embodiments, the STAT3 targeting oligonucleotide is an RNAi molecule.

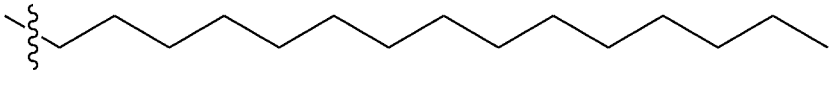
[00277] In some embodiments, the STAT3 targeting oligonucleotide comprises a sense strand of 36 nucleotides with positions numbered 1-36 from 5' to 3'.

[00278] In some embodiments, the STAT3 targeting oligonucleotide comprises a lipid conjugated to the 5' terminal nucleotide of the sense strand. In some embodiments, the STAT3 targeting oligonucleotide comprises a C16 lipid conjugated to the 5' terminal nucleotide of the sense strand. In some embodiments, the STAT3 targeting oligonucleotide comprises a C18 lipid conjugated to the 5' terminal nucleotide of the sense strand.

[00279] In some embodiments, any STAT3 targeting oligonucleotide sequence described herein comprises a lipid conjugated to the 5' terminal nucleotide of the sense strand. In some embodiments, any STAT3 targeting oligonucleotide sequence described herein comprises C16

lipid conjugated to the 5' terminal nucleotide of the sense strand. In some embodiments, any STAT3 targeting oligonucleotide sequence described herein comprises C18 lipid conjugated to the 5' terminal nucleotide of the sense strand.

[00280] In some embodiments, the STAT3 targeting oligonucleotide comprises a lipid conjugated to the 5' terminal nucleotide of the sense strand, wherein the lipid is



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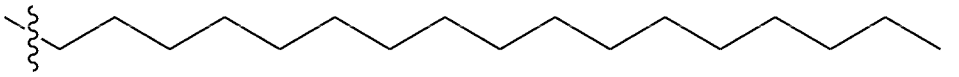
[00281] In some embodiments, the STAT3 targeting oligonucleotide comprises a lipid conjugated to the 5' terminal nucleotide of the sense strand, wherein the lipid is



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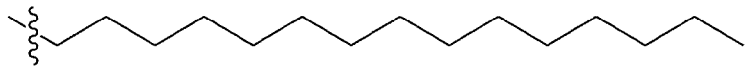
[00282] In some embodiments, a STAT3 targeting oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 140 and an antisense strand comprising the sequence set forth in SEQ ID NO: 333, wherein the sense strand comprises a lipid conjugated to the 5' terminal nucleotide. In some embodiments, a STAT3 targeting oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 140 and an antisense strand comprising the sequence set forth in SEQ ID NO: 333, wherein the sense strand comprises a C16 lipid conjugated to the 5' terminal nucleotide. In some embodiments, a STAT3 targeting oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 140 and an antisense strand comprising the sequence set forth in SEQ ID NO: 333, wherein the sense strand comprises a C18 lipid conjugated to the 5' terminal nucleotide.

[00283] In some embodiments, a STAT3 targeting oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 875 and an antisense strand comprising the sequence set forth in SEQ ID NO: 965, wherein the sense strand comprises a lipid conjugated to the 5' terminal nucleotide. In some embodiments, a STAT3 targeting oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 875 and an antisense strand comprising the sequence set forth in SEQ ID NO: 965, wherein the sense strand comprises a C16 lipid conjugated to the 5' terminal nucleotide. In some embodiments, a STAT3 targeting oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 875 and an antisense strand comprising the sequence set forth in SEQ ID NO: 965, wherein the sense strand comprises a C18 lipid conjugated to the 5' terminal nucleotide.

[00284] In some embodiments, a STAT3 targeting oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 140 and an antisense strand comprising the sequence set forth in SEQ ID NO: 333, wherein the sense strand comprises a lipid conjugated to the 5' terminal nucleotide, wherein the lipid is



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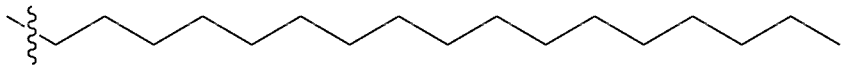
[00285] In some embodiments, a STAT3 targeting oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 140 and an antisense strand comprising the sequence set forth in SEQ ID NO: 333, wherein the sense strand comprises a lipid conjugated to the 5' terminal nucleotide, wherein the lipid is



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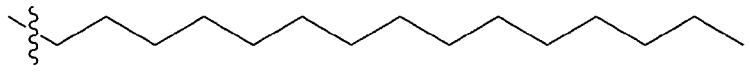
[00286] In some embodiments, a STAT3 targeting oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 875 and an antisense strand comprising the sequence set forth in SEQ ID NO: 965, wherein the sense strand comprises a lipid conjugated to the 5' terminal nucleotide, wherein the lipid is



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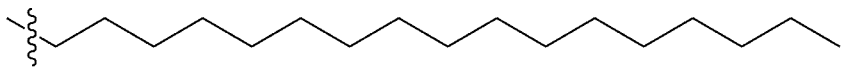
In some embodiments, a STAT3 targeting oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 875 and an antisense strand comprising the sequence set forth in SEQ ID NO: 965, wherein the sense strand comprises a lipid conjugated to the 5' terminal nucleotide, wherein the lipid is



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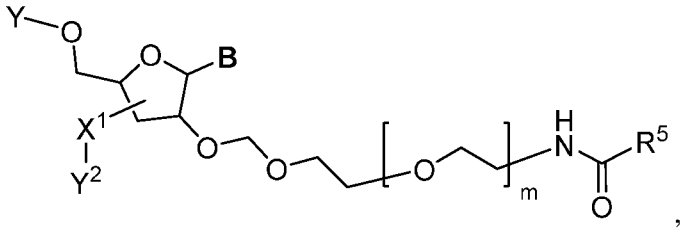
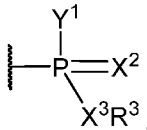
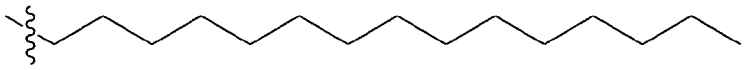
[00287] In some embodiments, a STAT3 targeting oligonucleotide comprises an antisense strand of 15 to 30 nucleotides and a sense strand of 15 to 40 nucleotide, wherein the sense and antisense strands form a duplex region, wherein the antisense strand comprises a region of complementarity to a *STAT3* 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 the 5' terminal nucleotide of the sense strand is represented by formula II-Ib:

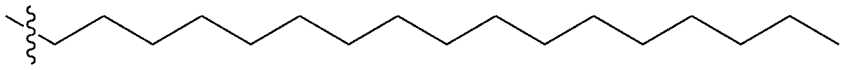


wherein B is selected from an adenine and a guanine nucleobase, and wherein R^5 is a hydrocarbon chain. In some embodiments, m is 1, X1 is O, Y2 is an internucleotide linking group attaching to the 5' terminal of a nucleoside,

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.

[00288] 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

 .

[00289] In some embodiments, the oligonucleotide comprises a sense strand comprising a sequence of SEQ ID NO: 140, wherein the sense strand comprises a C18 lipid.

Exemplary STAT3 Targeting Oligonucleotides

[00290]

[00291] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand and an antisense strand described herein, wherein the sense and antisense strands are modified based on the pattern below

Sense Strand: [ademXs-C18][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][mX][mX][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 7**).

In some embodiments, C# is C16 or C18.

[00292] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand and an antisense strand described herein, wherein the sense and antisense strands are modified based on the pattern below

Sense Strand: [ademXs-C#][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][mX][mX][mX][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 7**).

[00293] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprise SEQ ID NOs: 875 and 965, respectively.

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

Sense Strand: [ademXs-C18][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][mX][mX][mX][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][m]X[mX][mX][mXs][mXs][mX]

(key provided in **Table 7**). In some embodiments, C# is C16 or C18.

[00294] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand and an antisense strand comprising SEQ ID NOs: 875 and 965, respectively,

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

Sense Strand: [ademXs-C#][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][mX][mX][mX][mX][mX][mX][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 7**).

[00295] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense and antisense strand comprising SEQ ID NOs: 1222 and 1145, respectively.

[00296] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence of SEQ ID NO: 140. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence of SEQ ID NO: 875.

[00297] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence of SEQ ID NO: 333. In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence of SEQ ID NO: 965.

[00298] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence of SEQ ID NO: 875 and an antisense strand selected of SEQ ID NO: 965.

[00299] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence of SEQ ID NO: 1222.

[00300] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises an antisense strand sequence of SEQ ID NO:1145.

[00301] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises a sense strand sequence of SEQ ID NOs: 1222 and an antisense strand sequence of SEQ ID NO: 1145.

[00302] 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: 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: 1222 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.

[00303] 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%.

[00304] 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.

[00305] 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%.

[00306] 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 5' terminal nucleotide of the sense strand.

[00307] 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 5' terminal nucleotide of the sense strand.

[00308] 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 5' terminal nucleotide of the sense strand and reduces *STAT3* mRNA in humans.

[00309] 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 5' terminal nucleotide of the sense strand and reduces *STAT3* mRNA in humans by at least 75%.

[00310] 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 5' terminal nucleotide of the sense strand and reduces *STAT3* mRNA in humans by at least 75%.

[00311] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 1222 and the antisense strand sequence of SEQ ID NO: 1145, wherein the oligonucleotide reduces *STAT3* mRNA in humans.

[00312] In some embodiments, an oligonucleotide for reducing expression of *STAT3* mRNA comprises the sense strand sequence of SEQ ID NO: 1222 and the antisense strand sequence of SEQ ID NO: 1145, wherein the oligonucleotide reduces *STAT3* mRNA by at least 75%.

Formulations

[00313] 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.

[00314] 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.

[00315] 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).

[00316] 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).

[00317] 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.

[00318] 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.

[00319] 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.

[00320] Even though several embodiments are directed to liver-targeted delivery of any of the oligonucleotides herein, targeting of other tissues is also contemplated.

Programmed Death Ligand 1 (PD-L1) Inhibitors

[00321] In some embodiments, the disclosure provides a PD-L1 inhibitor for use in combination with an oligonucleotide described herein. In some embodiments, the PD-L1 inhibitor inhibits association of PD-L1 and PD-1. In some embodiments, the PD-L1 inhibitor is specific for PD-L1. In some embodiments, the PD-L1 inhibitor is an anti-PD-L1 antibody. In some embodiments, the PD-L1 inhibitor is specific for PD-1. In some embodiments, the PD-L1 inhibitor is an anti-PD-1 antibody. In some embodiments, the antibody is a full-length antibody. In some embodiments, the antibody is an antibody fragment. In some embodiments, the PD-L1 inhibitor is a small molecule.

[00322] In some embodiments, the anti-PD-L1 antibody is atezolizumab. In some embodiments, the anti-PD-L1 antibody is avelumab. In some embodiments, the anti-PD-L1 antibody is envafolimab. In some embodiments, the anti-PD-L1 antibody is durvalumab.

[00323] In some embodiments, the anti-PD-L1 antibody is any anti-PD-L1 antibody known in the art, including, but not limited to, the anti-PD-L1 antibodies disclosed in Akinleye & Rasool "Immune checkpoint inhibitors of PD-L1 as cancer therapeutics" *J. of Hematology & Oncology.* 12(92): 2019. In some embodiments, the anti-PD-L1 antibody is BMS-936559. In some embodiments, the anti-PD-L1 antibody is CK-301. In some embodiments, the anti-PD-L1 antibody is CS-1001. In some embodiments, the anti-PD-L1 antibody is SHR-1316. In some embodiments, the anti-PD-L1 antibody is BG-A333.

[00324] In some embodiments, the anti-PD-1 antibody is nivolumab. In some embodiments, the anti-PD-1 antibody is pembrolizumab. In some embodiments, the anti-PD-1 antibody is cemiplimab.

[00325] In some embodiments, the anti-PD-L1 antibody described herein binds to PD-L1 with an

affinity of about 30nM to about 100nM. In some embodiments, the anti-PD-L1 antibody described herein binds to PD-L1 with an affinity of about 30nM. In some embodiments, the anti-PD-L1 antibody described herein binds to PD-L1 with an affinity of about 40nM. In some embodiments, the anti-PD-L1 antibody described herein binds to PD-L1 with an affinity of about 50nM. In some embodiments, the anti-PD-L1 antibody described herein binds to PD-L1 with an affinity of about 60nM. In some embodiments, the anti-PD-L1 antibody described herein binds to PD-L1 with an affinity of about 70nM. In some embodiments, the anti-PD-L1 antibody described herein binds to PD-L1 with an affinity of about 80nM. In some embodiments, the anti-PD-L1 antibody described herein binds to PD-L1 with an affinity of about 90nM. In some embodiments, the anti-PD-L1 antibody described herein binds to PD-L1 with an affinity of about 100nM.

[00326] In some embodiments, the anti-PD-1 antibody described herein binds to PD-1 with an affinity of about 30nM to about 100nM. In some embodiments, the anti-PD-1 antibody described herein binds to PD-1 with an affinity of about 30nM. In some embodiments, the anti-PD-1 antibody described herein binds to PD-1 with an affinity of about 40nM. In some embodiments, the anti-PD-1 antibody described herein binds to PD-1 with an affinity of about 50nM. In some embodiments, the anti-PD-1 antibody described herein binds to PD-1 with an affinity of about 60nM. In some embodiments, the anti-PD-1 antibody described herein binds to PD-1 with an affinity of about 70nM. In some embodiments, the anti-PD-1 antibody described herein binds to PD-1 with an affinity of about 80nM. In some embodiments, the anti-PD-1 antibody described herein binds to PD-1 with an affinity of about 90nM. In some embodiments, the anti-PD-1 antibody described herein binds to PD-1 with an affinity of about 100nM.

[00327] In some embodiments, the antibody is generated using display technologies. Display technologies used to generate antibody polypeptides include any of the display techniques (e.g., display library screening techniques). In some embodiments, synthetic antibodies are designed, selected, or optimized by screening target antigens using display technologies (e.g., phage display technologies). Phage display libraries may comprise millions to billions of phage vectors, each expressing unique antibody fragments on their viral coats. Such libraries may provide richly diverse resources that are used to select potentially hundreds of antibody fragments with diverse levels of affinity for one or more antigens of interest (McCafferty, et al., 1990. Nature.348:552-4; Edwards, B.M. et al., 2003. JMB.334: 103-18; Schofield, D. et al., 2007. Genome Biol.8, R254 and Pershad, K. et al., 2010. Protein

Engineering Design and Selection.23:279-88; the contents of each of which are herein incorporated by reference in their entirety). Often, the antibody fragments present in such libraries comprise scFv antibody fragments, comprising a fusion protein of V_H and V_L antibody domains joined by a flexible linker. In some cases, scFvs may contain the same sequence with the exception of unique sequences encoding variable loops of the CDRs. In some cases, scFvs are expressed as fusion proteins, linked to viral coat proteins (e.g., the N-terminus of the viral pill coat protein). VL chains may be expressed separately for assembly with VH chains in the periplasm prior to complex incorporation into viral coats. Precipitated library members may be sequenced from the bound phage to obtain cDNA encoding desired scFvs. Antibody variable domains or CDRs from such sequences may be directly incorporated into antibody sequences for recombinant antibody production or mutated and utilized for further optimization through in vitro affinity maturation.

[00328] In some embodiments, the sequences of the polypeptides to be encoded in the viral genomes are produced using yeast surface display technology. In some embodiments, recombinant antibodies are developed by displaying the antibody fragment of interest as a fusion to on the surface of the yeast, where the protein interacts with proteins and small molecules in a solution. scFvs with affinity toward desired receptors may be isolated from the yeast surface using magnetic separation and flow cytometry. Several cycles of yeast surface display and isolation may be done to attain scFvs with desired properties through directed evolution.

[00329] Methods for determining the affinity of an antibody for its antigen are known in the art. An exemplary method for determining binding affinity employs surface plasmon resonance. Surface plasmon resonance is an optical phenomenon that allows for the analysis of realtime biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.). For further descriptions, see Jonsson, U., et al. (1993) Ann. Biol. Clin. 51: 19-26; Jonsson, U., i (1991) Biotechniques 11 :620-627; Johnsson, B., et al. (1995) J. Mol.Recognit. 8: 125-131; and Johnsson, B., et al. (1991) Anal. Biochem. 198:268-277.

Kits

[00330] In some embodiments, the disclosure provides a kit comprising a STAT3 oligonucleotide herein, and instructions for administering the STAT3 oligonucleotide to a

subject. In some embodiments, the disclosure provides a kit comprising a STAT3 oligonucleotide herein, and instructions for administering the STAT3 oligonucleotide to a subject that has received or is receiving a PD-L1 inhibitor. 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.

[00331] In some embodiments, a kit comprises a STAT3 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 a STAT3 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, wherein the subject has received or is receiving a PD-L1 inhibitor. In some embodiments, a kit comprises a STAT3 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. In some embodiments, a kit comprises a STAT3 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, wherein the subject has received or is receiving a PD-L1 inhibitor.

[00332] In some embodiments, a kit comprises a PD-L1 inhibitor, 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 in a subject in

need thereof, wherein the subject has received or is receiving a STAT3 oligonucleotide described herein. In some embodiments, a kit comprises a PD-L1 inhibitor, 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, wherein the subject has received or is receiving a STAT3 oligonucleotide described herein.

EXAMPLES

[00333] 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.

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

°C: 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

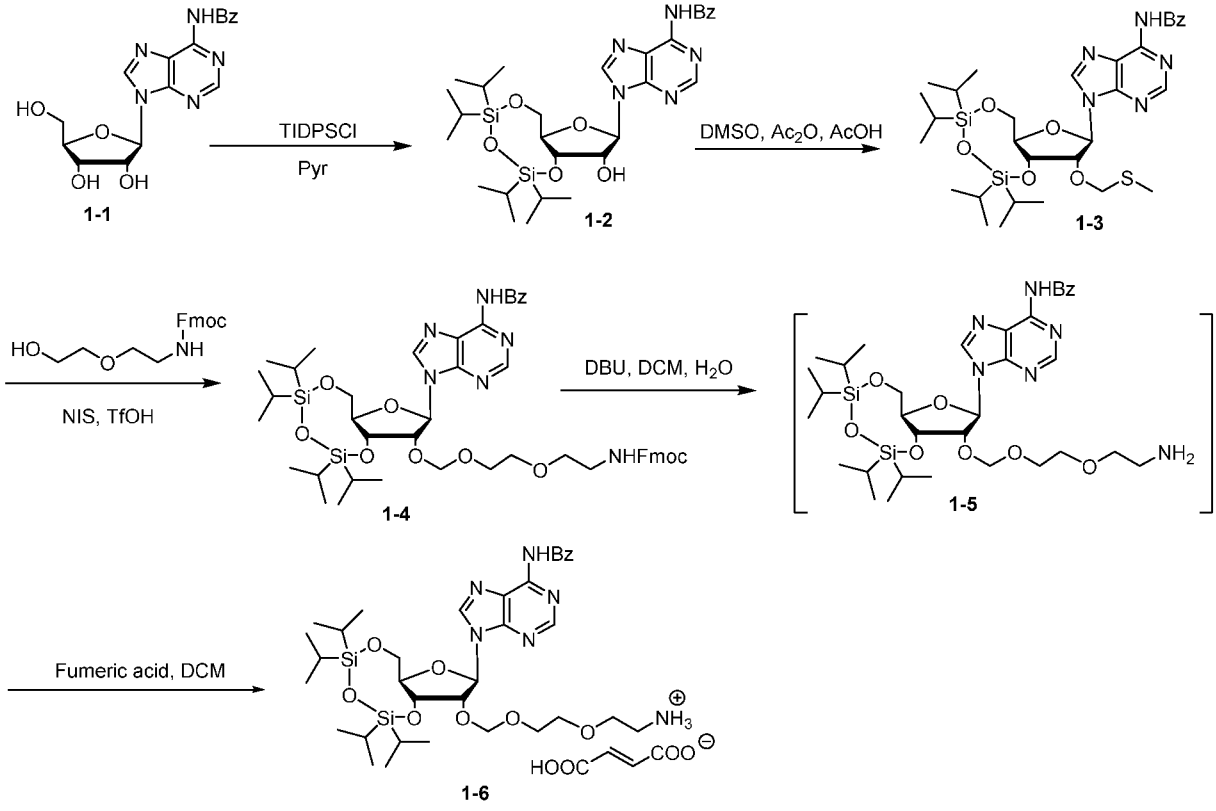
[00334] The following examples are intended to illustrate the disclosure and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade (C). If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 mm Hg and 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.

[00335] 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.

[00336] All reactions are carried out under nitrogen or argon unless otherwise stated.

[00337] 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. 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)



[00338] 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

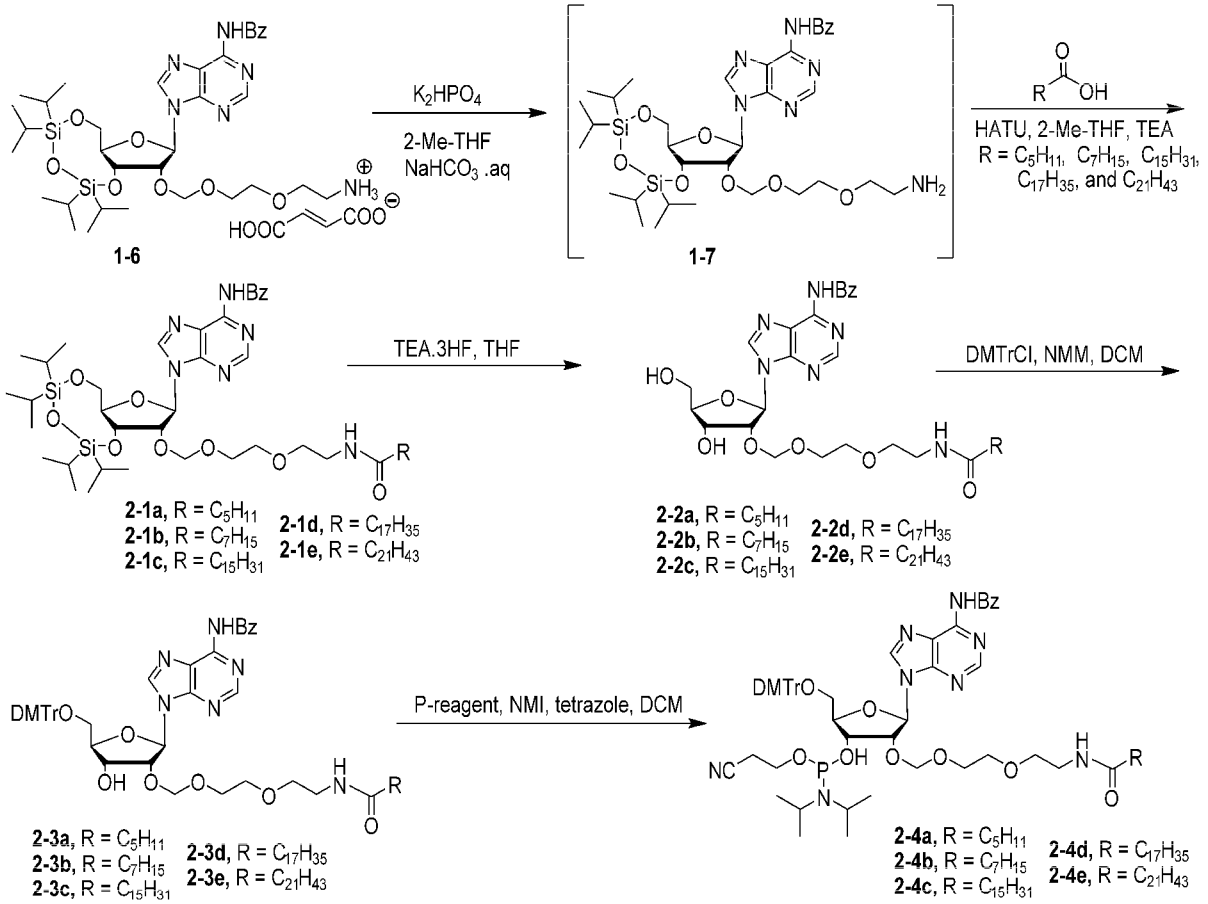
mmol) at 10 °C. The resulting mixture was stirred at 25 °C for 3 h and quenched with 20% citric acid (50 mL). The aqueous layer was extracted with EtOAc (3X50 mL) and the combined organic layers were concentrated *in vacuo*. The crude residue was recrystallized from a mixture of MTBE and n-heptane (1:15, 320 mL) to afford compound **1-2** (37.20 g, 90%) as a white oily solid.

[00339] 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.

[00340] 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.

[00341] 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)



[00342] 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.

[00343] 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.
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.

[00344] 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.

[00345] 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.

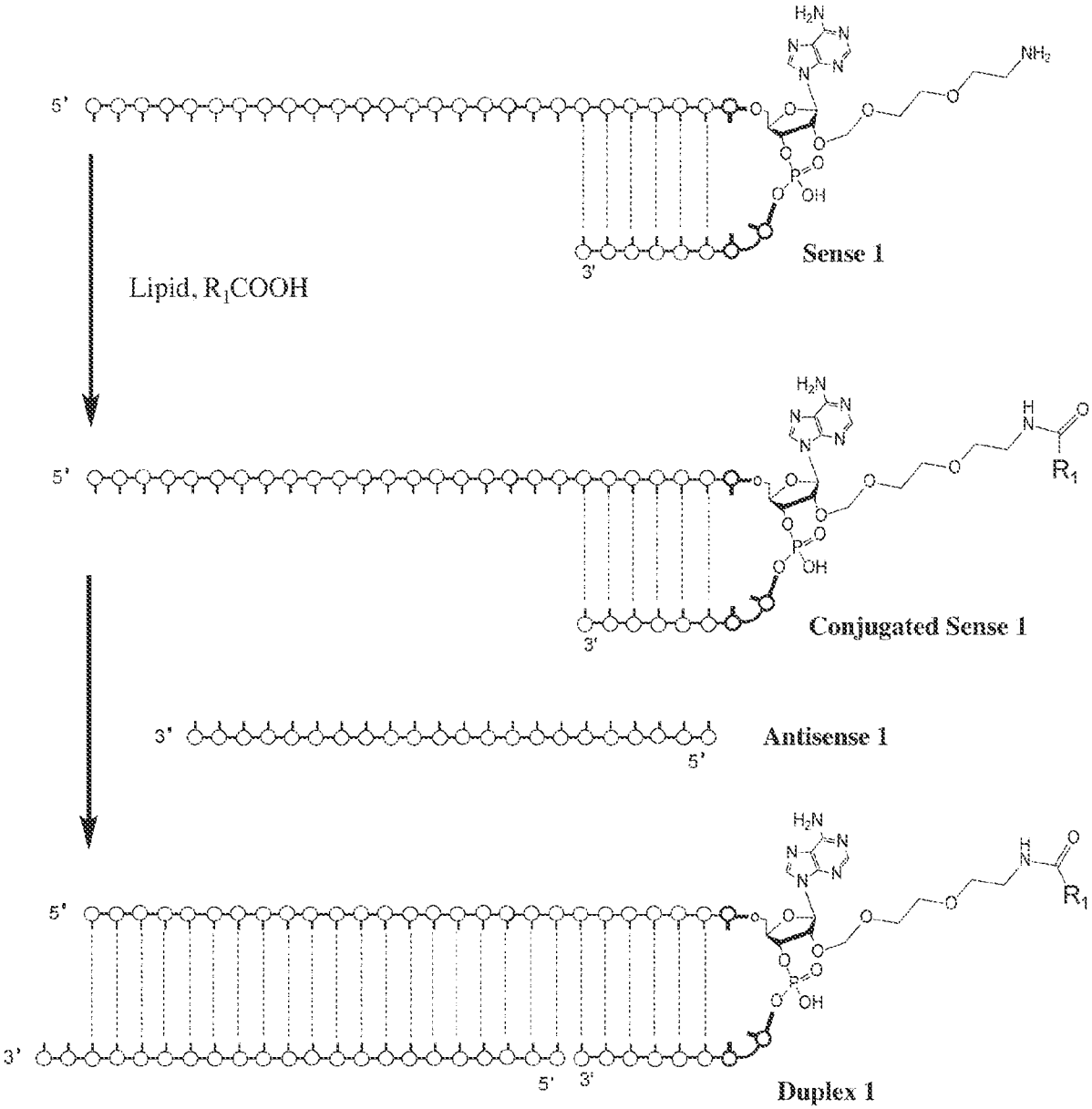
[00346] Compound **2-4c** was obtained (36.60 g, 66.3%) as an off-white solid: ^{1}H NMR (400 MHz, *d*$_6$-DMSO) 11.22 (s, 1H), 8.64-8.59 (m, 2H), 8.05-8.00 (m, 2H), 7.73-7.70 (m, 1H), 7.67-7.60 (m, 1H), 7.59-7.51 (m, 2H), 7.38-7.34 (m, 2H), 7.30-7.25 (m, 7H), 6.89-6.80 (m, 4H), 6.21-6.15 (m, 1H), 5.25-5.17 (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.

[00347] 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.

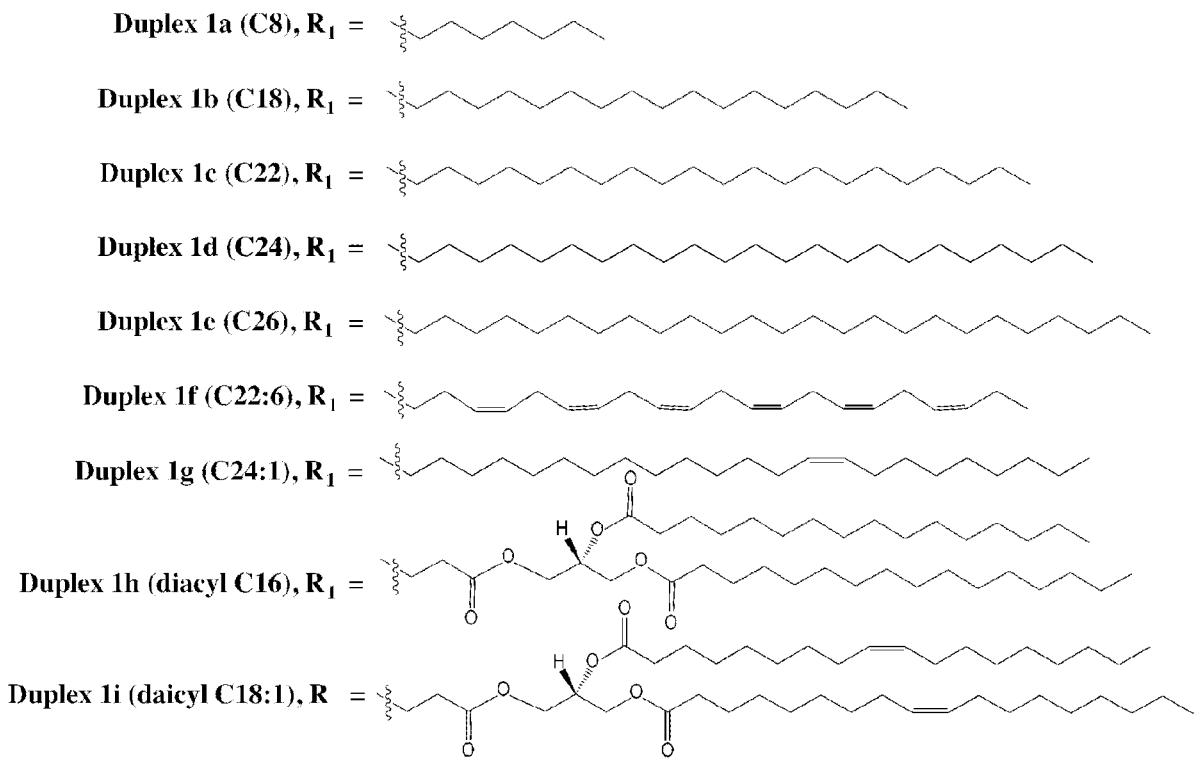
[00348] Compound **2-4e** was obtained (38.10 g, 54.0%) as a white solid: ^{1}H NMR (400 MHz, *d*$_6$-DMSO) 11.21 (s, 1H), 8.64-8.59 (m, 2H), 8.05-8.00 (m, 2H), 7.73-7.70 (m, 1H), 7.67-7.60 (m, 1H), 7.59-7.51 (m, 2H), 7.38-7.34 (m, 2H), 7.30-7.25 (m, 7H), 6.89-6.80 (m, 4H), 6.21-6.15 (m, 1H), 5.23-5.17 (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.



[00349] 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



Synthesis **Sense 1** and **Antisense 1** were prepared by solid-phase synthesis.

Synthesis of **Conjugated Sense 1a-1i**.

[00350] **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).

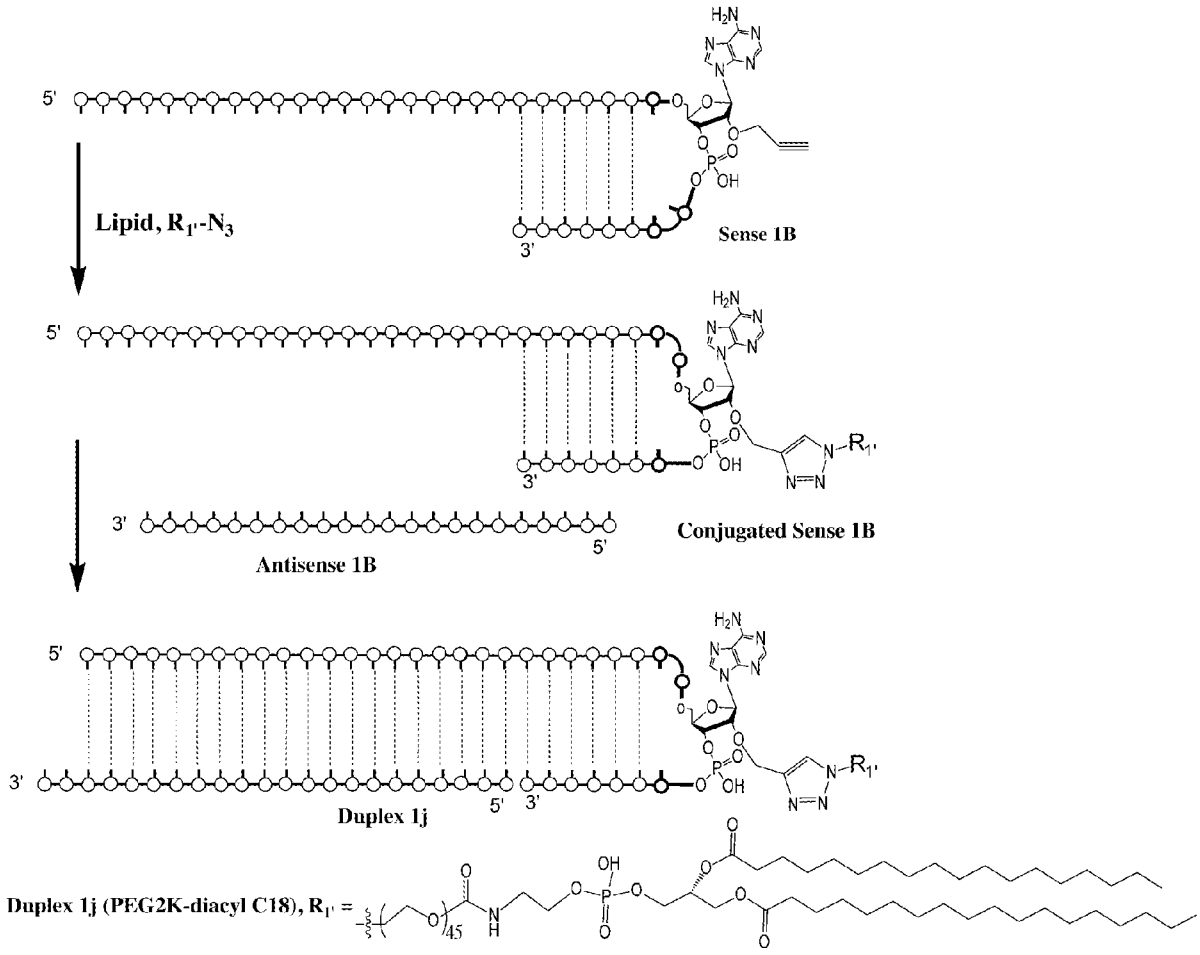
[00351] **Conjugated Sense 1b-1i** were prepared using similar procedures as described for the synthesis of **Conjugated Sense 1a** and obtained in 42%-69% yields.

[00352] Annealing of Duplex 1a-1j.

[00353] **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.

[00354] **Duplex 1b-1i** were prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00355] 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

[00356] **Sense 1B** and **Antisense 1B** were prepared by solid-phase synthesis.

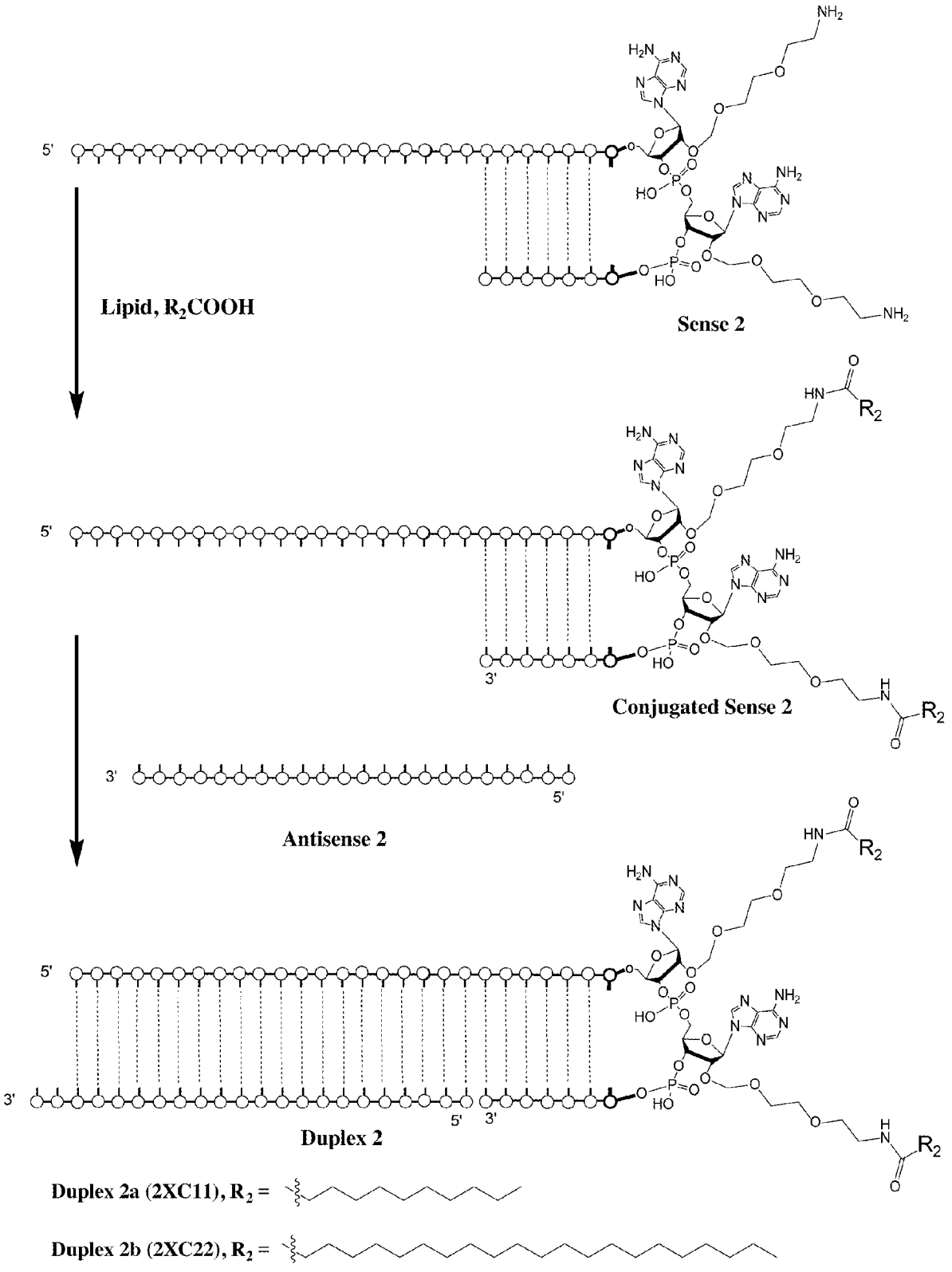
[00357] Synthesis of Conjugated Sense 1j.

[00358] 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).

[00359] **Duplex 1j (PEG2K-diacyl C18)** was prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00360] The following Scheme 1-3 depicts the synthesis of Nicked tetraloop GalXC conjugates with di-lipid on the loop using post-synthetic conjugation approach.


5'
Lipid, R2COOH
Sense 2
5'
3'
Conjugated Sense 2
3'
5'
Antisense 2
5'
3'
5'
3'
Duplex 2
Duplex 2a (2XC11), R2 =
Duplex 2b (2XC22), R2 =

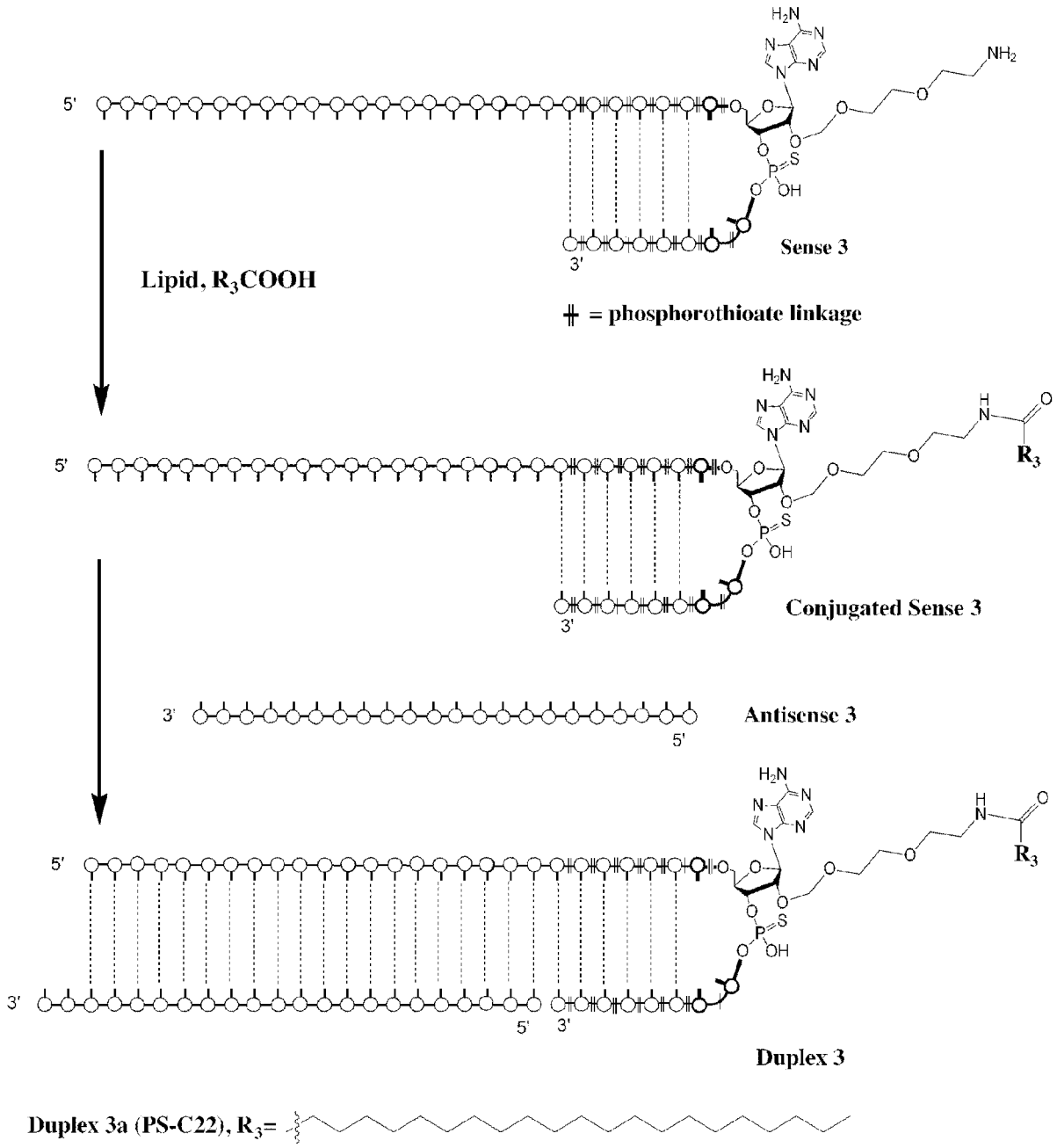
Scheme1-3

Sense 2 and **Antisense 2** were prepared by solid-phase synthesis.

[00361] **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.

[00362] **Duplex 2a (2XC11)** and **2b (2XC22)** were prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00363] The following Scheme 1-4 depicts the synthesis of GalXC of fully phosphorothioated stem-loop conjugated with mono-lipid using post-synthetic conjugation approach.



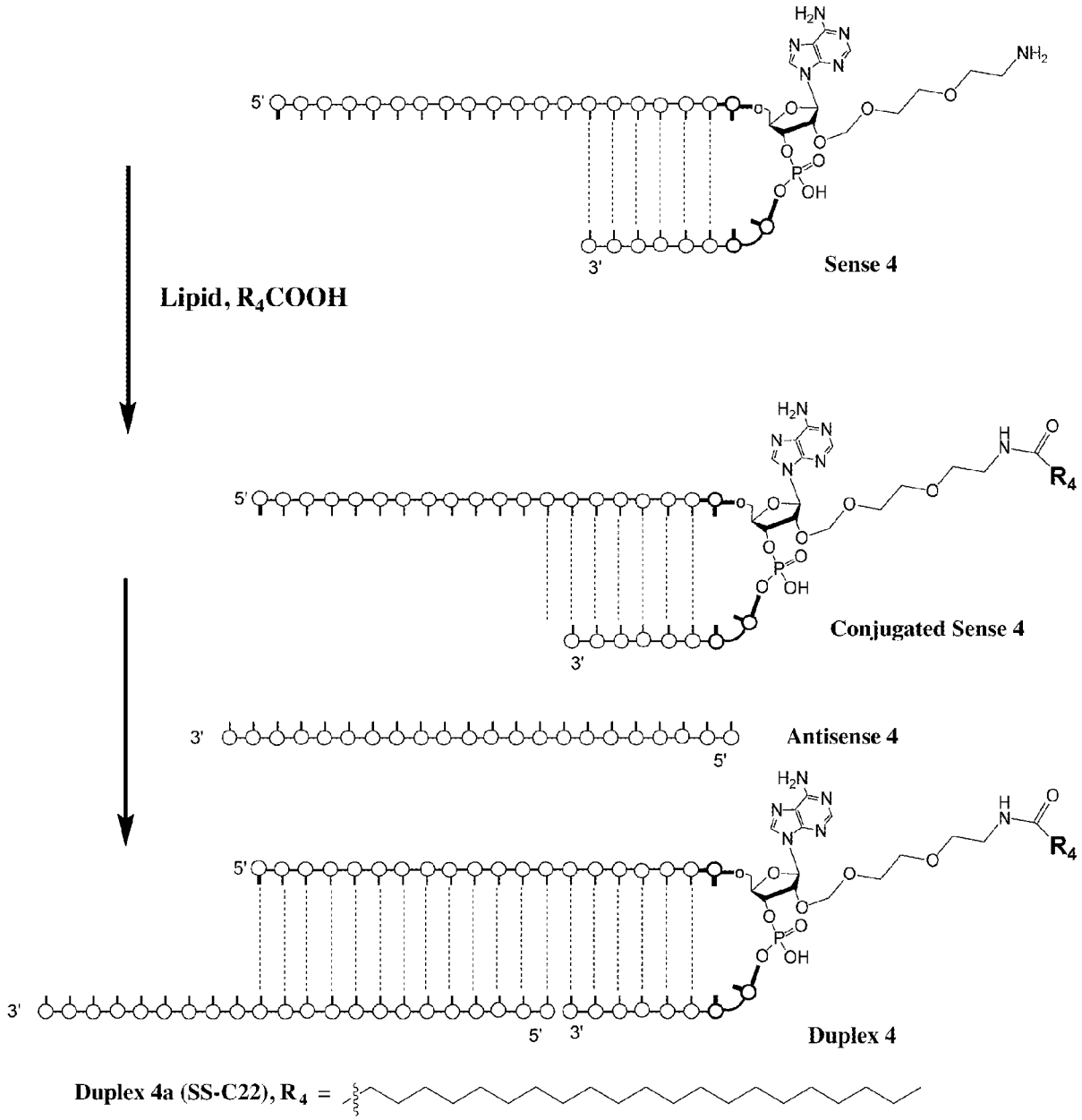
Scheme1-4

Sense 3 and **Antisense 3** were prepared by solid-phase synthesis.

[00364] **Conjugated Sense 3a** was prepared using similar procedures as described for the synthesis of **Conjugated Sense 1a** and obtained in a 65% yield.

[00365] **Duplex 3a (PS-C22)** was prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00366] The following Scheme1-5 depicts the synthesis of GalXC of short sense conjugated with mono-lipid using post-synthetic conjugation approach.



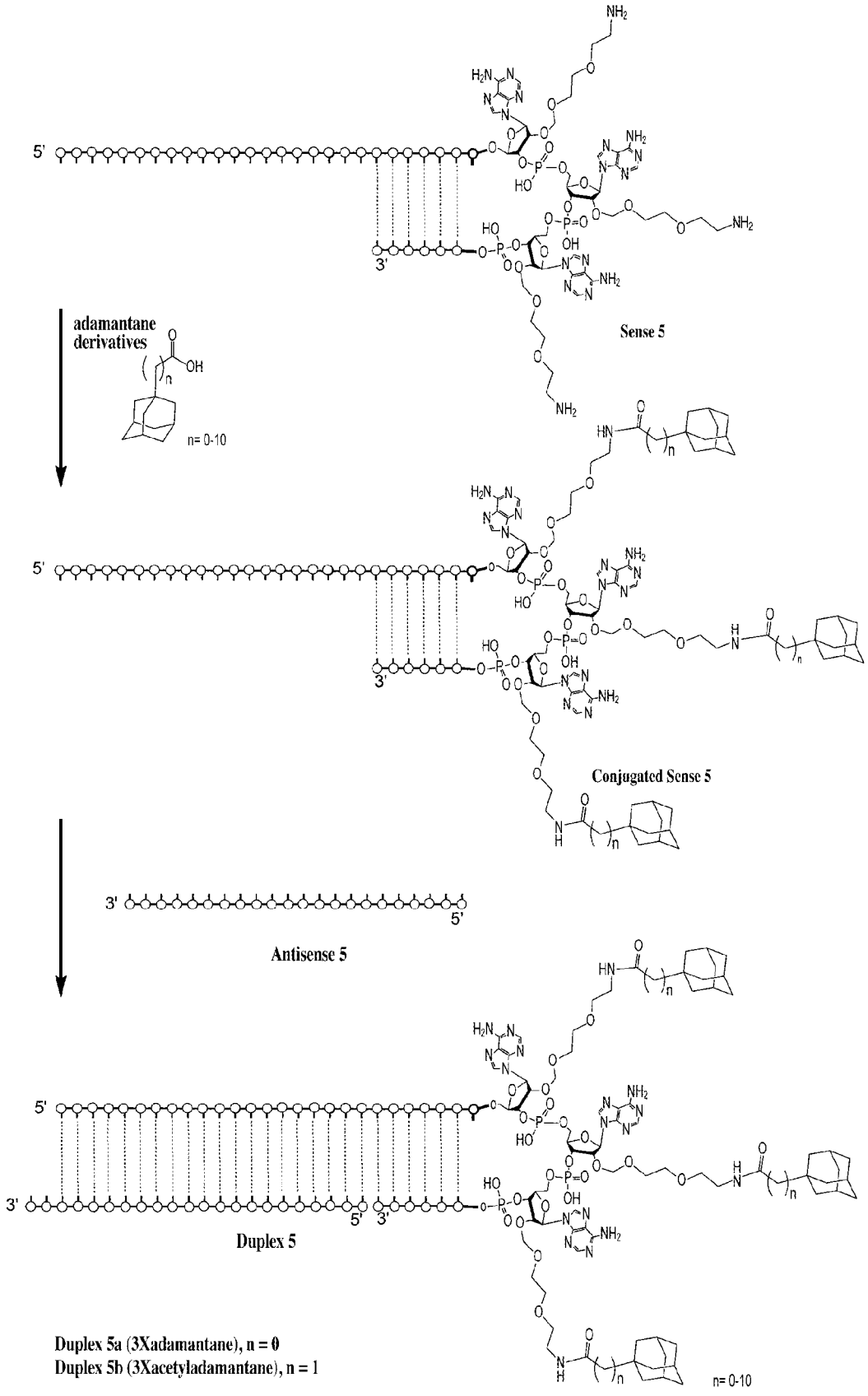
Scheme 1-5

Sense 4 and **Antisense 4** were prepared by solid-phase synthesis.

[00367] **Conjugated Sense 4a** was prepared using similar procedures as described for the synthesis of **Conjugated Sense 1a** and obtained in a 74% yield.

[00368] **Duplex 4a (SS-C22)** was prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00369] 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.


adamantane derivatives
n= 0-10
Sense 5
Conjugated Sense 5
Antisense 5
Duplex 5
Duplex 5a (3Xadamantane), n = 0
Duplex 5b (3Xacetyladamantane), n = 1
n= 0-10

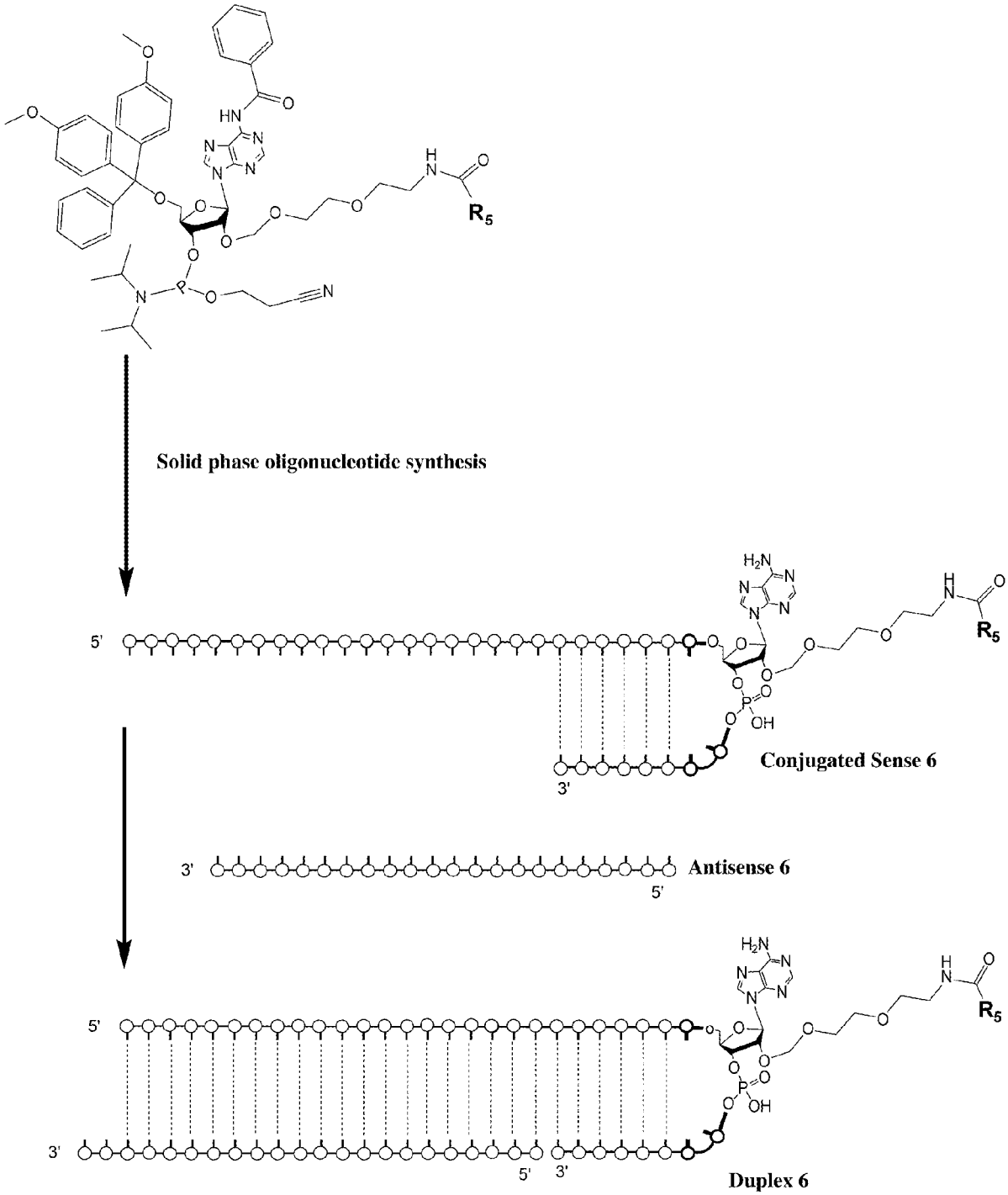
Scheme1-6

Sense 5 and **Antisense 5** were prepared by solid-phase synthesis.

[00370] **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.

[00371] **Duplex 5a (3Xadamantane)** and **Duplex 5b (3Xacetyladamantane)** were prepared using the same procedures as described for the annealing of **Duplex 1a (C8)**.

[00372] 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

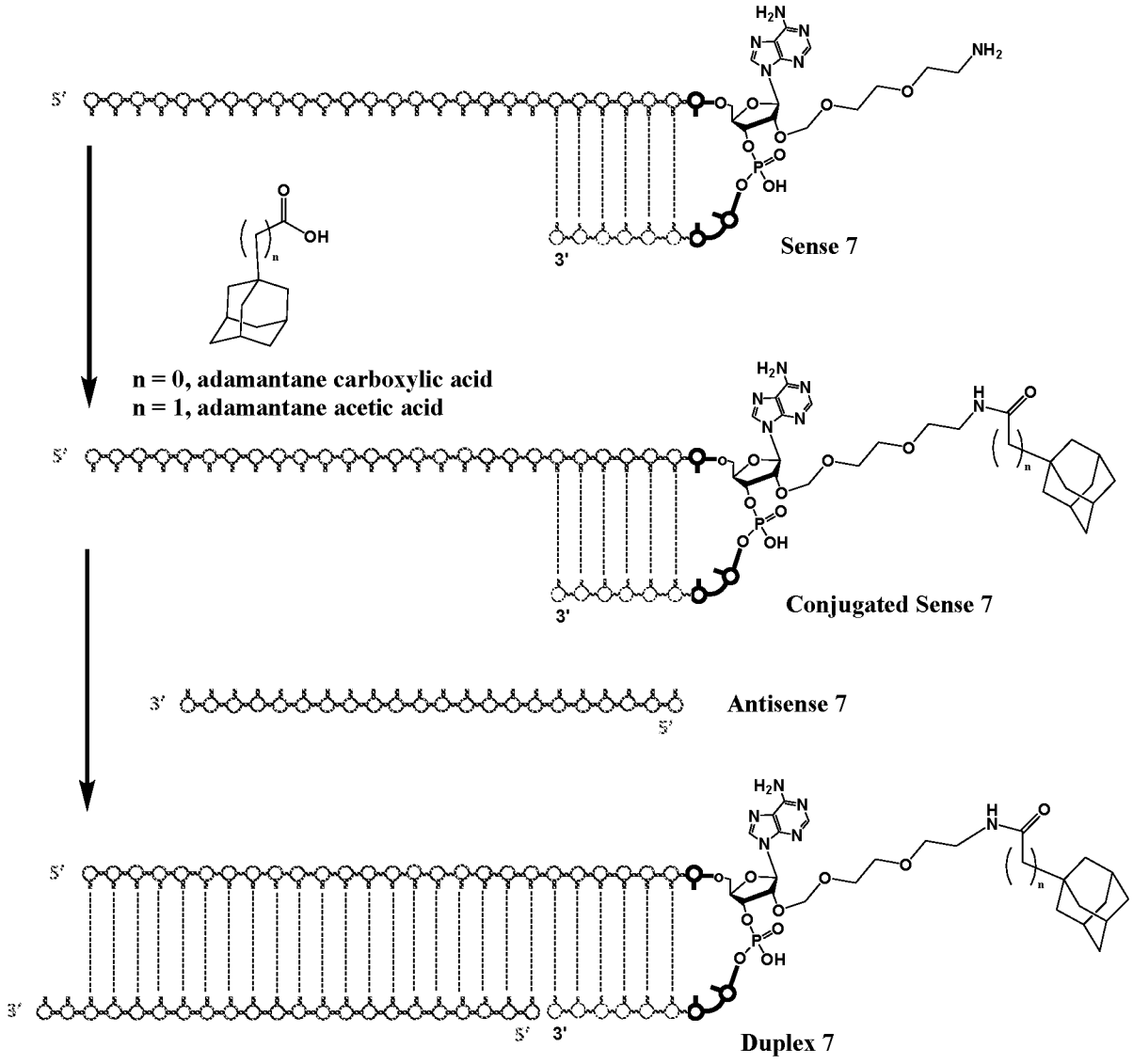
Synthesis of Conjugated Sense 6.

[00373] **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.**

[00374] **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

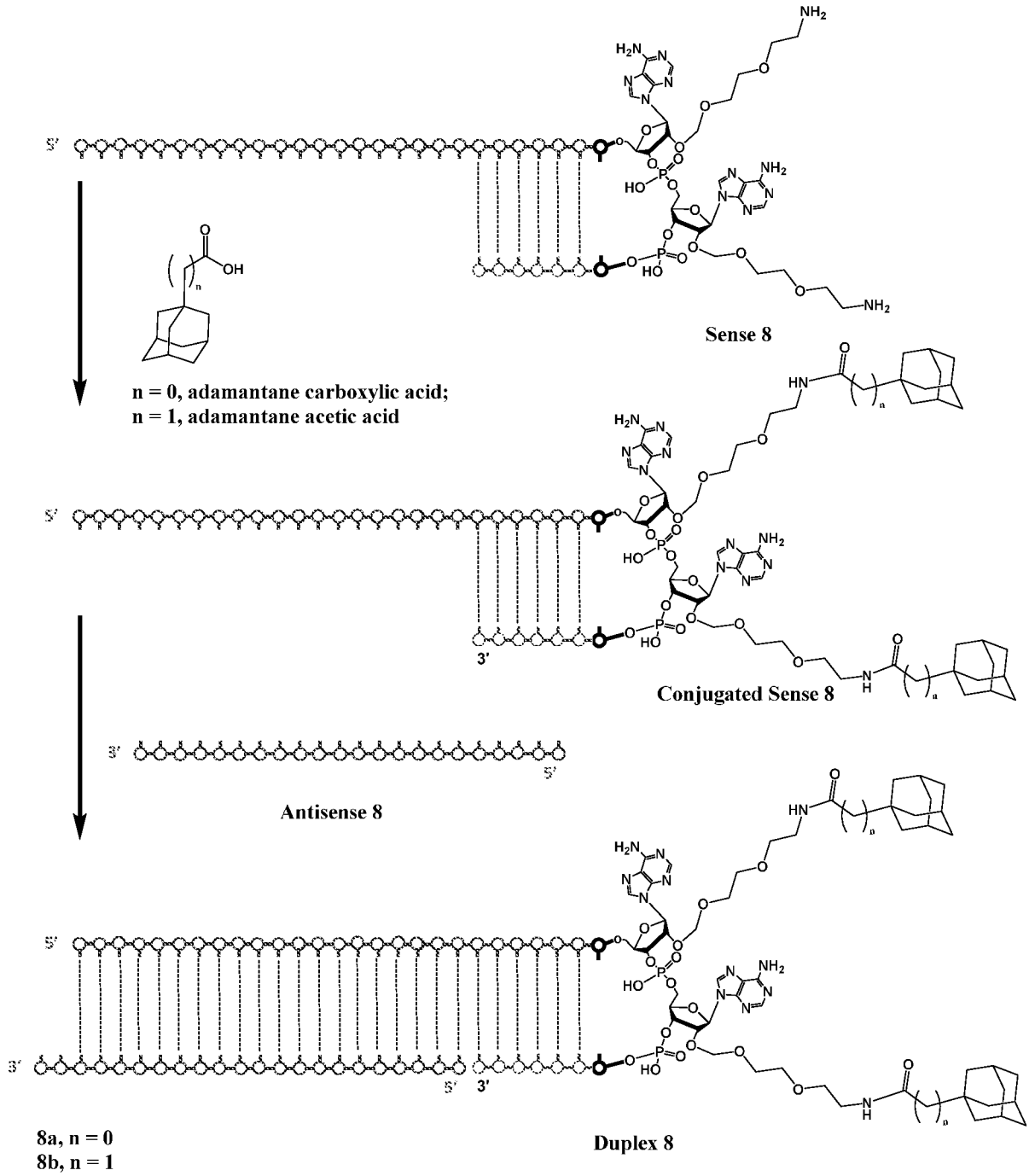
Synthesis of **Conjugated Sense 7a and 7b**

[00375] **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**

[00376] **Duplex 7a** and **Duplex 7b** were obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00377] **Scheme 9.** Synthesis of nicked tetraloop GalXC conjugated with two adamantane units on the loop *via* a post-synthetic conjugation approach.



Scheme 1-9

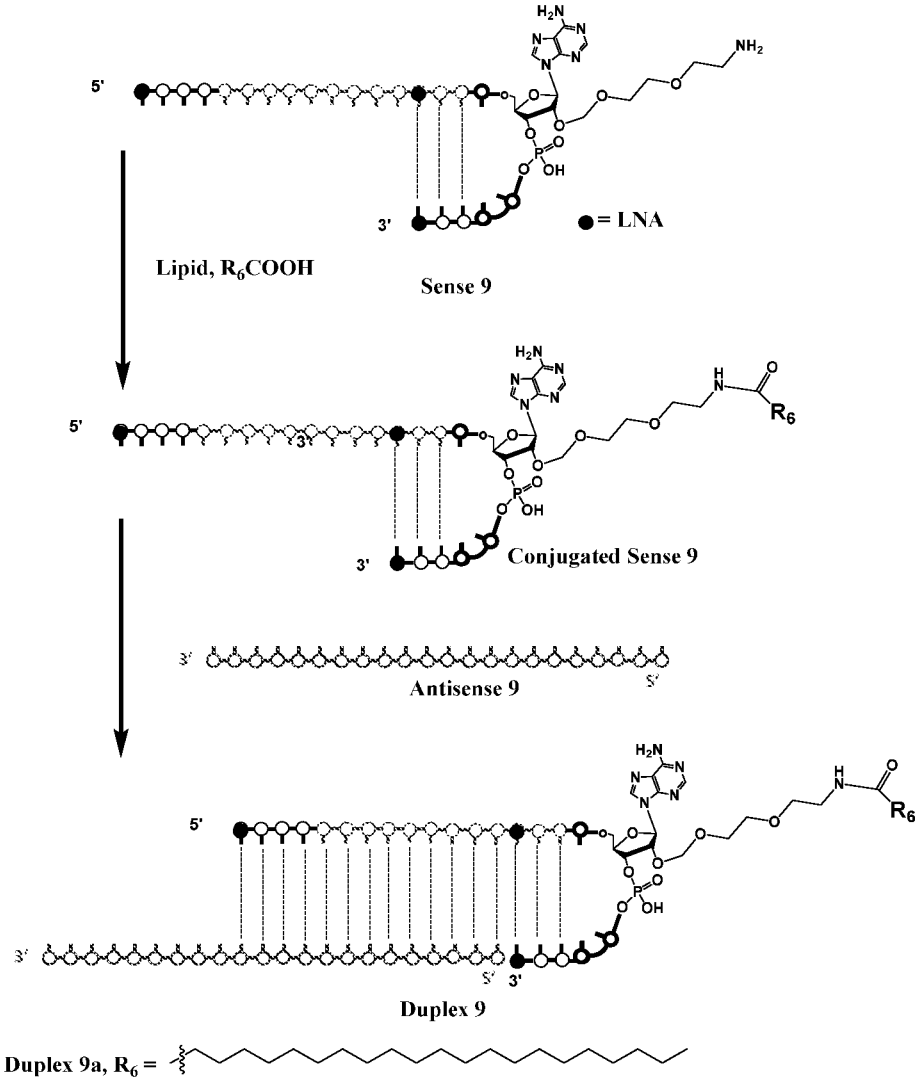
Synthesis of **Conjugated Sense 8a and 8b**

[00378] **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**

[00379] **Duplex 8a** and **Duplex 8b** were obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00380] 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

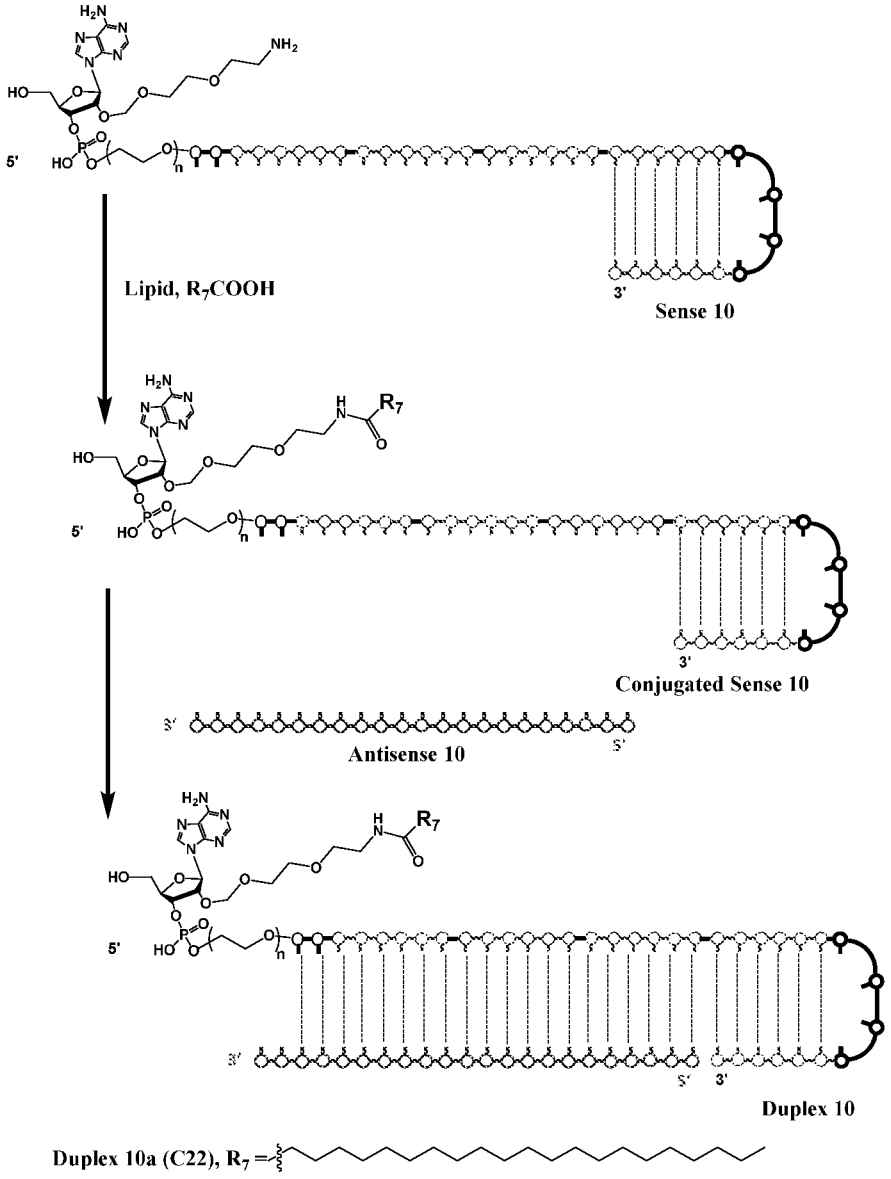
Synthesis of **Sense 9a**

[00381] **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**

[00382] **Duplex 9a** was obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00383] The following **Scheme1-11** depicts the synthesis of GalXC conjugated with mono-lipid at 5'-end using post-synthetic conjugation approach.



Scheme 1-11

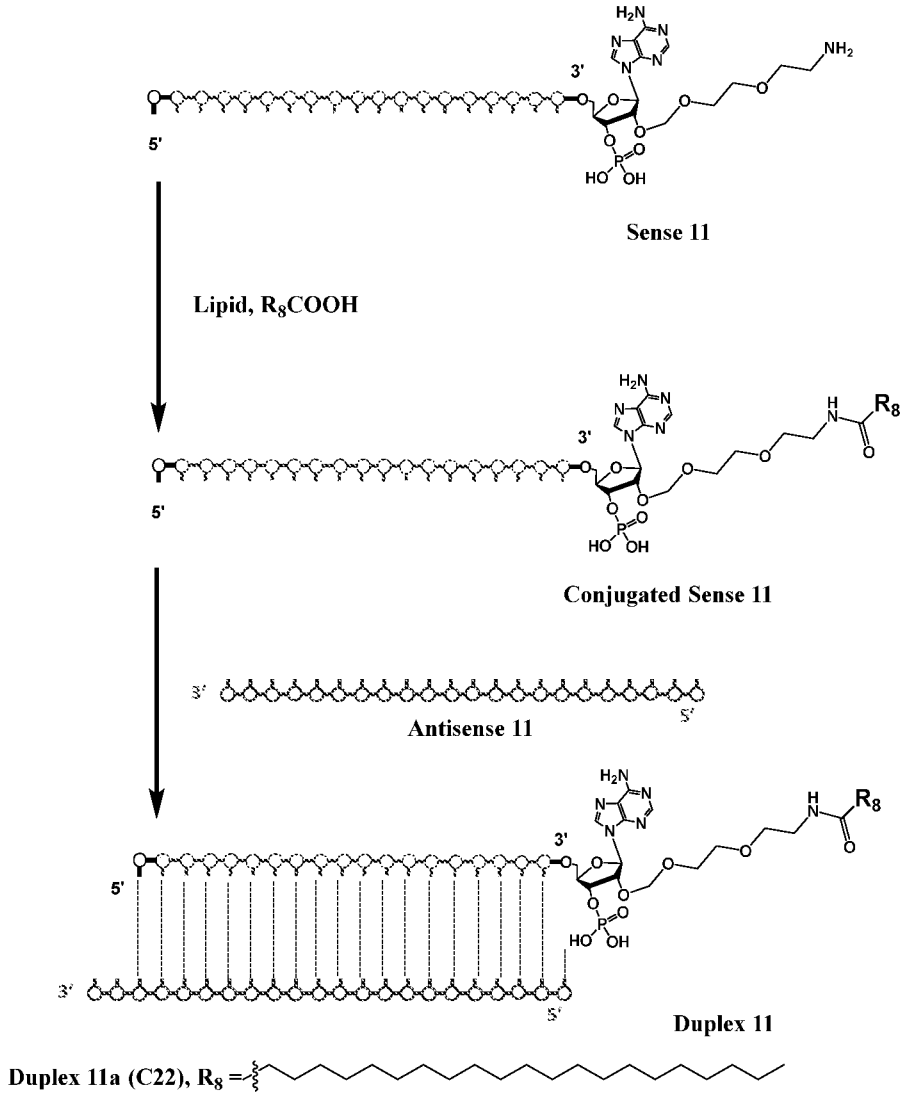
Synthesis of **Conjugated Sense 10a**

[00384] **Conjugated Sense 10a** was obtained using the same method or a substantially similar method to the synthesis of **Conjugated Sense 5**.

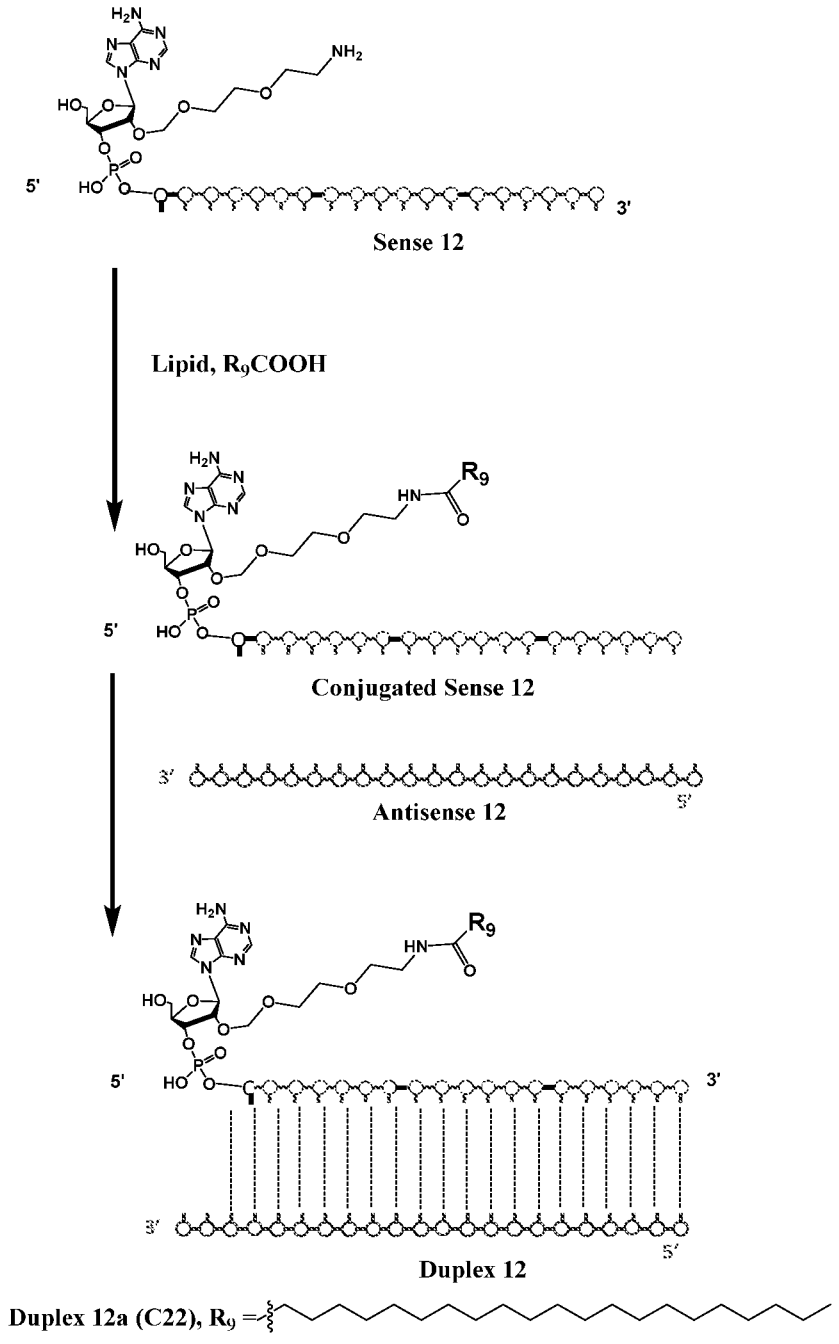
Synthesis example of **Duplex 10a**

[00385] **Duplex 10a** was obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00386] 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**

[00387] **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**

[00388] **Duplex 11a** and **12a** were obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00389] Conjugates **Duplex 8D** and **Duplex 9D** were obtained using the same method or a substantially similar method to the synthesis of **Duplex 5**.

[00390] 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: Tissue Specific Targets in MDSC Cell Populations and Tumor Draining Lymph Nodes.

[00391] 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, such as myeloid derived suppressor cells (MDSCs). *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 1**) were dosed once subcutaneously at 3 mg/kg.

Table 1: **GalXC Compound Candidates for Identifying Tool Compounds for Proof-of-concept Studies in Mice:**

Oligo	DP #	Sequence Type	SEQ ID NO	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	64	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

[00392] 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. 2A**). 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. 2B**). C18 lipid conjugation was performed for both GalXC-STAT3-4110 or 4123 for proof-of-concept studies (**Table 2**).

Table 2: 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 3: 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	81	82	C18
GalXC-STAT3-4123-C18	Unmodified	69	70	C18
	Modified	83	84	C18

[00393] 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 and MDSC subsets were isolated. 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 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). Following cell isolation mRNA was analyzed by qPCR (**FIGs. 3A and 3B**). *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.
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. 4A and 4B**). 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 4: STAT3 Inhibition Decreases the PD-L1 Levels in MDSCs and Mediates Acute Tumor Effects

[00394] 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. 5A**). The *Pdl1* levels were also dramatically reduced in TdLN after treatment with the GalXC-STAT3 conjugate, specifically GalXC-STAT3-C18-4123 (**FIG. 5B**). These data suggest a potential for downstream immunomodulation of PD-L1 after knockdown of STAT3.

[00395] 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. 6B**). 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. 6A**). 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 5: Preparation of Double-Stranded RNAi Oligonucleotides

Oligonucleotide Synthesis and Purification

[00396] 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.* 18:5433-5441 and Usman *et al.* (1987) *J. Am. Chem. Soc.* 109:7845-7845; *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;22:1859–1862. 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.

[00397] 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.

[00398] 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

[00399] 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 6: **Generation of *STAT3*-Targeting Double-Stranded RNAi Oligonucleotides**

Identification of STAT3 mRNA Target Sequences

[00400] 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 4).** 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 4**) 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 4: 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	8

[00401] RNAi oligonucleotides (formatted as DsiRNA oligonucleotides) were generated as described in **Example 5** 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:
rXmXrXmXrXrXrXrXrXrXrXrXmXrXmXrXrXrXrXrXrXrXXX

Anti-sense Strand:
mXmXmXmXrXrXrXrXrXrXmXrXmXrXrXrXrXrXrXrXrXrXmXrXmXmXmX

[00402] The ability of each of the modified DsiRNA in **Table 5** 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 5** 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: 1, Reverse 2- SEQ ID NO: 2, Probe 2- SEQ ID NO: 3) 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 5 and FIG. 7.** 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 5** to inhibit *STAT3* expression identified several candidate DsiRNAs. 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 5. 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

[00403] 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. 8A**). Of the tested oligonucleotides, 34 sequences were selected for further testing *in vivo* (**Table 6** and **FIG. 8B**).

Table 6. 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 7: RNAi Oligonucleotide Inhibition of STAT3 *In Vivo*

[00404] The *in vitro* screening assay in **Example 6** 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 6** 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 8** and **Table 9**). 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][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][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 7**).

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

[00405] Oligonucleotides in **Table 8** and **Table 9** 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 6**. 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 8. 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 9. 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

[00406] The results in **FIGs. 9A** and **9B** 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.

[00407] A subset of the GalNAc-conjugated *STAT3* oligonucleotides tested in **FIGs. 9A** and **9B** 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, STAT3-1287, 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. 10**). 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 8: Species Specific RNAi Oligonucleotide Inhibition of STAT3 *In Vivo*

[00408] 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

[00409] 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 10**. 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. 11**).

Table 10. 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

[00410] Human/Mouse GalNAc-conjugated *STAT3* oligonucleotides set forth in **Table 11** 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. 12**).

Table 11. 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

[00411] A subset of the GalNAc-conjugated *STAT3* oligonucleotides tested in **FIGs. 11** and **12** 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. 13A** and **13B**). Overall, the endogenous mouse *STAT3* expression studies identified several potential GalNAc-conjugated *STAT3* oligonucleotides for inhibiting mouse *STAT3* expression in liver.

Hs Specific

[00412] Using the HDI model described in **Example 7,** 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 12**) 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 12. 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

[00413] The results in **FIG. 14** 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.

[00414] A subset of the GalNAc-conjugated *STAT3* oligonucleotides tested in **FIG. 14** 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. 15**). 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. 16**).

Example 9: Specific STAT3 Inhibition by GalNAc-Conjugated STAT3 Oligonucleotides

[00415] 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 13** and **FIG. 17**). STAT3 721 and 1286 did not downregulate human *STAT1* but STAT3 1388 did (**Table 13**). Oligonucleotides did not

downregulate *STAT1* expression demonstrating a specificity for *STAT3* with limited off-target effects for *STAT1*.

Table 13. 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

Example 10: STAT3 Inhibition in Combination with Checkpoint Inhibition Significantly Improves Anti-Tumor Efficacy

[00416] To evaluate the performance of GalXC-STAT3-C18 conjugates as single agent or in combination with a checkpoint inhibitor, anti-PD-L1 mAb, Pan02 tumors ($2x10^6$ cells) were implanted in 6-8 week old C57BL/6 mice and upon reaching 300-400 mm^3 volume mice were subjected to randomization. Mice received either a single dose of GalXC-STAT3-C18-4123 subcutaneously at 25 mg/kg as single agent or in combination with an anti-PD-L1 mAb (anti-mouse PD-L1 mAb (B7-H1), Clone 10F.9G2) at 10 mg/kg (i.p.). Mice were first administered two doses three days apart, and two weeks later were administered two more doses three days apart [(q3dx2)x2]. Control groups were treated with either GalXC-Placebo as single agent or in combination with the anti-PD-L1 mAb as described for the GalXC-STAT3-C18-4123 compound. Two weeks after the last dose, the same dose regimen was repeated. Tumor sizes were measured twice a week throughout the study period.

[00417] As shown in **FIG. 18A**, the tumors that received GalXC-Placebo or GalXC-Placebo + mAb treatments, continued to grow to the same extent. However, the group that received GalXC-STAT3 demonstrated anti-tumor efficacy after the first round of treatment, but they continued to grow despite receiving a second dose. The group that received a combination of GalXC-STAT3 and mAb, demonstrated significantly more tumor regression as compared to

the single agent treatment. This demonstrates that combination therapy with a checkpoint inhibitor can achieve improved anti-tumor efficacy.

[00418] In a separate study, Pan02 tumors ($2x10^6$ cells) were implanted in 6-8 week old C57BL/6 mice and upon reaching 300-400 mm^3 volume, mice were administered GalXC-Placebo (25 mg/kg) in two doses, three days apart (days 42 and 45). Two weeks later, mice received two doses of GalXC-STAT3-C18-4123 three days apart subcutaneously at 25 mg/kg in combination with anti-PD-L1 mAb (anti-mouse PD-L1 mAb (B7-H1), Clone 10F.9G2) at 10 mg/kg (i.p.). Tumor sizes were measured twice a week throughout the study period. **FIG. 18B** shows a regression in tumor size following administration of the GalXC-STAT3/PD-L1 mAb combination treatment further demonstrating combination therapy can achieve improved anti-tumor efficacy.

Example 11: Correlation Between Treatment With a Combination of GalXC-STAT3 and PD-L1 mAb With Tumor Immune Phenotypes

[00419] To ascertain whether the combination efficacy pattern aligns with the tumor immune phenotype, tumor types with different phenotypes were selected for implantation in mice. Selected tumor types included Pan02 (**FIG. 18A**, checkpoint resistant tumors), 4T1 (triple negative breast, checkpoint resistant tumors), MC-38 (Colon Carcinoma, partially checkpoint sensitive tumors) and Hepa1-6 (Hepatocellular Carcinoma, checkpoint sensitive tumors). Pan02 (5e6 cells + matrigel, **FIG. 18A**) MC-38 (5e6 cells) and Hepa1-6 tumors (2e6 cells) were grown in C57BL/6 mice (7-8 weeks old) and 4T1 tumors (7-8 weeks old) were grown in Balb/c mice. When each tumor reached the sufficient tumor volume, they were sorted and subjected to treatment, as described in **Example 5** (4T1 tumors were treated three times with each dose three days apart (q3dx3), with a combination of subcutaneous GalXC-STAT3-C18-4123 with an anti-PD-L1 mAb or single agents GalXC-Placebo, GalXC-STAT3-C18-4123, or GalXC-Placebo with the mAb, as shown in **FIG. 19A.** Tumor volumes were measured twice a week throughout the study period. MC-38 and Hepa1-6 tumors were treated with a combination of subcutaneous GalXC-STAT3-C18-4123 with an anti-PD-L1 mAb or single agents GalXC-Placebo, GalXC-STAT3-C18-4123, or GalXC-Placebo with the mAb (2 doses at 3 days apart for 2 weeks) as shown in **FIGs. 19B** and **19C**.

[00420] Combination treatment demonstrated synergistic efficacy in the resistant tumor types where the tumors expected to have very little or no CD8+ T cell infiltration in the TME and a larger population of MDSCs ($CD8^{low}$ $MDSC^{high}$) (**FIGs. 18** and **19A**). The combination treatment showed improved efficacy compared to checkpoint alone treatment in partially sensitive tumors where the tumors had slightly higher levels of CD8+ T-cell infiltration and larger population of MDSCs ($CD8^{med}$ $MDSC^{high}$) (**FIG. 19B**). Interestingly, the combination treatment led to complete regression of the sensitive tumors ($CD8^{high}$ $MDSC^{high}$) (**FIG. 19C**). Tumors with higher levels of CD8+ T cell infiltration and MDSCs, when treated with the combination of GalXC-STAT3-C18-4123 + anti-PD-L1 mAb, were completely eradicated.

Example 12: Treatment Mediated Tumor Regression and Generation of Tumor Specific Memory

[00421] To evaluate if the combination treatment demonstrating complete regression also led to the generation of memory T-cells in treated mice, tumors that were completely regressed in **FIG. 19C** were re-challenged with Hep1-6 cells (2e6 cells) on the opposite flank of the mice on day 51. As shown in **FIG. 20**, even after the re-challenge, all mice remained tumor-free and survived for the period that they were kept and maintained (~2 months). These data demonstrate strong therapeutic antitumor efficacy of combination treatment leading to long term immunological memory.

Example 13: CD8+ T Cell Mediated Combination Efficacy is Also Perforin Dependent

[00422] To evaluate if the efficacy mediated by the combination treatment was CD8+ T cell mediated, an efficacy study was performed using 4T1 tumors (2e6 cells) in immunocompetent Balb/c mice (7-8 weeks old) as described in **Example 7**. The experiment was repeated in immunocompromised nude mice bearing 4T1 tumors. As shown in **FIG. 21A**, there was synergistic efficacy with combination treatment of GalXC-STAT3-C18-4123 plus anti-PD-L1 mAb in tumor bearing immunocompetent mice, but no efficacy observed in nude mice bearing 4T1 tumors (**FIG. 21B**), suggesting that there is a key role for CD8+ T cells in mediating anti-tumor efficacy. To confirm that efficacy is mediated by cytotoxic CD8+ T cells, tumor samples from the terminal timepoint of the study were stained for perforin. A significantly larger

population of perforin positive cells in the tumors that received combination treatment, as shown in **FIG. 22**, shows that the T cells involved in mediating efficacy were cytotoxic in nature.

Example 14: Effect of Combination Treatment on Spontaneous Tumor Metastasis in a Highly Metastatic Tumor Model

[00423] To evaluate whether combination treatment reduces the metastasis in a spontaneous metastatic tumor model, 4T1 tumors (2e6 cells/mouse) were implanted in Balb/c mice (7-8 weeks old) as described in **Example 7**. When tumors reached the size of 500 mm^3, they were treated with GalXC-Placebo, GalXC-STAT3-C18-4123, GalXC-Placebo + anti-PD-L1 mAb or GalXC-STAT3 + anti-PD-L1 mAb (q3d x 3, GalXC oligonucleotides administered at 50 mg/kg and anti-PD-L1 mAb administered at 10 mg/kg) and the tumors were monitored for tumor growth. Twelve days after the last dose, mice were sacrificed, and lungs were photographed. As shown in **FIG. 23**, lungs from single agent or placebo treatments showed tumor metastases throughout the whole organ whereas the mice administered the combination treatment (GalXC-STAT3-C18-4123 + anti-PD-L1 mAb) showed no visible metastases in the lungs of all five mice, suggesting that the treatment not only reduced the local tumor growth as shown in the figure, but also reduced the spontaneous metastases to lung. The same experiment was repeated in nude mice also shown in **FIG. 23**. All the lungs, including those from the mice that received the combination treatment had tumor metastases, further confirming the role of CD8+ T cells in anti-tumor efficacy.

Example 15: Treatment Mediated Immune Modulation in Tumors

[00424] To understand how the combination treatment of GalXC-STAT3-C18-4123 with an anti-PD-L1 mAb changes the immune profile in tumor, CT26 tumors were implanted in Balb/c mice. These tumors are partially sensitive to checkpoint inhibitors and have the profile similar to MC38 ($CD8^{med}$ MDSC $^{med/high}$). When the tumors reached a sufficient size, they were treated with GalXC-Placebo, GalXC-STAT3-C18-4123, GalXC-Placebo + anti-PD-L1 mAb, or GalXC-STAT3-C18-4123 + anti-PD-L1 mAb (q3d x 2, 25 mg/kg or 10 mg/kg). Seven days post last dose, tumors were collected, subjected to homogenization, and nanostring analysis was performed (mRNA extracted from paraffin embedded samples and mRNA expression was

analyzed via the ncounter^{R}Mouse Pancancer IO 360^{TM} Panel (Nanostring Technologies, Seattle, WA).

[00425] The analysis showed that the genes that are suppressive in nature (checkpoints, STAT3 mediated genes, suppressive cytokine/chemokines, angiogenesis & matrix remodeling related genes) were reduced and genes that favor T-cell activation (genes that involve in T-cell migration, activation, memory and cytotoxicity) increased after the combination treatment compared to the single agent or GalXC-Placebo, anti-PD-L1 mAb treatments suggesting that the combination treatment is changing the TME from suppressive to a favorable TME for T-cell infiltration (**FIG. 24**).

Example 16: STAT3 Oligonucleotides for Treatment of Disease

[00426] To investigate efficacy of STAT3 oligonucleotides alone or in combination with an anti-PD-L1 mAb, subjects are administered a STAT3 oligonucleotide or a STAT3 oligonucleotide in combination with an anti-PD-L1 mAb. Specifically, subjects are administered a STAT3 oligonucleotide wherein the sense strand comprises the sequence set forth in SEQ ID NO: 1222, and wherein the antisense strand comprises the sequence set forth in SEQ ID NO: 1145 as illustrated below (depicted in **FIG. 25**):

Sense Strand: [ademAs-C18][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][mA][mA][mA][mG][mG][mC][mU][mG][mC]

Hybridized to:

Antisense Strand: [MePhosphonate-4O-mUs][fUs][fAs][fA][fU][mU][fU][mU][mA][fA][mG][mC][mU][fG][mA][mU][mA][mA][mU][mUs][mGs][mG]

(key provided in **Table 7**)

[00427] The STAT3 oligonucleotide described above is administered alone or in combination with an anti-PD-L1 antibody. The STAT3 oligonucleotide is administered prior to, concurrently with, or after administration of the anti-PD-L1 antibody. Following administration, tumor size and subject survival are measured.

Example 17: STAT3 Inhibition in Combination with Checkpoint Inhibition Significantly Improves Anti-Tumor Efficacy

[00428] Studies were conducted in 3 different mouse tumor models, B16F10, Pan02 and MC-38. B16F10 and Pan02 are murine melanoma and pancreatic cancer models that are thought to be resistant to checkpoint inhibitors (CPI) due to the presence of a large population myeloid-derived suppressor cells (MDSC) and little or no CD8+ T-cells in the tumor microenvironment (TME). The MC-38 tumor model is a murine colon carcinoma model known to be partially sensitive to CPI and carries modest levels of MDSCs and CD8+ T-cells in its TME. The experiment described in this example was designed to evaluate the efficacy of the DCR-STAT3 (a human specific STAT3 sequence with C18 lipid conjugation at 5'end of the passenger strand corresponding to SEQ ID NOs: 1222 and 1145, "DCR-STAT3") in CPI-resistant and sensitive preclinical models.

[00429] Mice were administered either GalXC-Placebo or DCR-STAT3 with and without a anti-PD-L1 mouse antibody. The GalXC-Placebo and DCR-STAT3 were administered subcutaneously at 25 mg/kg and the anti-PD-L1 antibody was administered intraperitoneally at 10 mg/kg. In the B16F10 tumor model, doses were administered on Days 6 (6 days post tumor implant), 9, and 12. In the Pan02 model, doses were administered on Days 38 (38 days post tumor implant), 41, 48 and 51. In the MC-38 tumor model, doses were administered on Days 5 (5 days post tumor implant), 8, 12, and 15.

[00430] In the CPI-resistant B16F10 model, following 3 doses of DCR-STAT3 or DCR-STAT3 + anti-PD-L1 antibody, tumor sizes on Day 13 were reduced by 36% ($p < 0.01$) and 64% ($p < 0.0001$), respectively, relative to the GalXC-Placebo group. The anti-PD-L1 antibody alone had no effect on tumor growth and tumors grew to the same size as the GalXC-Placebo group. The tumor sizes in the combination group (DCR-STAT3 + anti-PD-L1 antibody) were reduced by 43% ($p < 0.05$) relative to DCR-STAT3 alone, and 64% ($p < 0.0001$) relative to anit-PD-L1 antibody alone. Similar pattern was observed in Pan02 study as well. Following 4 doses of DCR-STAT3 or DCR-STAT3 + anti-PD-L1 antibody, tumor sizes on Day 58 were reduced by 39% ($p < 0.01$) and 75% ($p < 0.0001$) respectively relative to control group. The anti-PD-L1 antibody had no effect on tumor growth and tumors grew to the same size as the GalXC-Placebo group. The tumor sizes in the combination group were reduced by 59% ($p < 0.01$) relative to DCR-STAT3 alone and 76% ($p < 0.0001$) relative to anti-PD-L1 antibody alone suggesting that the

DCR-STAT3 was active as single agent, and the single agent activity was further enhanced when it was combined with the antibody in this CPI resistant tumor models.

[00431] In the CPI partially sensitive MC-38 model, following 4 doses of anti-PD-L1 antibody or DCR-STAT3, tumor sizes on Day 18 were reduced by 57% ($p < 0.01$) and 45% ($p < 0.01$) respectively, relative to the GalXC-Placebo group. On Day 18, following 4 doses of DCR-STAT3 + anti-PD-L1 antibody, tumor sizes were reduced by 95% ($p < 0.0001$), relative to the GalXC-Placebo group. Compared to the anti-PD-L1 antibody or DCR-STAT3, tumor sizes were reduced by 89% ($p < 0.05$) and 91%, ($p < 0.01$), respectively, in DCR-STAT3 + anti-PD-L1 antibody group. Administration of either the anti-PD-L1 antibody or DCR-STAT3 were both active as single agents, but the combination of both further enhanced the efficacy of either single agent.

[00432] The data from these 3 experiments provide evidence that DCR-STAT3 was active as single agent in CPI-resistant tumors where the anti-PD-L1 antibody was inactive and when DCR-STAT3 was combined with the anti-PD-L1 antibody, it led to synergistic anti-tumor activity. DCR-STAT3 was also active in CPI-sensitive tumors where anti-PD-L1 also demonstrated single-agent activity, and when used in combination, majority of the tumors regressed by nearly 100%.

SEQUENCE LISTING

Name	Description	Species	Sequence	SEQ ID NO
Forward 2			GATGATTTCAGCAAATGACATGTTG	1
Reverse 2			CAGTGAAAGCAGCAAAGAAGG	2
Probe 2			/56-FAM/AGGACATCA/ZEN/GCGGTAAGACCCAGA/3IABkFQ/	3
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]	4
STAT3-1286	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fA][fA][fU][mU][fU][mU][mA][fA]	5

			[mG][mC][mU][fG][mA][mU][mA][mA][mU][mUs][mGs][mG]	
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]	6
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]	7
NM_213659.3 Mus musculus STAT3 nucleotide sequence			AATTATGCATGGAGGCGTGTCTTGGCCA GTGGCGGCTGGGTGGGGATTGGCTGGAG GGGCTGTAATTCAGCGGTTTCCGGAGCTG CAGTGTAGACAGGGAGGGGGAACCTGGG GTTCCGACGTCGCGGCGGAGGGAACGAG CCCTAACCGGATCGCTGAGGTACAACCC CGCTCGGTGTCGCCTGACCGCGTCGGCTA 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	8

			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 AGTTCTCGTCCACCACCAAGCGGGGCT 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 AAAAAAAAAAAAAATAAGAATTAAAGG 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	
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][	12

			mA][mA][mG][fU][mC][mG][mU][mC][mC][mUs][mGs][mG]	
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][	24

			mU][mC][mA][fA][mC][mU][mC][mA][mG][mGs][mGs][mG]	
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][	36

			mA][mA][mU][fU][mC][mA][mA][mC][mU][mCs][mGs][mG]	
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][	48

			mA][mU][mG][fA][mU][mA][mU][mU][mG][mUs][mGs][mG]	
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][	60

			mA][mU][mC][fA][mA][mU][mG][mA][mA][mUs][mGs][mG]	
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][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-	Modified 22mer		[MePhosphonate-4O-mUs][fUs][fU][fC][fA][mG][fC][mU][mU][fA][	72

4123			mU][mU][mG][fU][mA][mU][mA][mA][mC][mUs][mGs][mG]	
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-STAT3-4123-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]	83

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 GTGGTGGAGCGGCAGCCCTGCATGCCCA TGCATCCTGACCGGCCCCTCGTCATCAAG	85

			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][ade	87

			mA-C18][mA][mA][mG][mG][mC][mU][mG][mC]	
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
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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
STAT3-722	Antisense 19mer		UAUAGUUGAAAUCAAAGUC	301
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
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STAT3-1047	Antisense 19mer		UCCAGUUUCUUAAUUUGUU	314

STAT3-1067	Antisense 19mer		AAACUUUUUGCUGCAACUC	315
STAT3-1068	Antisense 19mer		GAAACUUUUUGCUGCAACU	316
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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
STAT3-1280	Antisense 19mer		UAAGCUGAUAAUUCAACUC	327
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
STAT3-1672	Antisense 19mer		AAAAAAGUUUACAUUCUUG	346
STAT3-1673	Antisense 19mer		UAAAAAAGUUUACAUUCUU	347
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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
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STAT3-2143	Antisense 19mer		AAAUGACAUGUUGUUCAGC	373
STAT3-2144	Antisense 19mer		CAAAUGACAUGUUGUUCAG	374
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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
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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
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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	CUUUGUGGUUCCAGAUUUUAGCAGCCG AAAGGCUGC	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	AUCUAGAACAGAAAAUGAAAGCAGCCGAAAGGCUGC	909

STAT3-0678	Unmodified 36 mer	Hs-Mf-Mm	AGGAUCUAGAACAGAAAAUAGCAGCCGAAAGGCUGC	910
STAT3-4837	Unmodified 36 mer	Hs-Mf-Mm	AAAAAUUUAUAUUAUUGUGAGCAGCCGAAAGGCUGC	911
STAT3-4833	Unmodified 36 mer	Hs-Mf-Mm	GUGUAAAAAUUUAUAUUAUAGCAGCCGAAAGGCUGC	912
STAT3-1068	Unmodified 36 mer	Hs	AGUUGCAGCAAAAAGUUUCAGCAGCCGAAAGGCUGC	913
STAT3-1673	Unmodified 36 mer	Hs	AAGAAUGUAAACUUUUUUAAGCAGCCGAAAGGCUGC	914
STAT3-0426	Unmodified 36 mer	Hs	UGCAAGAGUCGAAUGUUCUAGCAGCCGAAAGGCUGC	915
STAT3-2404	Unmodified 36 mer	Hs	AGAUUCAUUGAUGCAGUUUAGCAGCCGAAAGGCUGC	916
STAT3-1067	Unmodified 36 mer	Hs	GAGUUGCAGCAAAAAGUUUAGCAGCCGAAAGGCUGC	917
STAT3-0433	Unmodified 36 mer	Hs	GUCGAAUGUUCUCUAUCAGAGCAGCCGAAAGGCUGC	918
STAT3-1670	Unmodified 36 mer	Hs	CCCAAGAAUGUAAACUUUUAGCAGCCGAAAGGCUGC	919
STAT3-1388	Unmodified 36 mer	Hs	GUGAUGAACAUGGAAGAAUAGCAGCCGAAAGGCUGC	920
STAT3-0429	Unmodified 36 mer	Hs	AAGAGUCGAAUGUUCUCUAAGCAGCCGAAAGGCUGC	921
STAT3-2405	Unmodified 36 mer	Hs	GAUUCAUUGAUGCAGUUUGAGCAGCCGAAAGGCUGC	922
STAT3-0430	Unmodified 36 mer	Hs	AGAGUCGAAUGUUCUCUAUAGCAGCCGAAAGGCUGC	923
STAT3-0432	Unmodified 36 mer	Hs	AGUCGAAUGUUCUCUAUCAAGCAGCCGAAAGGCUGC	924

STAT3-1815	Unmodified 36 mer	Hs	CUGGUGUGAAUUAUUCAGGAGCAGCCG AAAGGCUGC	925
STAT3-0424	Unmodified 36 mer	Hs	CCUGCAAGAGUCGAAUGUUAGCAGCCG AAAGGCUGC	926
STAT3-2024	Unmodified 36 mer	Hs	ACCUUCCUGCUAAGAUUCAAGCAGCCGA AAGGCUGC	927
STAT3-1813	Unmodified 36 mer	Hs	ACCUGGUGUGAAUUAUUCAAGCAGCCG AAAGGCUGC	928
STAT3-1674	Unmodified 36 mer	Hs	AGAAUGUAAACUUUUUUACAGCAGCCG AAAGGCUGC	929
STAT3-1241	Unmodified 36 mer	Hs	CAGUUCACUACUAAAGUCAAGCAGCCG AAAGGCUGC	930
STAT3-1672	Unmodified 36 mer	Hs	CAAGAAUGUAAACUUUUUUAGCAGCCG AAAGGCUGC	931
STAT3-0425	Unmodified 36 mer	Hs	CUGCAAGAGUCGAAUGUUCAGCAGCCG AAAGGCUGC	932
STAT3-1817	Unmodified 36 mer	Hs	GGUGUGAAUUAUUCAGGGUAGCAGCCG AAAGGCUGC	933
STAT3-1671	Unmodified 36 mer	Hs	CCAAGAAUGUAAACUUUUUAGCAGCCG AAAGGCUGC	934
STAT3-2136	Unmodified 36 mer	Hs-Mm	AGCAGCAGCUGAACAACAUAGCAGCCG AAAGGCUGC	935
STAT3-2143	Unmodified 36 mer	Hs-Mm	GCUGAACAACAUGUCAUUUAGCAGCCG AAAGGCUGC	936
STAT3-2144	Unmodified 36 mer	Hs-Mm	CUGAACAACAUGUCAUUUGAGCAGCCG AAAGGCUGC	937
STAT3-2138	Unmodified 36 mer	Hs-Mm	CAGCAGCUGAACAACAUGUAGCAGCCG AAAGGCUGC	938
STAT3-4909	Unmodified 36 mer	Hs-Mm	UUUAACUUCCAGAAAUAAAAGCAGCCG AAAGGCUGC	939

STAT3-2139	Unmodified 36 mer	Hs-Mm	AGCAGCUGAACAACAUGUCAGCAGCCG AAAGGCUGC	940
STAT3-2411	Unmodified 36 mer	Hs-Mm	UUGAUGCAGUUUGGAAAUAAGCAGCCG AAAGGCUGC	941
STAT3-2145	Unmodified 36 mer	Hs-Mm	UGAACAACAUGUCAUUUGCAGCAGCCG AAAGGCUGC	942
STAT3-4831	Unmodified 36 mer	Hs-Mm	UAGUGUAAAAAUUUAUAUUAGCAGCCG AAAGGCUGC	943
STAT3-2622	Unmodified 36 mer	Hs-Mm	UAACUUUGUGGUUCCAGAUAGCAGCCG AAAGGCUGC	944
STAT3-2135	Unmodified 36 mer	Hs-Mm	AAGCAGCAGCUGAACAACAAGCAGCCG AAAGGCUGC	945
STAT3-1383	Unmodified 36 mer	Hs-Mm	CAAAAGUGAUGAACAUGGAAGCAGCCG AAAGGCUGC	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][ade	1040

			mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
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][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1047

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][ade	1055

			mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
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][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1062

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][ade	1070

			mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
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][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1077

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][ade	1085

			mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
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][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1092

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][ad	1100

			emA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
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][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1107

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][ade	1115

			mA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	
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][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC]	1122

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	1131

			][mA][mA][mC][fA][mC][mC][mA][mA][mA][mGs][mGs][mG]	
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	1140

			][mC][mU][mC][fA][mG][mG][mG][mA][mA][mUs][mGs][mG]	
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]	1149

			[mA][mU][mA][fA][mU][mU][mC][mA][mC][mAs][mGs][mG]	
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]	1158

			[mU][mU][mU][fC][mU][mC][mU][mA][mU][mUs][mGs][mG]	
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][	1167

			mU][mU][mU][fC][mA][mG][mC][mA][mA][mAs][mGs][mG]	
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][	1176

			mU][mU][mG][fA][mU][mU][mC][mU][mU][mCs][mGs][mG]	
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][	1185

			mG][mA][mC][fU][mC][mU][mU][mG][mC][mAs][mGs][mG]	
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]	1194

			[mA][mC][mA][fU][mU][mC][mG][mA][mC][mUs][mGs][mG]	
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			GTCGCAGCCGAGGGAACAAGCCCCAACCGGATCCTGGACAGGCACCCCGGCTTGGCGCTGTCTCTCCCCCTCGGCTCGGAGAGGCCCTTCGGCCTGAGGGAGCCTCGCCGCCCGTCCCCGGCACACGCGCAGCCCCGGCCTCTCGGCCTCTGCCGGAGAAACAGTTGGGACCCCTGATTTTAGCAGGATGGCCCAATGGAATCAGCTACAGCAGCTTGACACACGGTACCTGGAGCAGCTCCATCAGCTCTACAGTGACAGCTTCCCAATGGAGCTGCGGCAGTTTCTGGCCCCTTGGATTGAGAGTCAAGATTGGGCATATGCGGCCAGCAAAGAATCACATGCCACTTTGGTGTTTCATAATCTCCTGGGAGAGATTGACCAGCAGTATAGCCGCTTCCTGCAAGAGTCGAATGTTCTCTATCAGCACAATCTACGAAGAATCAAGCAGTTTCTTCAGAGCAGGTATCTTGAGAAGCCAATGGAGATTGCCCGGATTGTGGCCCGGTGCCTGTGGGAAGAATCACGCCTTCTACAGACTGCAGCCACTGCGGCCCAGCAAGGGGGCCAGGCCAACCACCCCACAGCAGCCGT	1217

			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 AGGCAGAAGATGCAGCAGCTGGAACAGA	1218

			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
STAT3-1286	Modified 36-mer	Hs	[ademAs-C18][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][mA][mA][mA][mG][mG][mC][mU][mG][mC]	1222
STAT3 mouse compound	Modified 36-mer	Mouse	[ademUs-C18][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][mA][mA][mA][mG][mG][mC][mU][mG][mC]	1223

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: 140, wherein the sense strand comprises at least one lipid moiety conjugated to the 5'terminal nucleotide of the sense strand.

2. The oligonucleotide of claim 1, wherein the antisense strand is 19 to 27 nucleotides in length.

3. The oligonucleotide of any one of claims 1-2, wherein the antisense strand is 21 to 27 nucleotides in length, optionally wherein the antisense strand is 22 nucleotides in length.

4. The oligonucleotide of any one of claims 1-3, wherein the sense strand is 19 to 40 nucleotides in length, optionally wherein the sense strand is 36 nucleotides in length.

5. The oligonucleotide of any one of claims 1-4, wherein the duplex region is at least 19 nucleotides in length.

6. The oligonucleotide of any one of claims 1-5, wherein the duplex region is at least 20 nucleotides in length, optionally wherein the duplex region is 21 nucleotides in length.

7. The oligonucleotide of any one of claims 1-6, wherein the region of complementarity to *STAT3* is at least 19 contiguous nucleotides in length.

8. The oligonucleotide of any one of claims 1-7, wherein the region of complementarity to *STAT3* is at least 21 contiguous nucleotides in length.

9. The oligonucleotide of any one of claims 1-8, wherein the antisense strand comprises a sequence as set forth in SEQ ID NO: 965.

10. The oligonucleotide of any one of claims 1-9, wherein the sense strand comprises a sequence as set forth in SEQ ID NO: 875.

11. The oligonucleotide of any one of claims 1-10, 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.

12. 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: 140, wherein the sense strand comprises at its 3′ end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense strand and the sense strand form a duplex structure of at least 19 nucleotides in length, and wherein the sense strand comprises a lipid moiety conjugated to the 5' terminal nucleotide of the sense strand.

13. 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 set forth in SEQ ID NO: 140, and

(ii) a sense strand of 19-50 nucleotides in length comprising a region of complementarity to the antisense strand, wherein the sense strand comprises a lipid moiety conjugated to the 5' terminal nucleotide of the sense 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.

14. The oligonucleotide of any one of claims 11-13, wherein L is a tetraloop, optionally wherein L is 4 nucleotides in length.

15. The oligonucleotide of any one of claims 11-14, wherein L comprises a sequence set forth as GAAA.

16. The oligonucleotide of any one of claims 1-15, 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.

17. The oligonucleotide of claim 16, 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.

18. The oligonucleotide of any one of claims 1-17, 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.

19. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleotide.

20. The oligonucleotide of claim 19, wherein the modified nucleotide comprises a 2′-modification.

21. The oligonucleotide of claim 20, 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.

22. The oligonucleotide of any one of claims 19-21, wherein about 10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprise a 2'-fluoro modification.

23. The oligonucleotide of any one of claims 19-22, 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.

24. The oligonucleotide of any one of claims 19-23, 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.

25. The oligonucleotide of any one of claims 19-24, wherein the sense strand comprises 36 nucleotides with positions 1-36 from 5' to 3', wherein positions 8-11 comprise a 2'-fluoro modification.

26. The oligonucleotide of any one of claims 19-25, 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.

27. The oligonucleotide of any one of claims 22-26, wherein the remaining nucleotides comprise a 2'-O-methyl modification.

28. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified internucleotide linkage.

29. The oligonucleotide of claim 28, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

30. The oligonucleotide of claim 29, wherein the sense strand comprises a phosphorothioate linkage between positions 1 and 2 of the sense strand.

31. The oligonucleotide of claim 29, wherein the antisense strand comprises 22 nucleotides with positions 1-22 from 3' to 5', wherein the antisense strand comprises a phosphorothioate linkage between positions 1 and 2, 2 and 3, 3 and 4, 20 and 21, and 21 and 22.

32. The oligonucleotide of any one of claims 29-31, wherein the sense strand comprises a phosphorothioate linkage between positions 1 and 2 of the sense strand and the antisense strand comprises 22 nucleotides with positions 1-22 from 3' to 5', wherein the antisense strand comprises a phosphorothioate linkage between positions 1 and 2, 2 and 3, 3 and 4, 20 and 21, and 21 and 22.

33. 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.

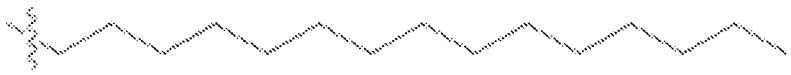
34. The oligonucleotide of claim 33, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate.

35. The oligonucleotide of any one of the preceding claims, wherein the lipid moiety is a saturated or unsaturated fatty acid moiety.

36. The oligonucleotide of any one of the preceding claims, wherein the lipid moiety is a saturated fatty acid moiety that ranges in size from C10 to C24 in length.

37. The oligonucleotide of claim 36, wherein the lipid moiety is a C16 saturated fatty acid moiety.

38. The oligonucleotide of claim 37, wherein the C16 saturated fatty acid moiety is represented by:



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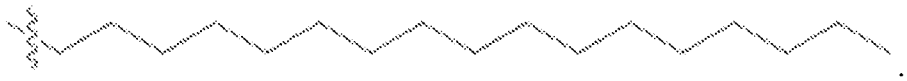
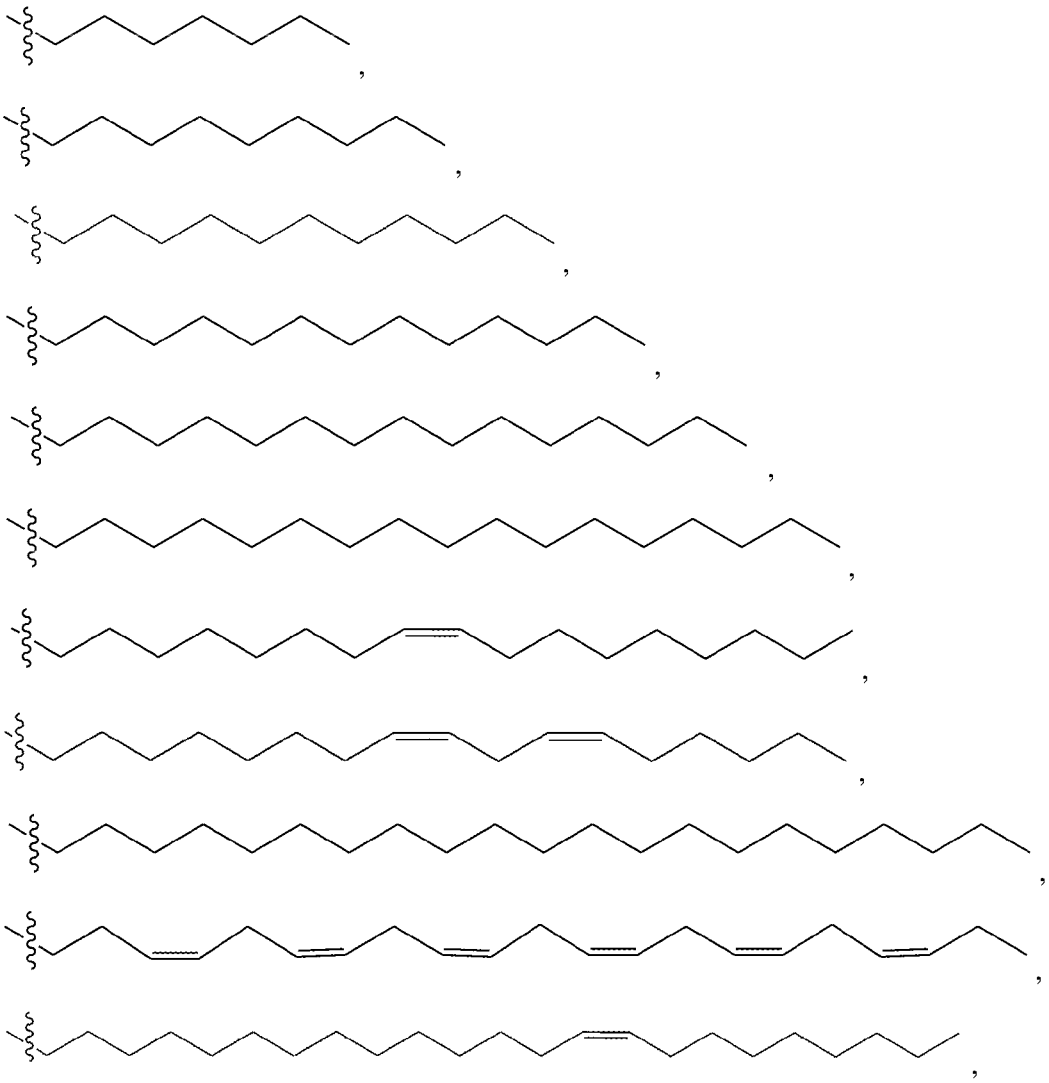
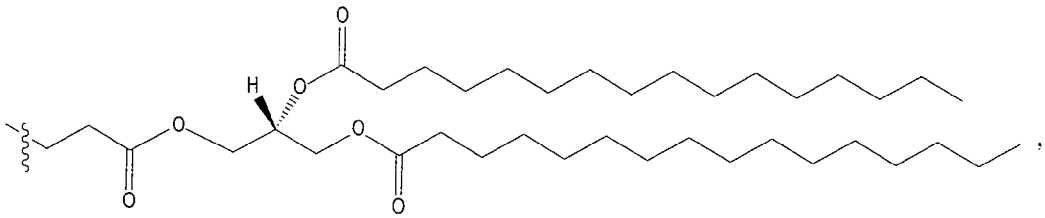
39. The oligonucleotide of claim 36, wherein the lipid moiety is a C18 saturated fatty acid moiety.

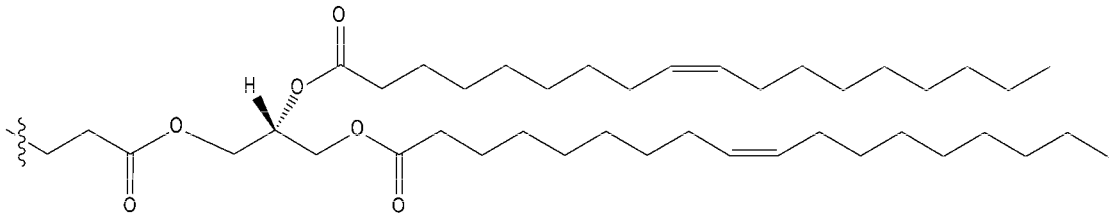
40. The oligonucleotide of claim 39, wherein the C18 saturated fatty acid moiety is represented by:



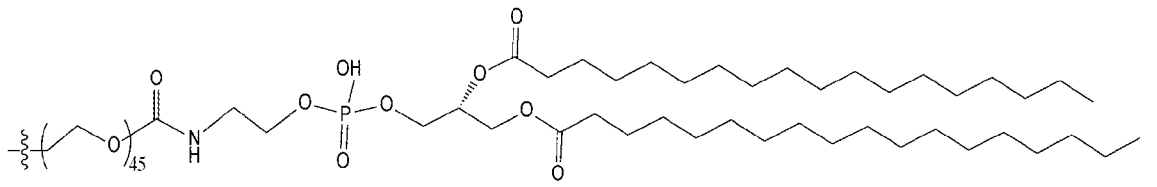
41. The oligonucleotide of any one of the preceding claims, wherein the lipid moiety is selected from:







, and



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42. The oligonucleotide of any one of the preceding claims, wherein the lipid moiety is conjugated to the 2′ carbon of the ribose ring of the 5′ terminal nucleotide.

43. The oligonucleotide of any one of claims 1-42, wherein the sense strand comprises the sequence set forth in SEQ ID NO: 1222.

44. The oligonucleotide of any one of claims 1-43, wherein the antisense strand comprises the sequence set forth in SEQ ID NO: 1145.

45. The oligonucleotide of any one of claims 1-44, wherein the sense strand comprises the sequence set forth in SEQ ID NO: 1222, and wherein the antisense strand comprises the sequence set forth in SEQ ID NO: 1145.

46. A double-stranded oligonucleotide for reducing STAT3 expression, wherein the oligonucleotide comprises a sense strand comprising the sequence set forth in SEQ ID NO: 1222 and the antisense strand comprises the sequence set forth in SEQ ID NO: 1145, wherein the

sense strand and antisense strand form an asymmetric duplex region of 20 nucleotides in length and having an overhang of 2 nucleotides at the 3' terminus of the antisense strand.

47. The oligonucleotide of any one of claims 1-45, wherein the region of complementary is fully complementary to the STAT3 target sequence.

48. The oligonucleotide of any one of claims 1-45, wherein the region of complementary is partially complementary to the STAT3 target sequence.

49. The oligonucleotide of claim 48, wherein the region of complementary comprises no more than 4 mismatches to the STAT3 target sequence.

50. The oligonucleotide of any one of claims 1-49, wherein the region of complementary is fully complementary to the STAT3 target sequence at nucleotide positions 2-8 or 2-11 of the antisense strand, wherein nucleotide positions are numbered 5′ to 3′.

51. The oligonucleotide of any one of claims 1-50, wherein the oligonucleotide is a Dicer substrate that, upon endogenous Dicer processing, yields double-stranded nucleic acids of 19-21 nucleotides in length capable of reducing *STAT3* mRNA expression in a mammalian cell.

52. The oligonucleotide of any one of claims 1-51, wherein the oligonucleotide reduces expression of *STAT3* mRNA in one or more immune cells associated with a tumor microenvironment.

53. A pharmaceutical composition comprising the oligonucleotide of any one of claims 1-52, and a pharmaceutically acceptable carrier, delivery agent, or excipient.

54. A method of treating cancer in a subject, the method comprising administering to the subject an effective amount of the oligonucleotide of any one of claims 1-52 or the pharmaceutical composition of claim 53.

55. The method of claim 54, comprising administering a PD-L1 inhibitor to the subject.

56. A method of treating cancer in a subject that has received or is receiving a PD-L1 inhibitor, the method comprising administering the oligonucleotide of any one of claims 1-52 or the pharmaceutical composition of claim 53 to the subject, thereby treating cancer in the subject.

57. A method of treating cancer in a subject that has received or is receiving an oligonucleotide targeting *STAT3*, wherein the oligonucleotide targeting *STAT3* is the oligonucleotide of any one of claims 1-52, the method comprising administering a PD-L1 inhibitor to the subject, thereby treating cancer in the subject.

58. A method for treating a disease, disorder or condition associate with STAT3 expression in a subject, the method comprising administering to the subject an effective amount of the oligonucleotide of any one of claims 1-52 or the pharmaceutical composition of claim 53.

59. The method of claim 58, comprising administering a PD-L1 inhibitor to the subject.

60. A method for treating a disease, disorder or condition associate with STAT3 expression in a subject that has received or is receiving a PD-L1 inhibitor, the method comprising administering the oligonucleotide of any one of claims 1-52 or the pharmaceutical composition of claim 53 to the subject, thereby treating cancer in the subject.

61. A method for treating a disease, disorder or condition associate with STAT3 expression in a subject that has received or is receiving an oligonucleotide targeting *STAT3*, wherein the oligonucleotide targeting *STAT3* is the oligonucleotide of any one of claims 1-52, the method comprising administering a PD-L1 inhibitor to the subject, thereby treating cancer in the subject.

62. The method of any one of claims 58-61, wherein the disease, disorder or condition associated with STAT3 expression is a cancer.

63. The method of any one of claims 54-57 and 62, wherein the cancer is selected from carcinoma, sarcoma, melanoma, lymphoma, and leukemia, prostate cancer, breast cancer, hepatocellular carcinoma (HCC), colorectal cancer, pancreatic cancer and glioblastoma.

64. The method of any one of claims 54-58 and 62-63, wherein the cancer comprises an immunosuppressive tumor microenvironment.

65. The method of any one of claims 54-58 and 62-63, wherein the cancer comprises an inflamed tumor microenvironment.

66. The method of claim 65, wherein the inflamed tumor microenvironment comprises infiltrating T cells.

67. The method of any one of claims 55-57, 59-66, wherein the PD-L1 inhibitor is an antibody.

68. The method of claim 67, wherein the antibody is an anti-PD-L1 antibody.

69. The method of claim 68, wherein the anti-PDL1 antibody is selected from FAZ053, atezolizumab, avelumab, durvalumab, envafolimab, and BMS-936559.

70. The method of claim 67, wherein the antibody is an anti-PD-1 antibody.

71. The method of claim 70, wherein the anti-PD-1 antibody is selected from nivolumab, pembrolizumab, and cemiplimab.

72. Th method of any one of claims 54-57 and 62-71, wherein treating cancer comprises reducing or inhibiting tumor growth in the subject.

73. A method of reducing expression of *STAT3* mRNA in a cell, comprising contacting the cell with the oligonucleotide of any one of claims 1-52.

74. A kit comprising a container comprising the oligonucleotide of any one of claims 1-52, 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.

75. The kit of claim 74, wherein the disease, disorder or condition associated with STAT3 expression is a cancer.

76. A kit comprising a container comprising the oligonucleotide of any one of claims 1-52, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject with cancer that has received or is receiving a PD-L1 inhibitor.

77. A kit comprising a container comprising a PD-L1 inhibitor, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject with cancer that has received or is receiving the oligonucleotide of any one of claims 1-52.

78. A kit comprising an oligonucleotide, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administering the oligonucleotide to a subject in need thereof that has received or is receiving a PD-L1 inhibitor, wherein the oligonucleotide is the oligonucleotide of any one of claims 1-52.

79. A kit comprising a PD-L1 inhibitor, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administering the inhibitor to a subject in need thereof that has received or is receiving an oligonucleotide, wherein the oligonucleotide is the oligonucleotide of any one of claims 1-52.

80. The kit of 78 or 79, wherein the subject has a disease, disorder, or condition associated with activated *STAT3* expression.

81. The kit of any one of claims 78-80, wherein the subject has cancer.

82. A method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of the subject, wherein the treatment is administration of an oligonucleotide targeting STAT3, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

83. A method for determining responsiveness in a subject with cancer who has received or is receiving a treatment, comprising:

(i) obtaining a biological sample from the subject; and

(ii) detecting of the presence of MDSCs or a marker of MDSC activity in the biological sample

wherein the treatment is administration of an oligonucleotide targeting STAT3, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

84. The method of any one of claims 82-83, wherein detecting comprises determining an amount of MDSCs or an amount of a marker of MDSC activity.

85. The method of any one of claims 82-84, wherein the reduction of MDSCs or marker of MDSC activity is relative to an amount or level of MDSCs or marker of MDSC activity prior to treatment of the subject.

86. The method of any one of claims 82-84, wherein the reduction of MDSCs or marker of MDSC activity is relative to an amount or level of MDSCs or marker of MDSC activity of a population of patients that did not receive the treatment.

87. The method of any one of claims 82-86, wherein the reduction of MDSCs or marker of MDSC activity is based on an amount or level of MDSCs or marker of MDSC activity of a population of patients that responded to the treatment.

88. The method of any one of claims 82-87, wherein the MDSCs are granulocytic-MDSCs (G-MDSCs).

89. The method of any one of claims 82-88, wherein the MDSCs are monocytic-MDSCs (M-MDSCs).

90. The method of any one of claims 82-89, wherein the MDSCs express Arg1.

91. The method of any one of claims 82-90, wherein the MDSCs express IDO.

92. The method of any one of claims 82-91, wherein the presence of MDSCs or a marker of activity of MDSC is determined by flow cytometry.

93. The method of any one of claims 82-92, wherein the biological sample is a blood or serum sample.

94. The method of any one of claims 82-93, wherein responding to treatment comprises a reduction or inhibition of tumor growth and/or tumor size.

95. The method of any one of claims 82-94, wherein the oligonucleotide targeting STAT3 is the oligonucleotide of any one of claims 1-52.

GalNAC
(STAT3-4110)
(STAT3-4123)
Stem-loop
Lipid Conjugate
(STAT3-4110)
(STAT3-4123)
Terminal
Nucleotide
Lipid
Conjugate
Legend
4'-O-monomethylphosphonate-2'-O-methyl modified nucleotide
2'-OMe
2'-F
GalNAc conjugated nucleotide
Lipid conjugate (length 18)
Numeric labels: nucleotide positions from 5'-end to 3'-end for each strand
tetraloop nick
phosphorothioate linkage
Linkage clarifications
phosphorothioate
phosphodiester
B = any nucleobase

FIG. 1A

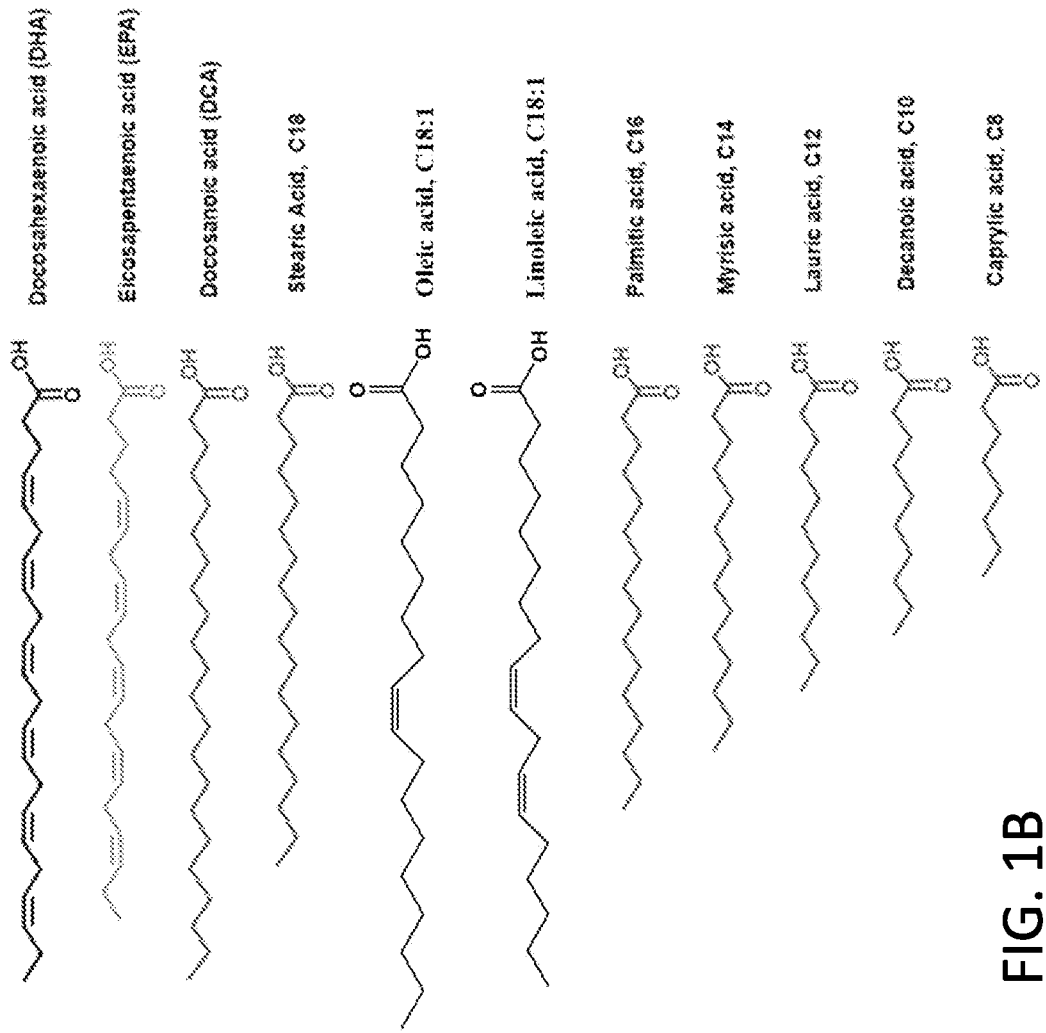
Docosahexaenoic acid (DHA)
Eicosapentaenoic acid (EPA)
Docosanoic acid (DCA)
Stearic Acid, C18
Oleic acid, C18:1
Linoleic acid, C18:1
Palmitic acid, C16
Myristic acid, C14
Lauric acid, C12
Decanoic acid, C10
Caprylic acid, C8

FIG. 1B

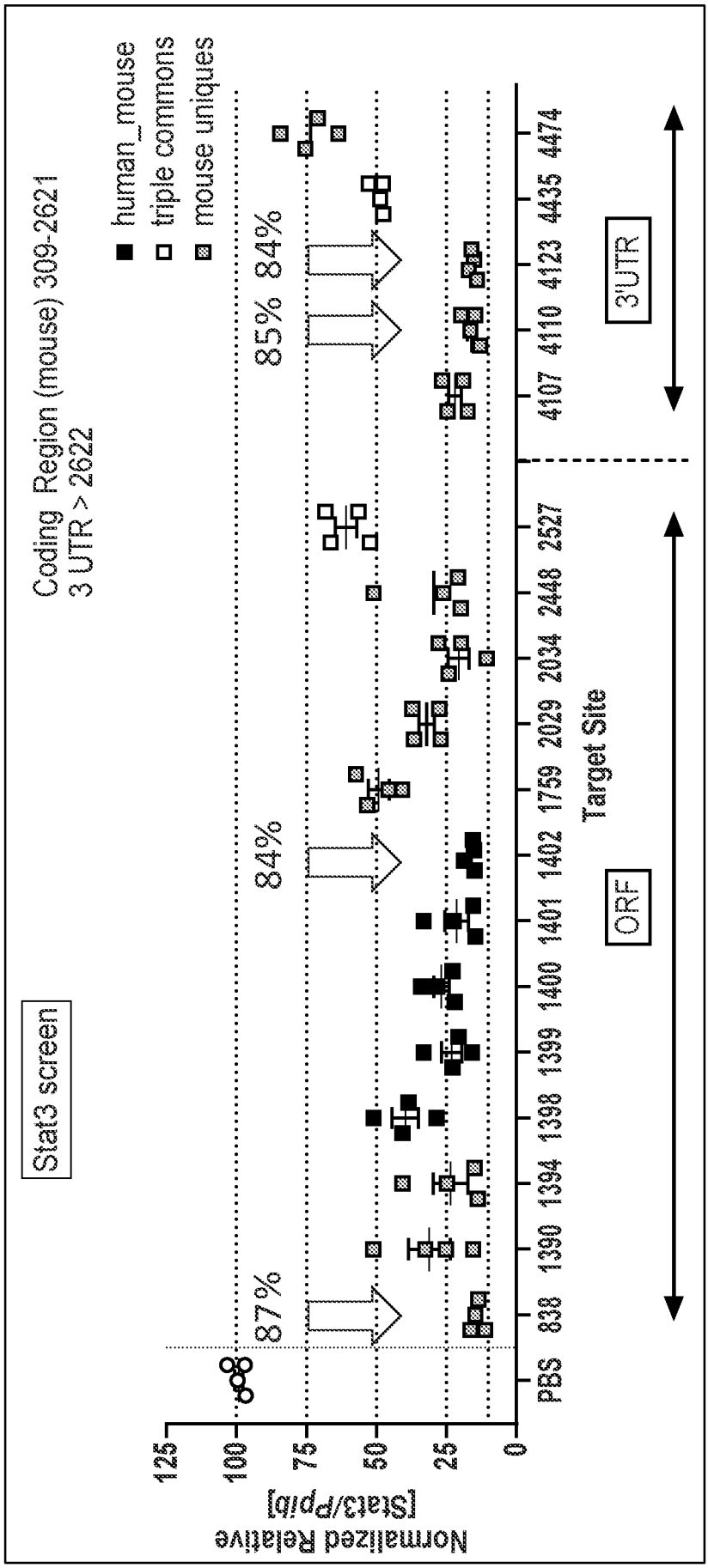
Stat3 screen
Coding Region (mouse) 309-2621
3 UTR > 2622
human_mouse
triple commons
mouse uniques
87%
84%
85%
84%
ORF
3'UTR
Target Site
PBS 838 1390 1394 1398 1399 1400 1401 1402 1759 2029 2034 2448 2527 4107 4110 4123 4435 4474
0 25 50 75 100 125
Normalized Relative [Stat3/Ppib]

FIG. 2A

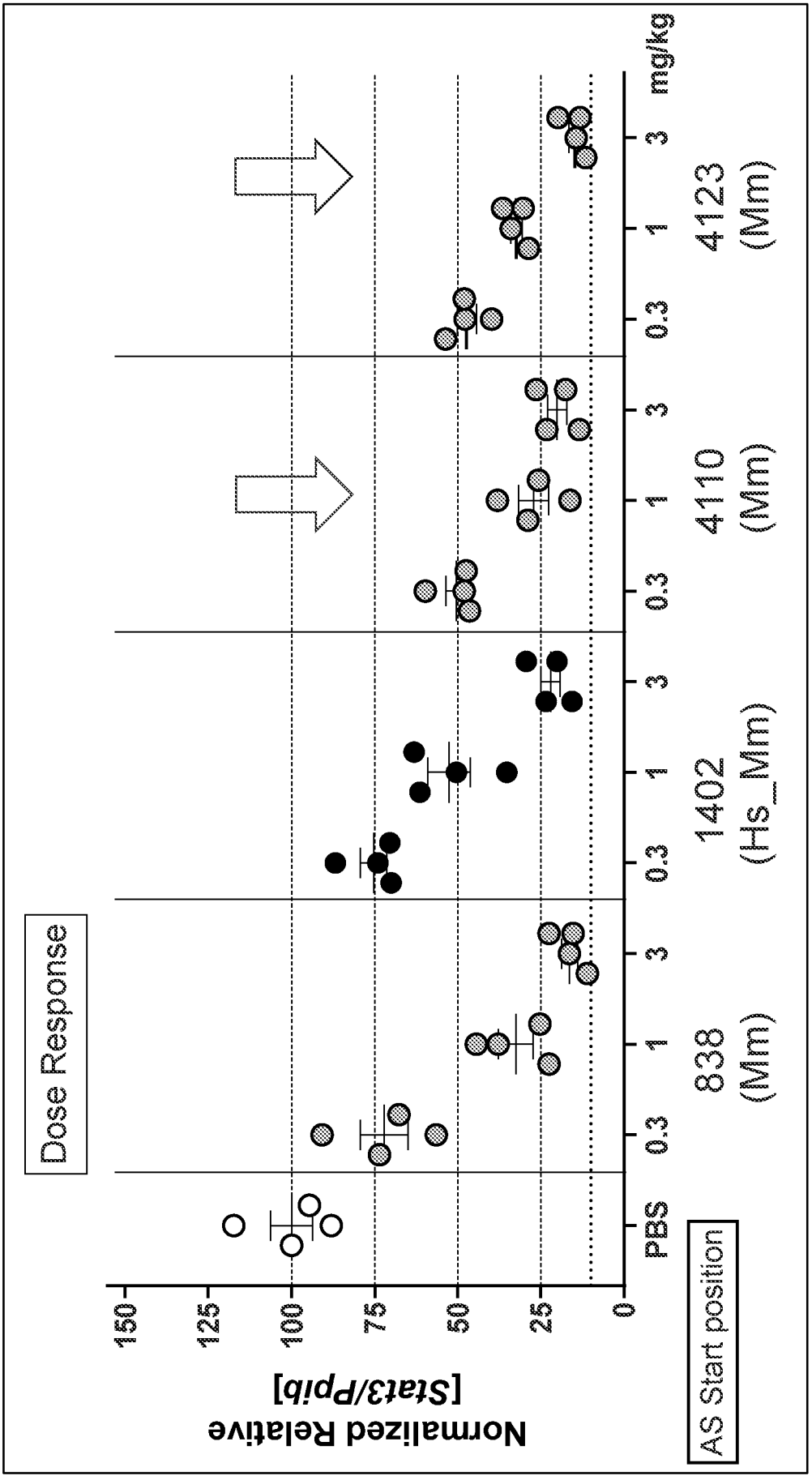
Normalized Relative
[Stat3/Ppib]
150
125
100
75
50
25
0
Dose Response
AS Start position
PBS
0.3
1
3
0.3
1
3
0.3
1
3
0.3
1
3
mg/kg
838
(Mm)
1402
(Hs_Mm)
4110
(Mm)
4123
(Mm)

FIG. 2B

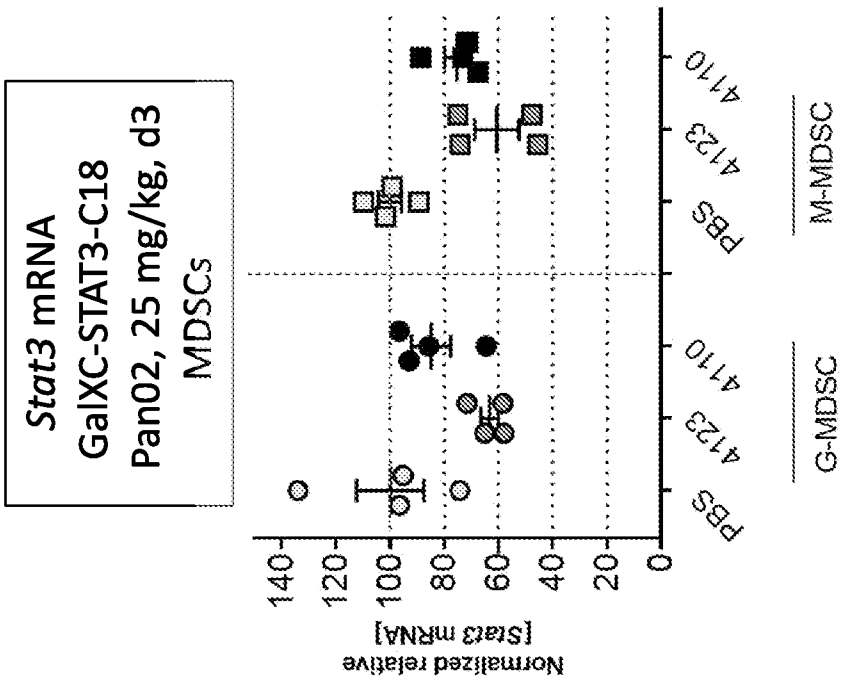
Stat3 mRNA
GalXC-STAT3-C18
Pan02, 25 mg/kg, d3
MDSCs
Normalized relative [Stat3 mRNA]
140
120
100
80
60
40
20
0
PBS
4123
4110
PBS
4123
4110
G-MDSC
M-MDSC

FIG. 3A

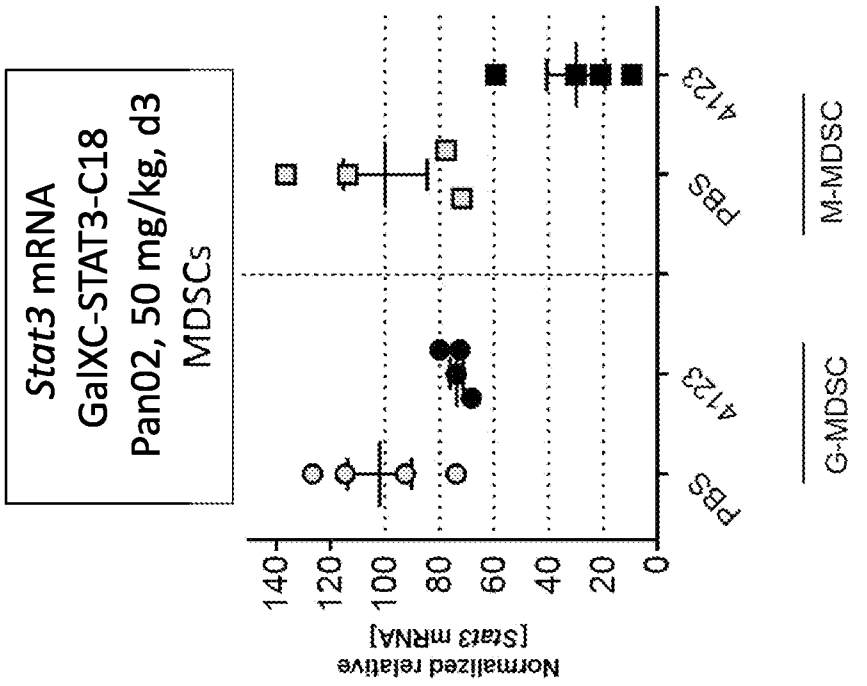
Stat3 mRNA
GalXC-STAT3-C18
Pan02, 50 mg/kg, d3
MDSCs
Normalized relative
[Stat3 mRNA]
140
120
100
80
60
40
20
0
PBS
4123
PBS
4123
G-MDSC
M-MDSC

FIG. 3B

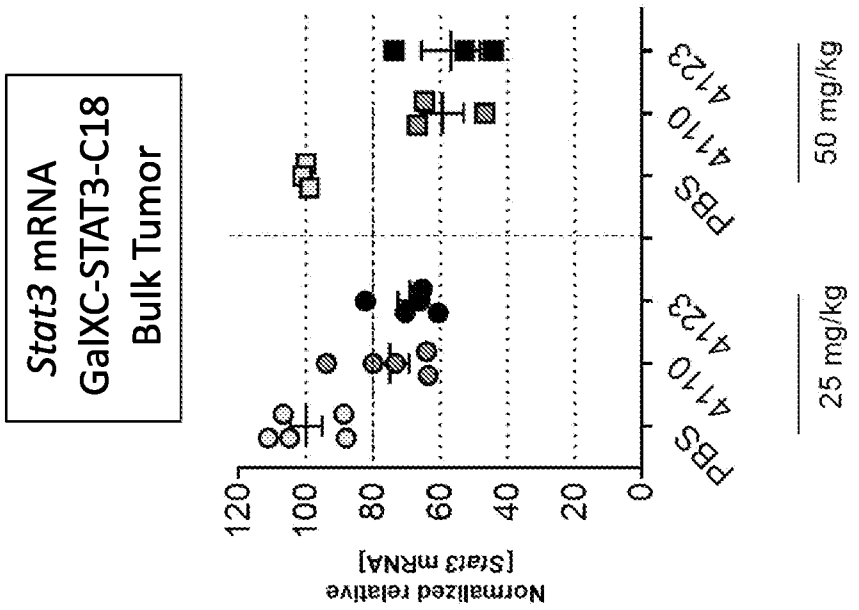
Stat3 mRNA
GalXC-STAT3-C18
Bulk Tumor
Normalized relative
[Stat3 mRNA]
120
100
80
60
40
20
0
PBS
4110
4123
PBS
4110
4123
25 mg/kg
50 mg/kg

FIG. 4A

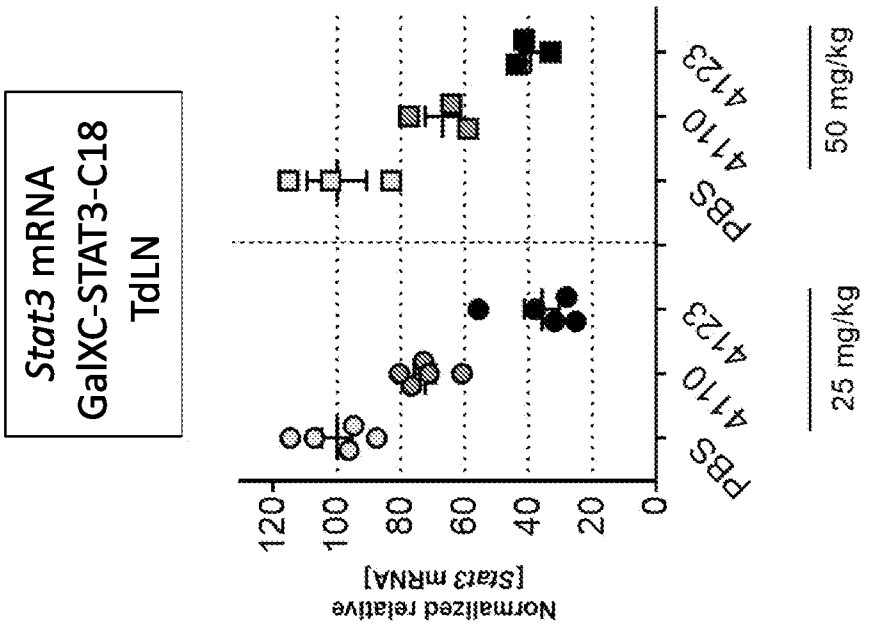
Stat3 mRNA
GalXC-STAT3-C18
TdLN
Normalized relative
[Stat3 mRNA]
120
100
80
60
40
20
0
PBS
A110
A123
PBS
A110
A123
25 mg/kg
50 mg/kg

FIG. 4B

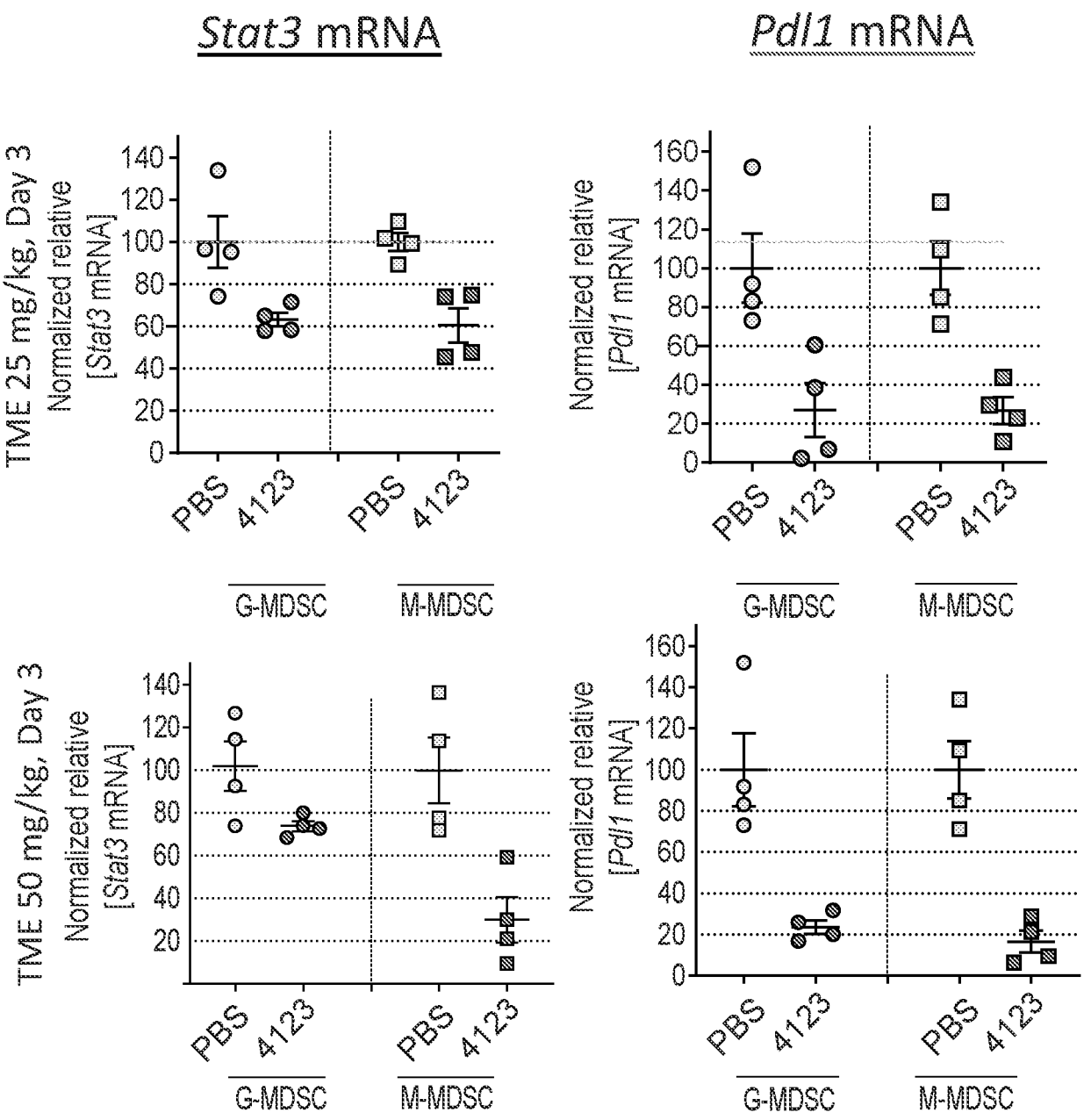
Stat3 mRNA
Pd/1 mRNA
TME 25 mg/kg, Day 3
TME 50 mg/kg, Day 3
Normalized relative [Stat3 mRNA]
Normalized relative [Pd/1 mRNA]
PBS
4123
G-MDSC
M-MDSC

FIG. 5A

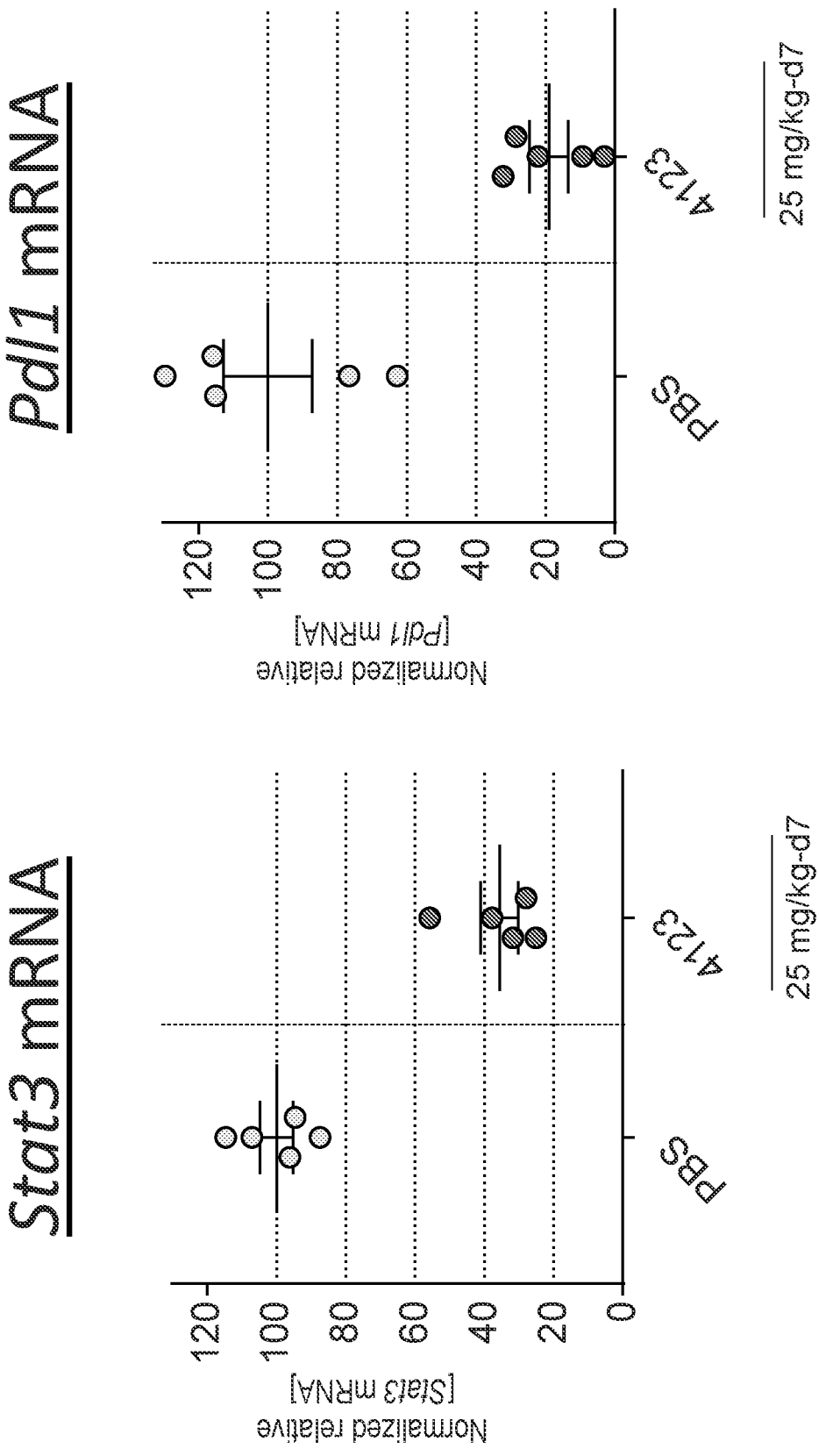
TdLN 25 mg/kg, Day 7
Stat3 mRNA
Normalized relative
[Stat3 mRNA]
120
100
80
60
40
20
0
PBS
A123
25 mg/kg-d7
Pdl1 mRNA
Normalized relative
[Pdl1 mRNA]
120
100
80
60
40
20
0
PBS
A123
25 mg/kg-d7

FIG. 5B

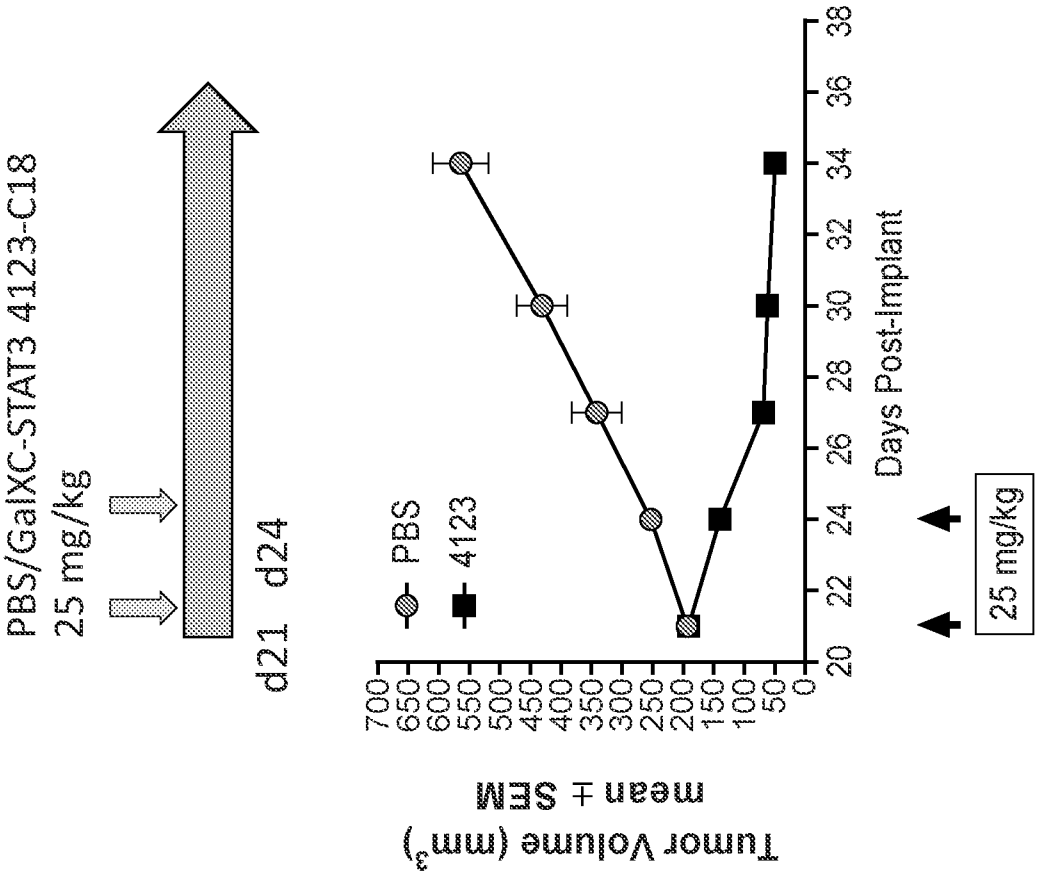
PBS/GalXC-STAT3 4123-C18
25 mg/kg
d21 d24
Tumor Volume (mm³)
mean ± SEM
PBS
4123
Days Post-Implant
25 mg/kg

FIG. 6B

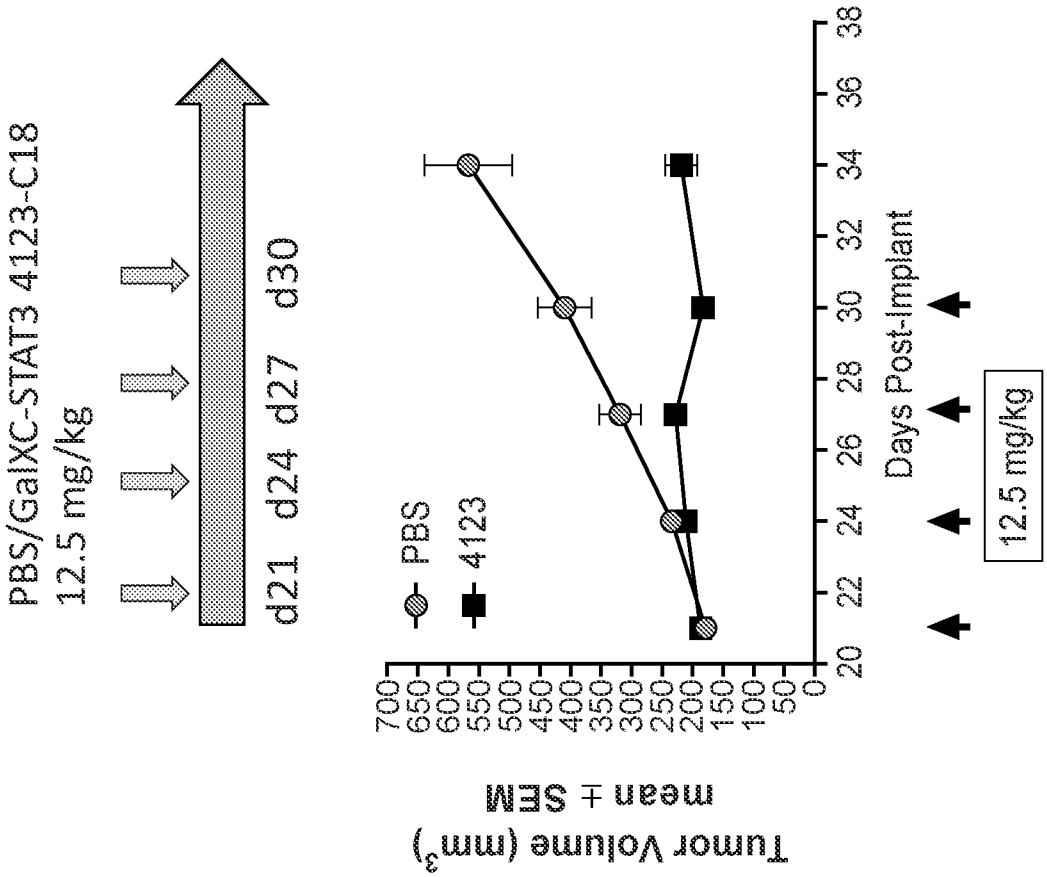
PBS/GalXC-STAT3 4123-C18
12.5 mg/kg
d21 d24 d27 d30
Tumor Volume (mm³)
mean ± SEM
PBS
4123
Days Post-Implant
12.5 mg/kg

FIG. 6A

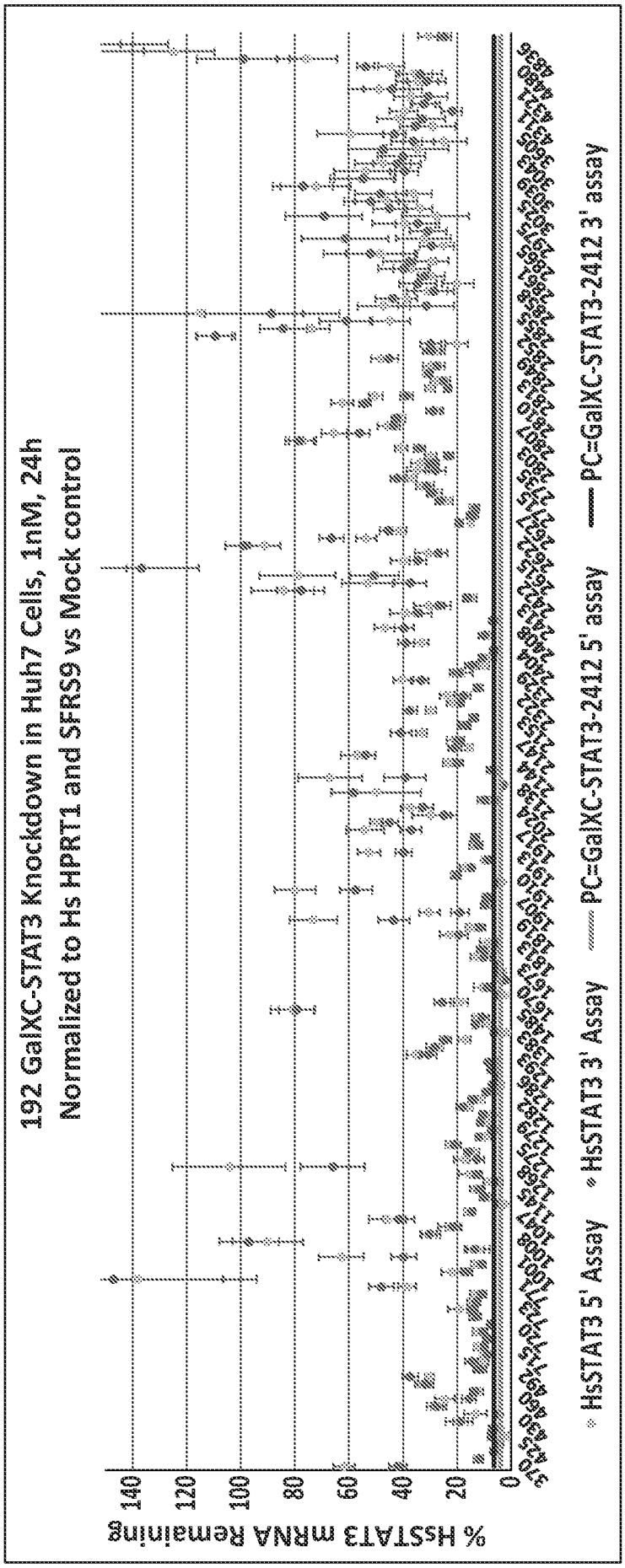
192 GalXC-STAT3 Knockdown in Huh7 Cells, 1nM, 24h
Normalized to Hs HPRT1 and SFRS9 vs Mock control
% HsSTAT3 mRNA Remaining
140
120
100
80
60
40
20
0
HsSTAT3 5' Assay
HsSTAT3 3' Assay
PC=GalXC-STAT3-2412 5' assay
PC=GalXC-STAT3-2412 3' assay

FIG. 7

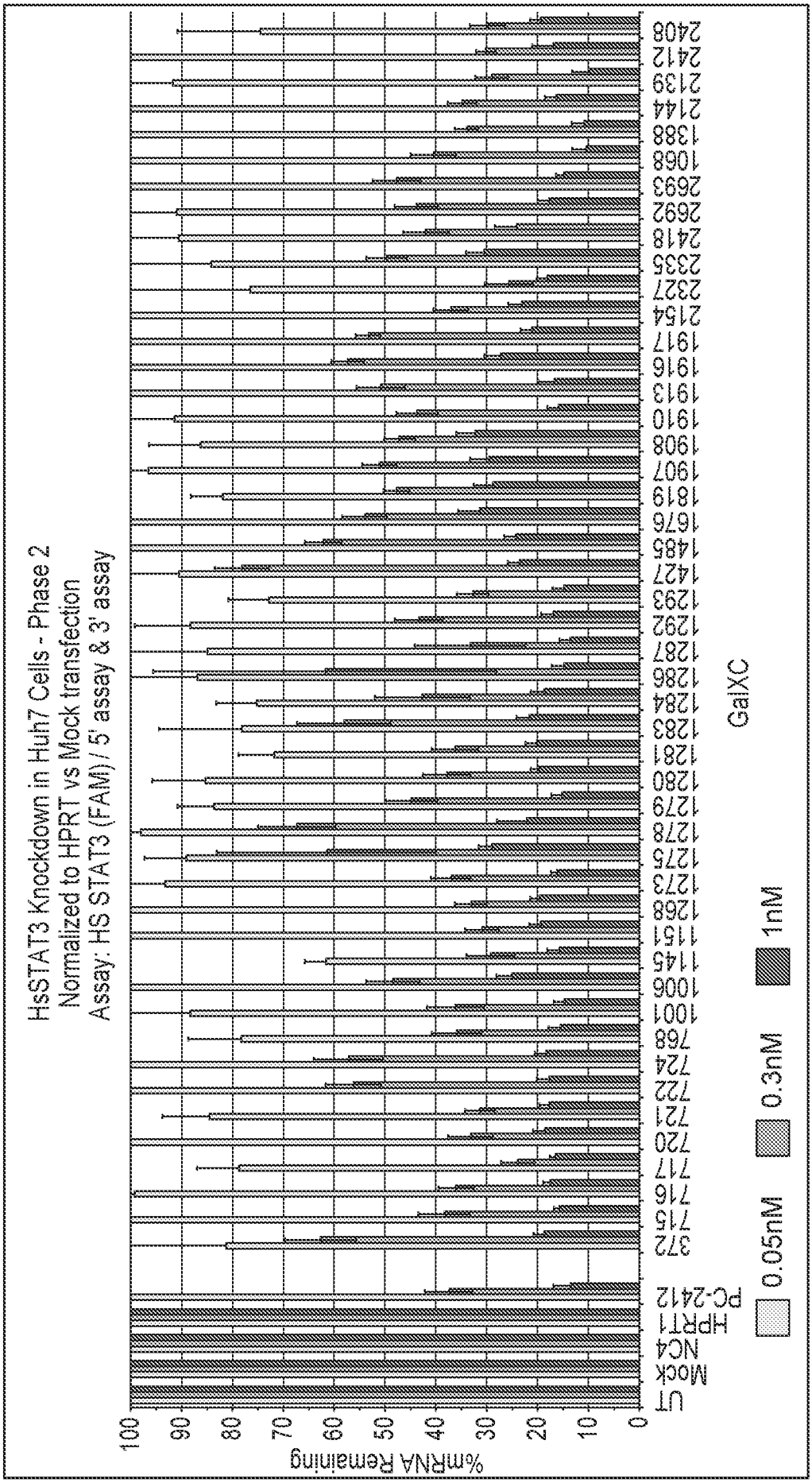
HsSTAT3 Knockdown in Huh7 Cells - Phase 2
Normalized to HPRT vs Mock transfection
Assay: HS STAT3 (FAM) / 5' assay & 3' assay
%mRNA Remaining
100
90
80
70
60
50
40
30
20
10
0
UT
Mock
NC4
HPRT1
PC-2412
372
715
716
717
720
721
722
724
768
1001
1006
1145
1151
1268
1273
1275
1278
1279
1280
1281
1283
1284
1286
1287
1292
1293
1427
1485
1676
1819
1907
1908
1910
1913
1916
1917
2154
2327
2335
2418
2692
2693
1068
1388
2144
2139
2412
2408
GalXC
0.05nM
0.3nM
1nM

FIG. 8A

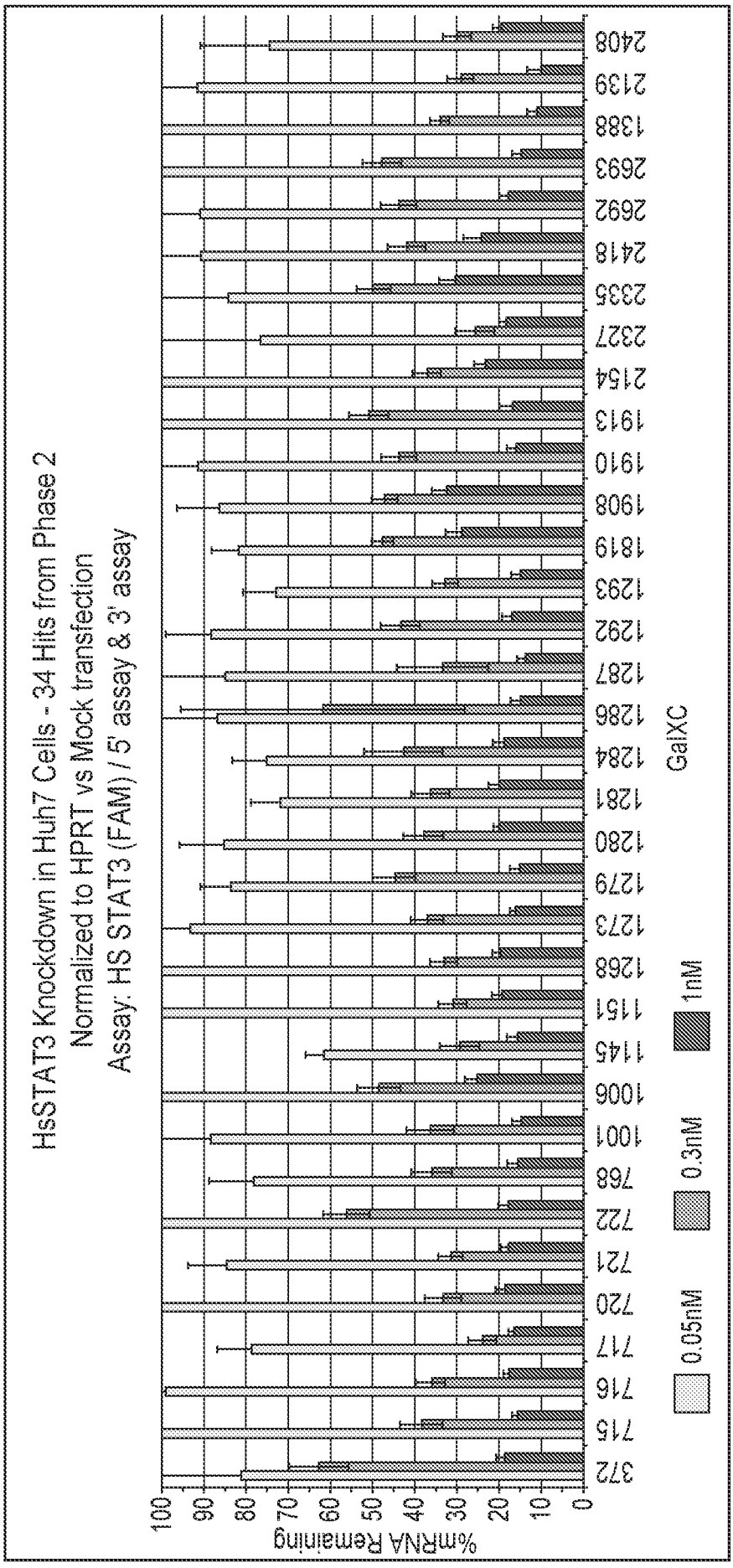
HsSTAT3 Knockdown in Huh7 Cells - 34 Hits from Phase 2
Normalized to HPRT vs Mock transfection
Assay: HS STAT3 (FAM) / 5' assay & 3' assay
%mRNA Remaining
100
90
80
70
60
50
40
30
20
10
0
372
715
716
717
720
721
722
768
1001
1006
1145
1151
1268
1273
1279
1280
1281
1284
1286
1287
1292
1293
1819
1908
1910
1913
2154
2327
2335
2418
2692
2693
1388
2139
2408
GalXC
0.05nM
0.3nM
1nM

FIG. 8B

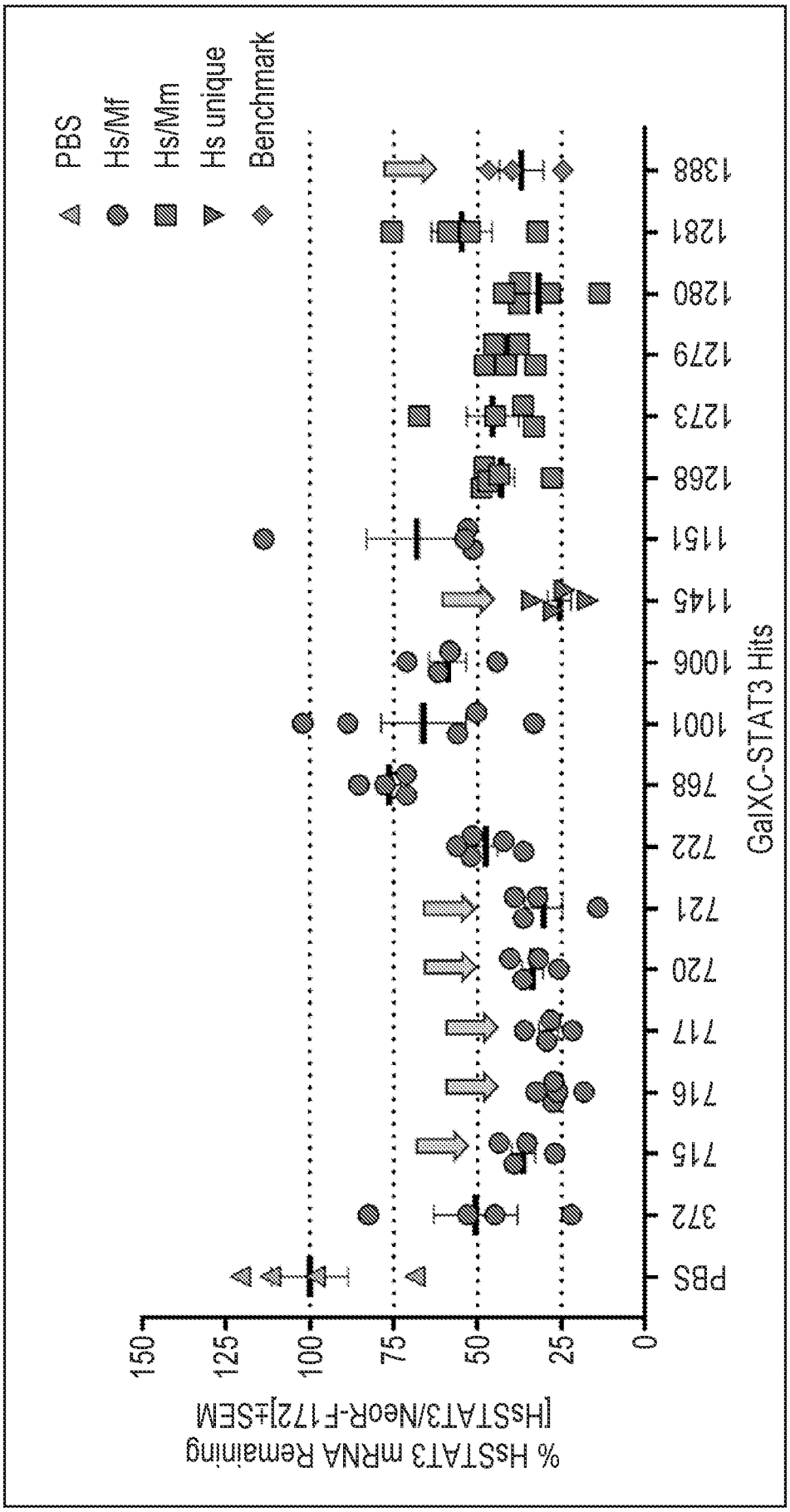
PBS
Hs/Mf
Hs/Mm
Hs unique
Benchmark
% HsSTAT3 mRNA Remaining
[HsSTAT3/NeoR-F172]±SEM
150
125
100
75
50
25
0
PBS
372
715
716
717
720
721
722
768
1001
1006
1145
1151
1268
1273
1279
1280
1281
1388
GalXC-STAT3 Hits

FIG. 9A

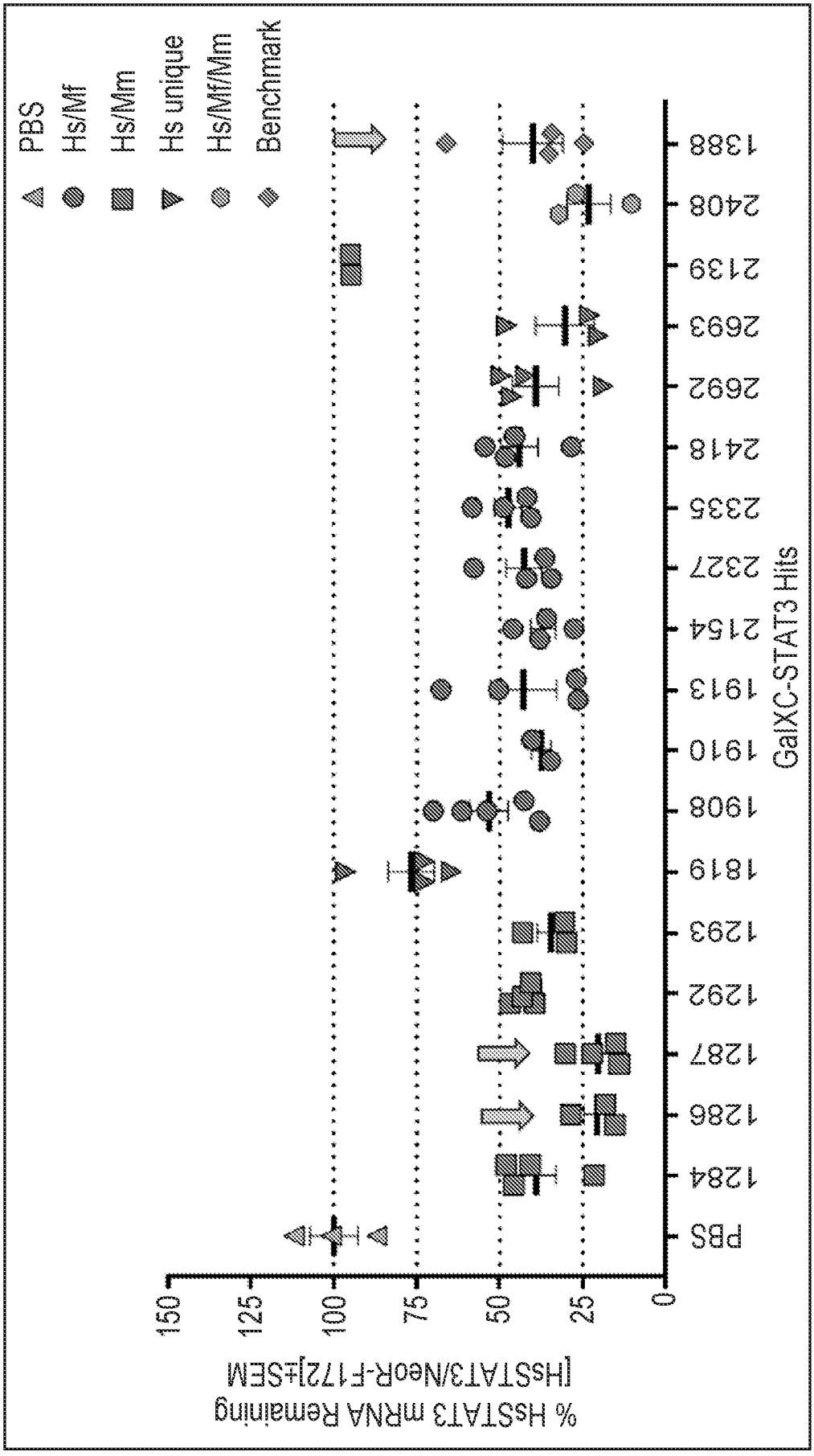
PBS
Hs/Mf
Hs/Mm
Hs unique
Hs/Mf/Mm
Benchmark
% HsSTAT3 mRNA Remaining
[HsSTAT3/NeoR-F172]±SEM
150
125
100
75
50
25
0
PBS
1284
1286
1287
1292
1293
1819
1908
1910
1913
2154
2327
2335
2418
2692
2693
2139
2408
1388
GalXC-STAT3 Hits

FIG. 9B

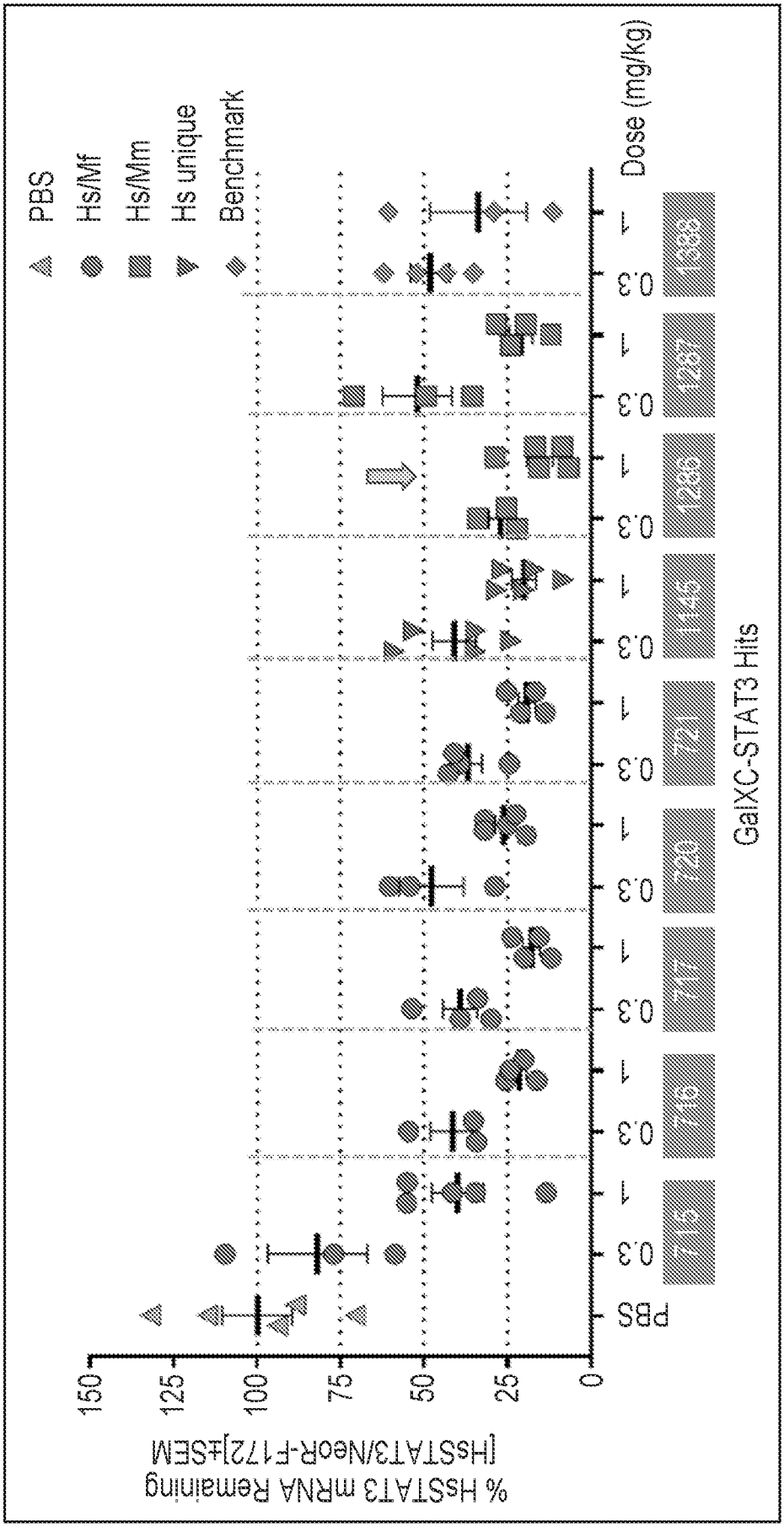
% hSSTAT3 mRNA Remaining
[hSSTAT3/NeoR-F172]±SEM
150
125
100
75
50
25
0
PBS
0.3
1
0.3
1
0.3
1
0.3
1
0.3
1
0.3
1
0.3
1
Dose (mg/kg)
PBS
Hs/Mf
Hs/Mm
Hs unique
Benchmark
716
716
717
720
721
1145
1269
1297
1698
GalXC-STAT3 Hits

FIG. 10

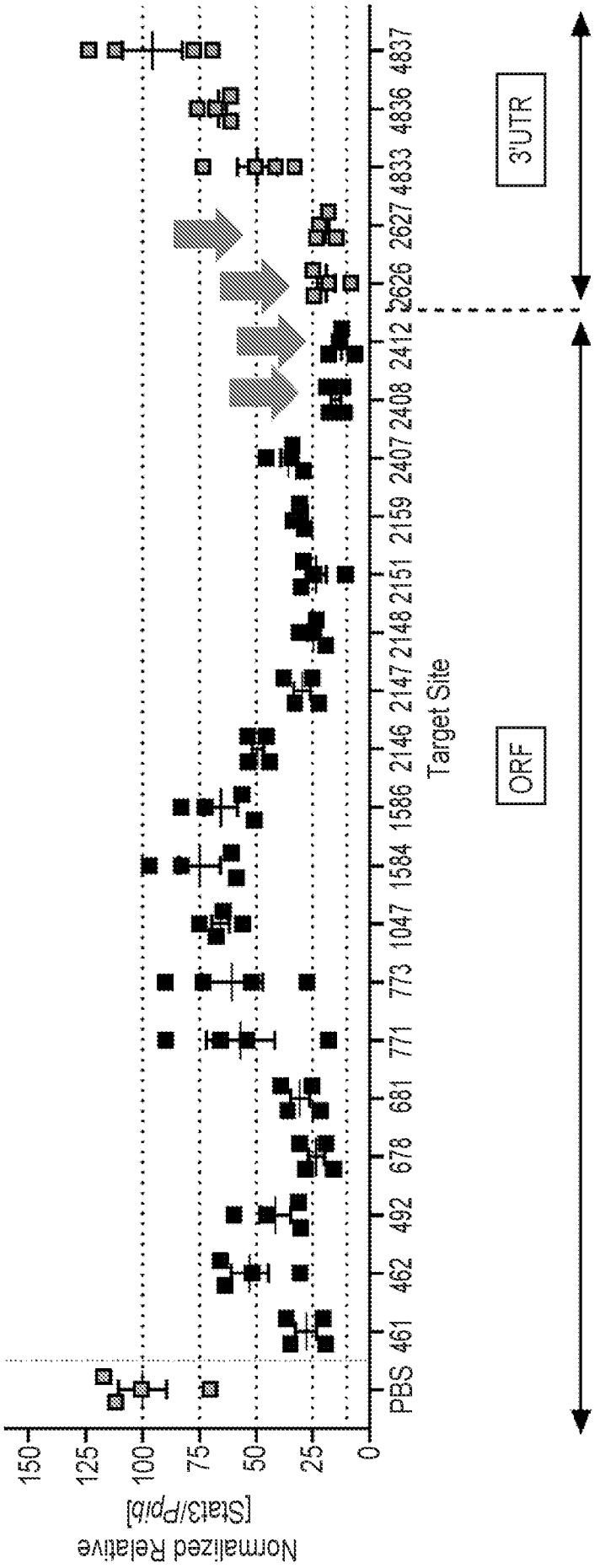
Normalized Relative
[Stat3/Ppib]
150
125
100
75
50
25
0
PBS 461 462 492 678 681 771 773 1047 1584 1586 2146 2147 2148 2151 2159 2407 2408 2412 2626 2627 4833 4836 4837
Target Site
ORF
3'UTR

FIG. 11

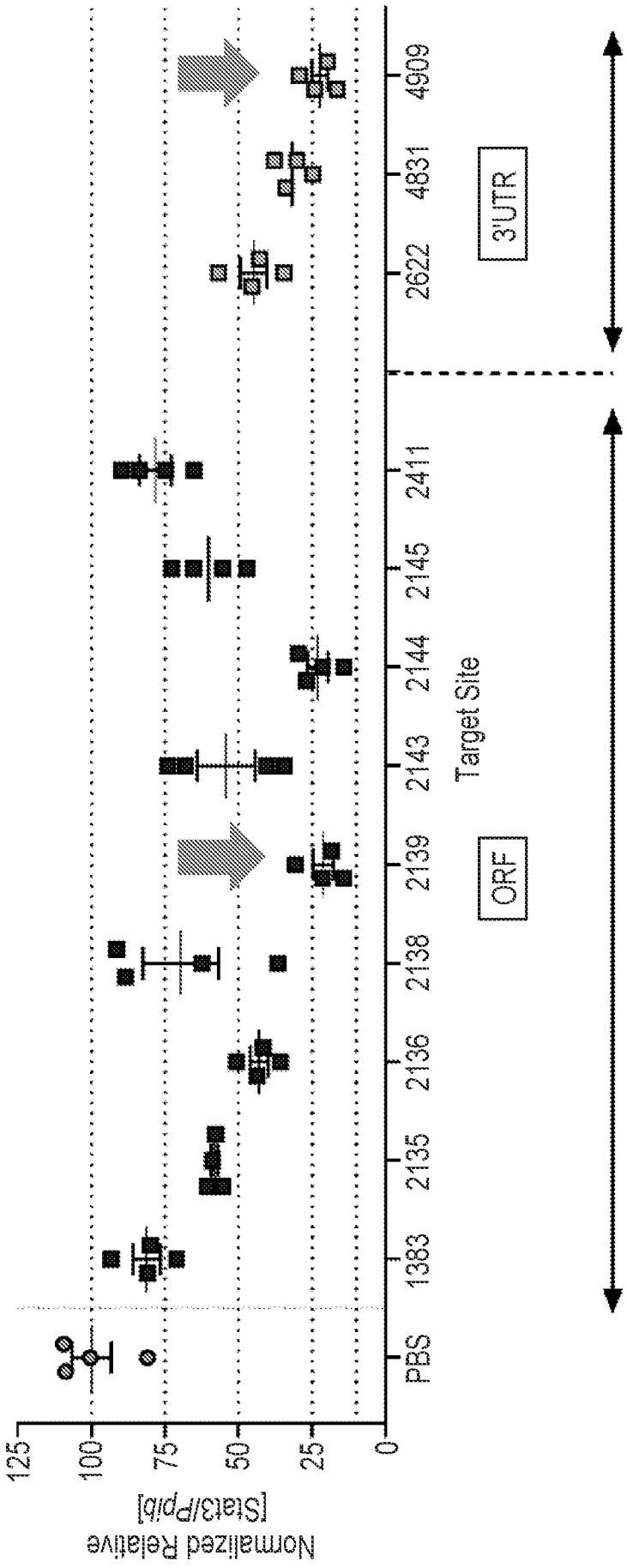
Normalized Relative
[Stat3/Ppib]
125
100
75
50
25
0
PBS
1383
2135
2136
2138
2139
2143
2144
2145
2411
2622
4831
4909
Target Site
ORF
3'UTR

FIG. 12

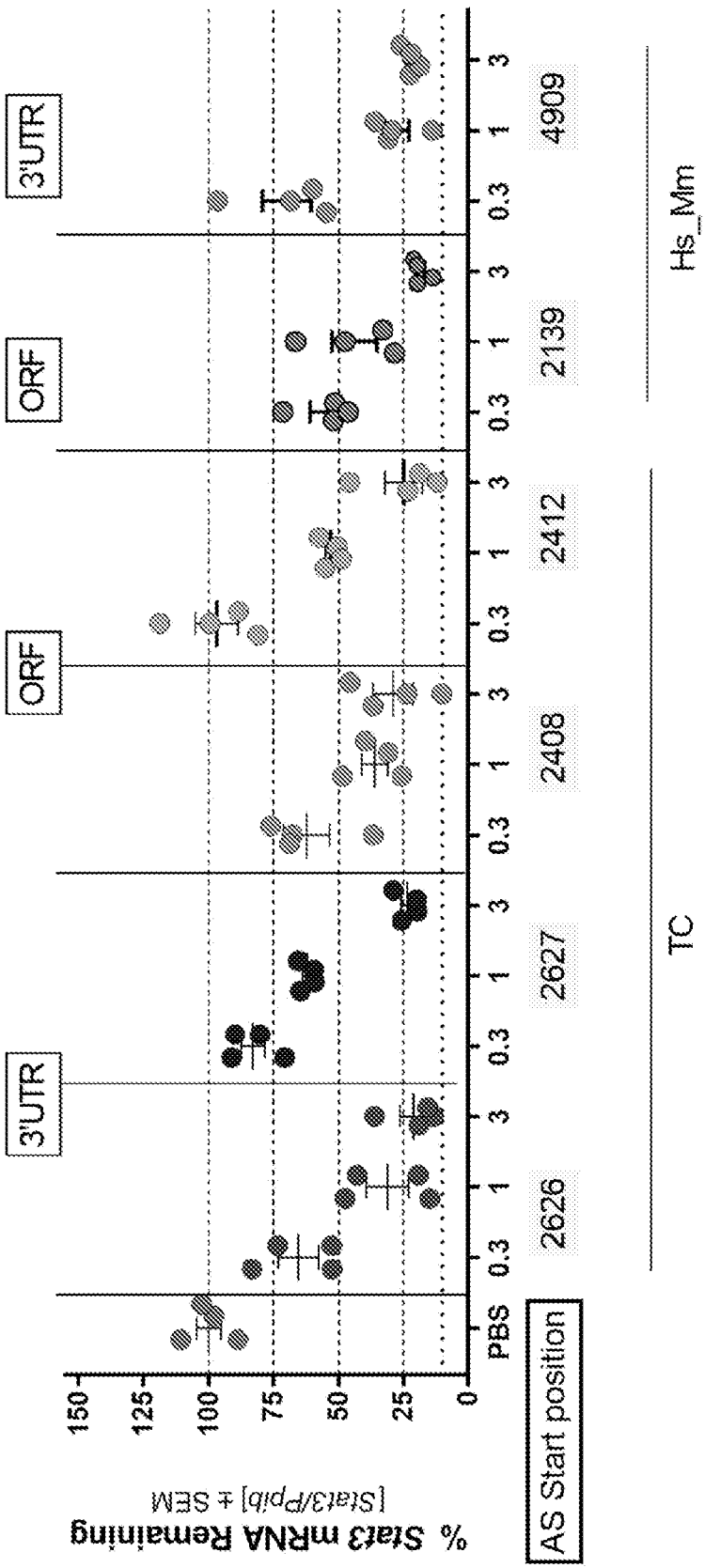
% Stat3 mRNA Remaining
[Stat3/Ppib] ± SEM
150
125
100
75
50
25
0
PBS
0.3
1
3
0.3
1
3
0.3
1
3
0.3
1
3
0.3
1
3
3'UTR
ORF
ORF
3'UTR
AS Start position
2626
2627
2408
2412
2139
4909
TC
Hs_Mm

FIG. 13A

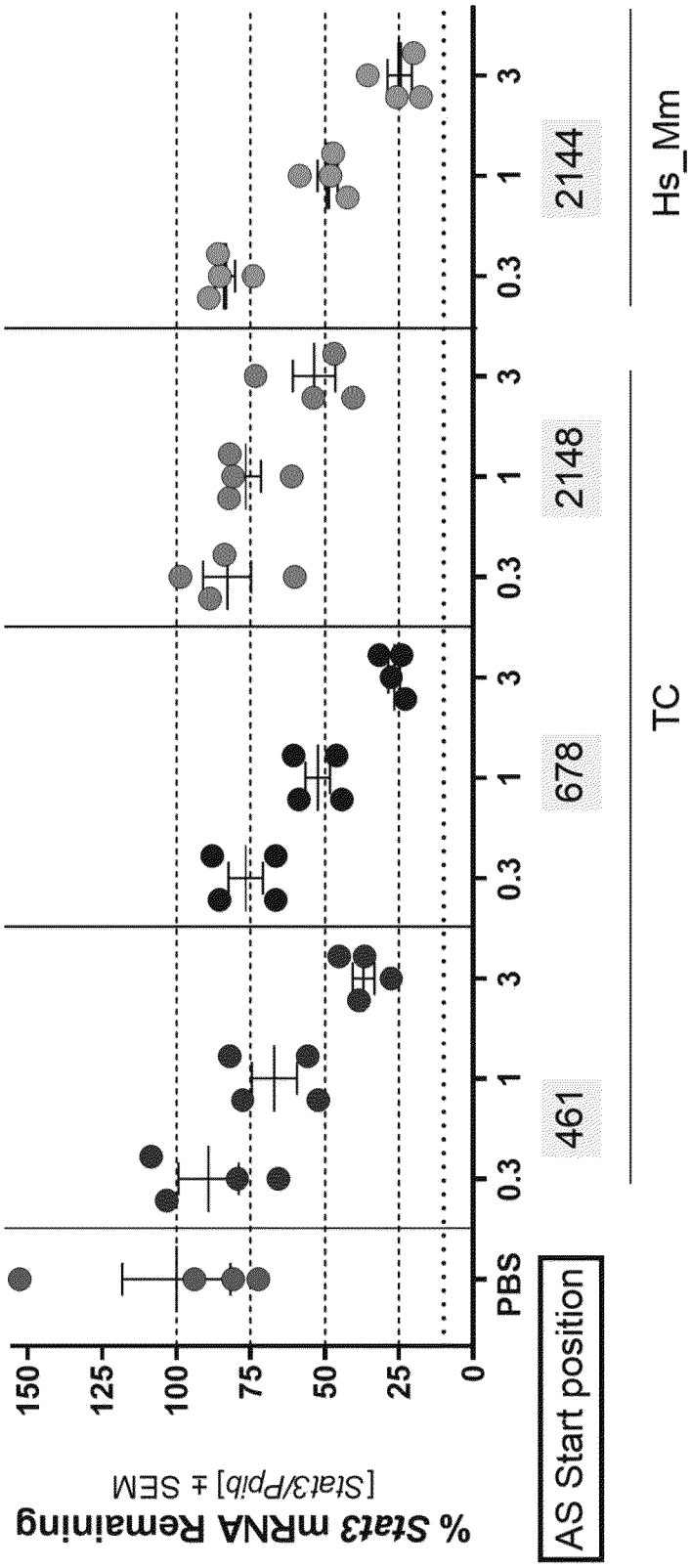
% Stat3 mRNA Remaining
[Stat3/Ppib] ± SEM
150
125
100
75
50
25
0
PBS
0.3
1
3
0.3
1
3
0.3
1
3
0.3
1
3
AS Start position
461
678
2148
2144
TC
Hs_Mm

FIG. 13B

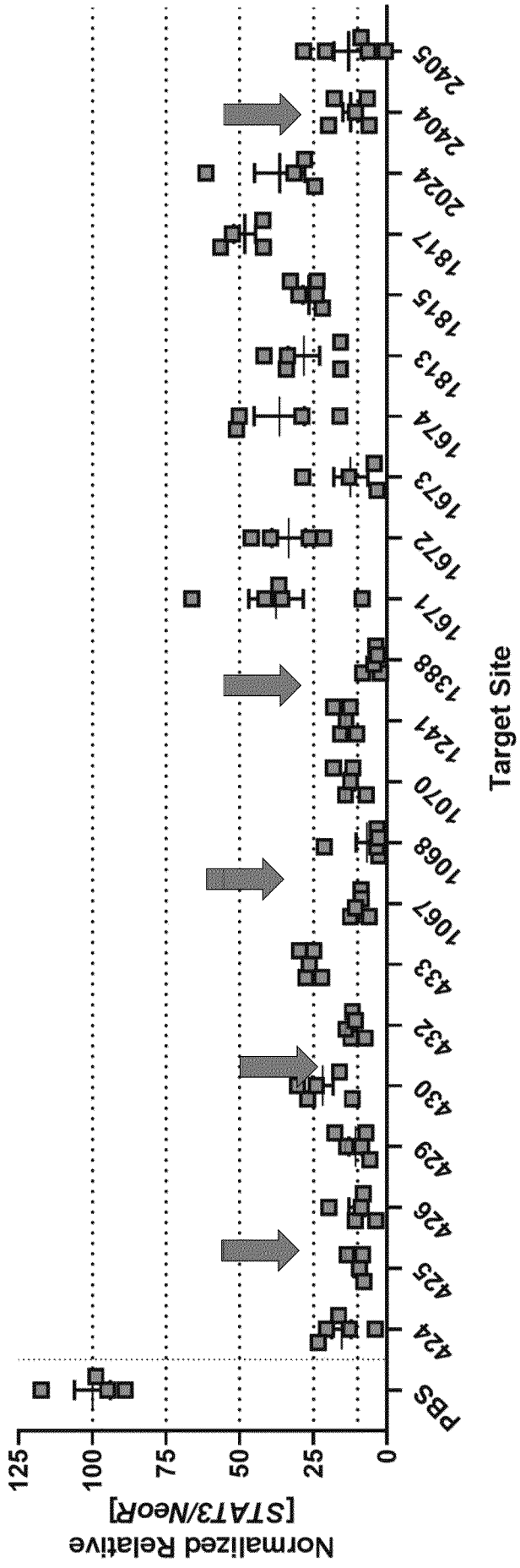
Normalized Relative [STAT3/NeoR]
125
100
75
50
25
0
PBS
424
425
426
429
430
432
433
1067
1068
1070
1241
1388
1671
1672
1673
1674
1813
1815
1817
2024
2404
2405
Target Site

FIG. 14

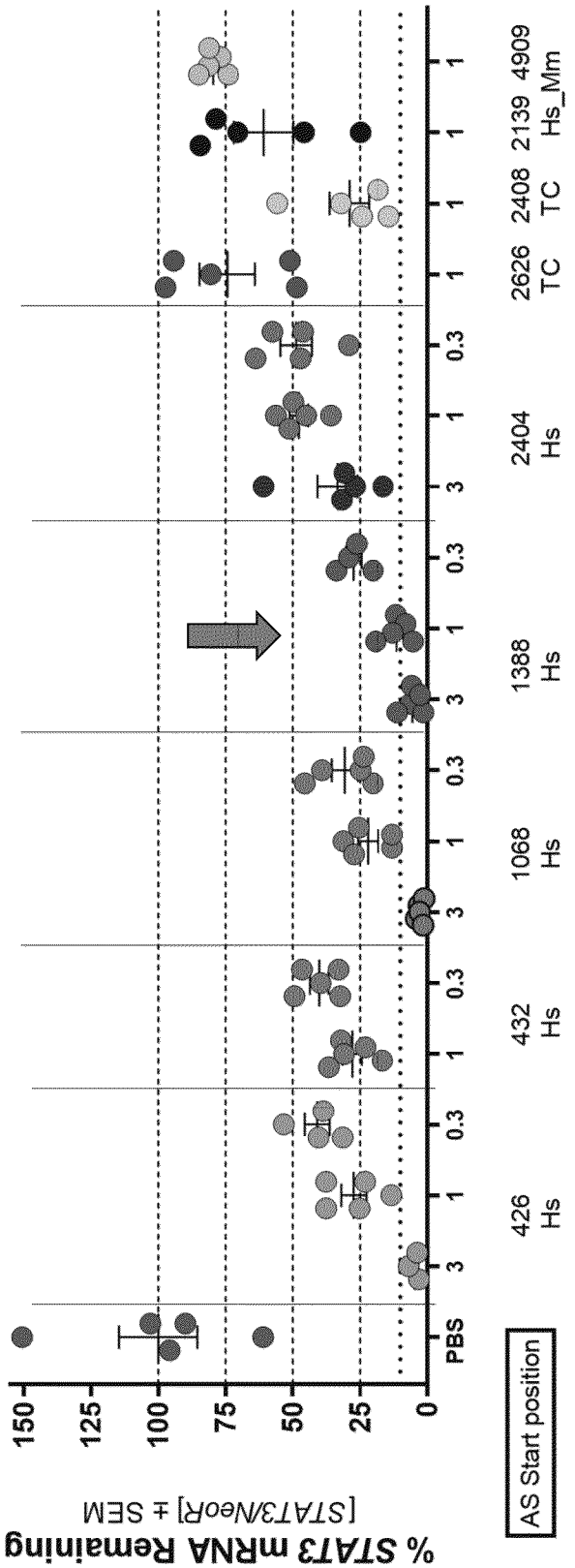
% STAT3 mRNA Remaining
[STAT3/NeoR] ± SEM
150
125
100
75
50
25
0
PBS
3
1
0.3
AS Start position
426 Hs
432 Hs
1068 Hs
1388 Hs
2404 Hs
2626 TC
2408 TC
2139 Hs_Mm
4909

FIG. 15

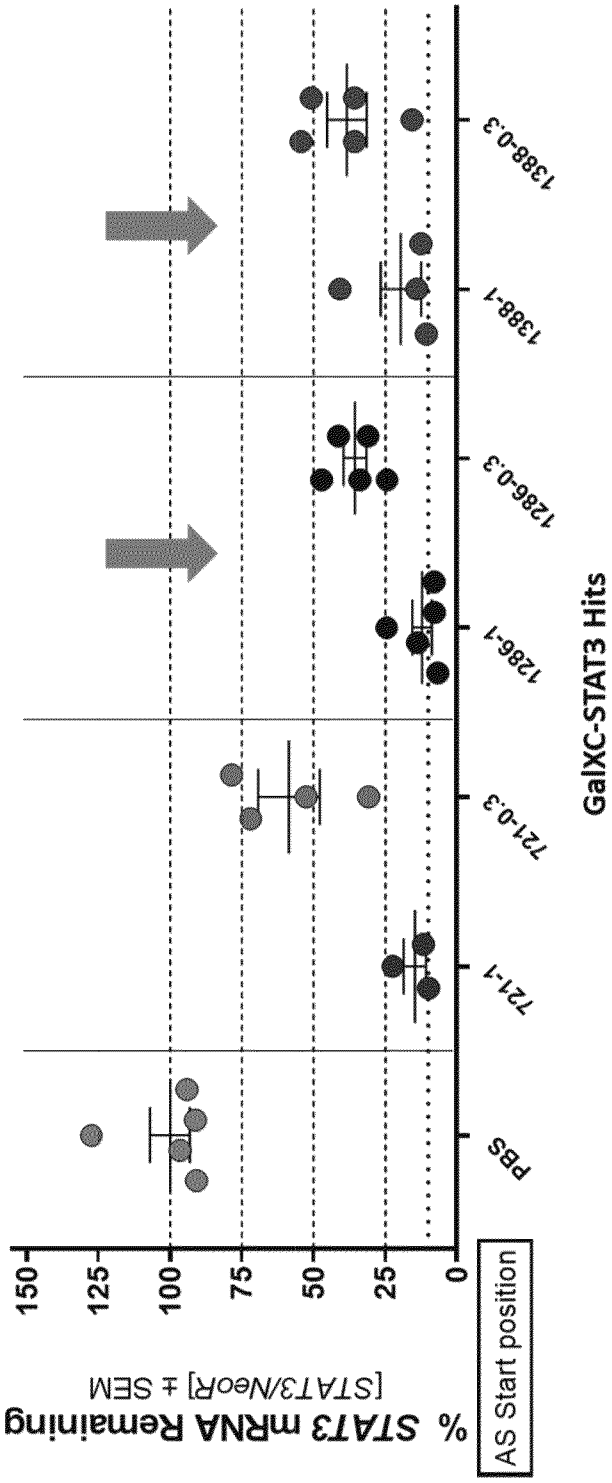
% STAT3 mRNA Remaining
[STAT3/NeoR] ± SEM
150
125
100
75
50
25
0
AS Start position
PBS
721-1
721-0.3
1286-1
1286-0.3
1388-1
1388-0.3
GalXC-STAT3 Hits

FIG. 16

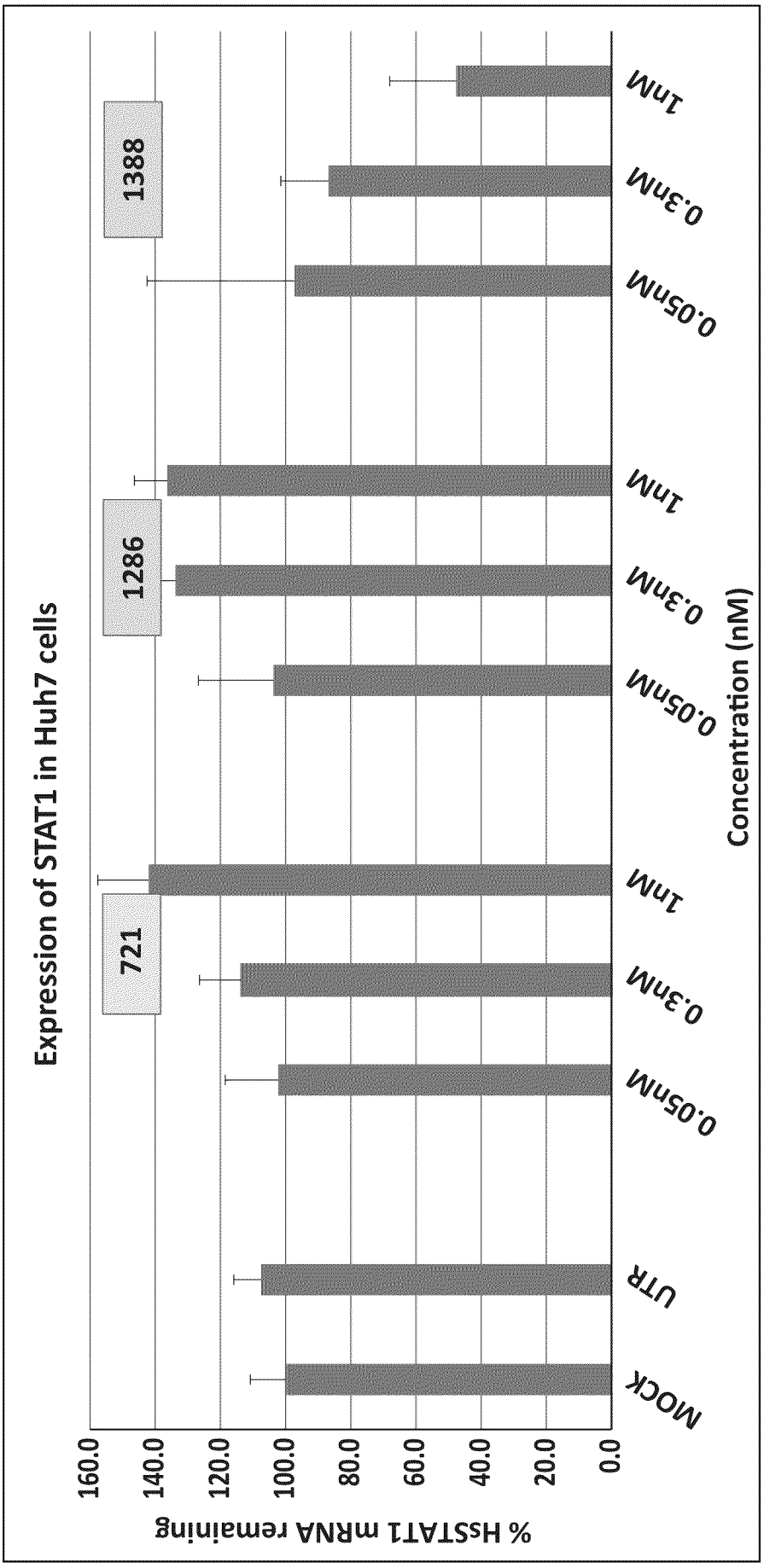
Expression of STAT1 in Huh7 cells
% hSSTAT1 mRNA remaining
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
MOCK
UTR
0.05nM
0.3nM
1nM
721
1286
1388
Concentration (nM)

FIG. 17

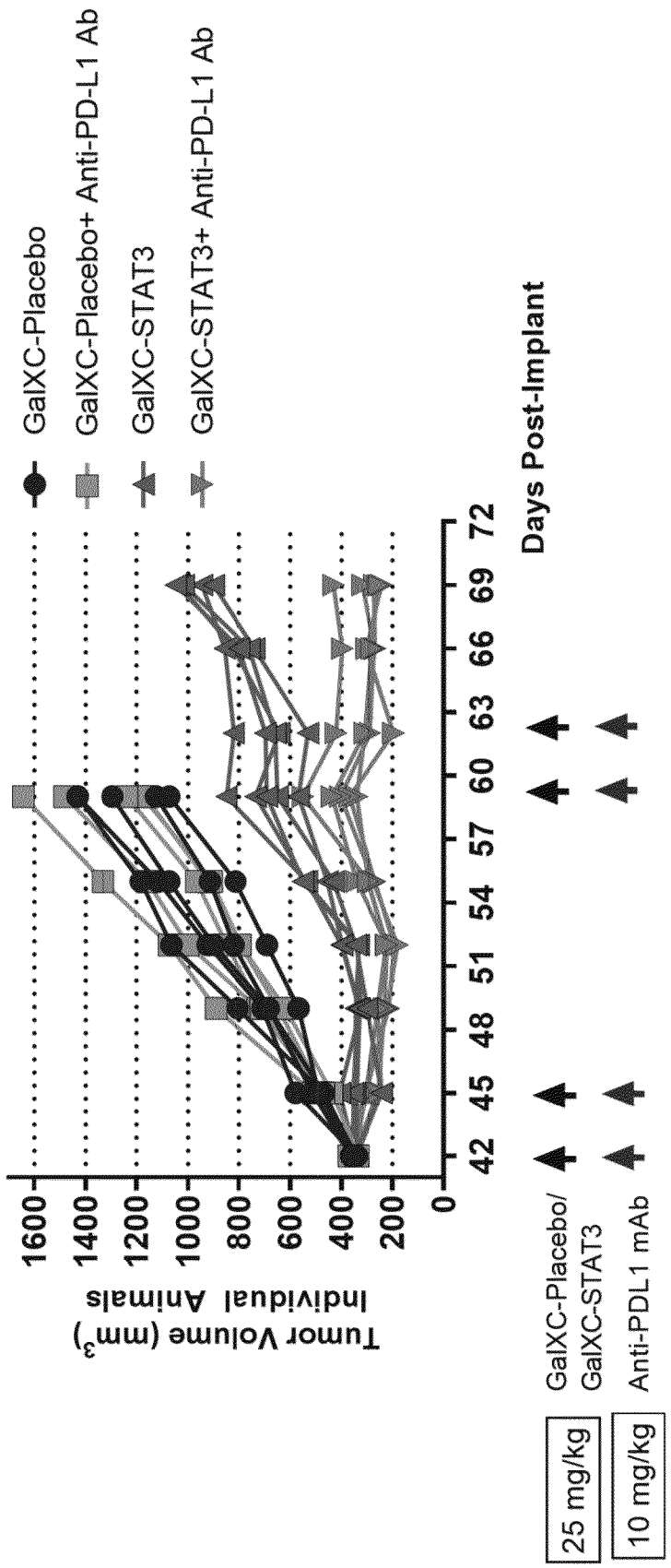
GalXC-Placebo
GalXC-Placebo+ Anti-PD-L1 Ab
GalXC-STAT3
GalXC-STAT3+ Anti-PD-L1 Ab
Tumor Volume (mm3)
Individual Animals
1600
1400
1200
1000
800
600
400
200
0
42 45 48 51 54 57 60 63 66 69 72
Days Post-Implant
GalXC-Placebo/
GalXC-STAT3
25 mg/kg
Anti-PDL1 mAb
10 mg/kg

FIG. 18A

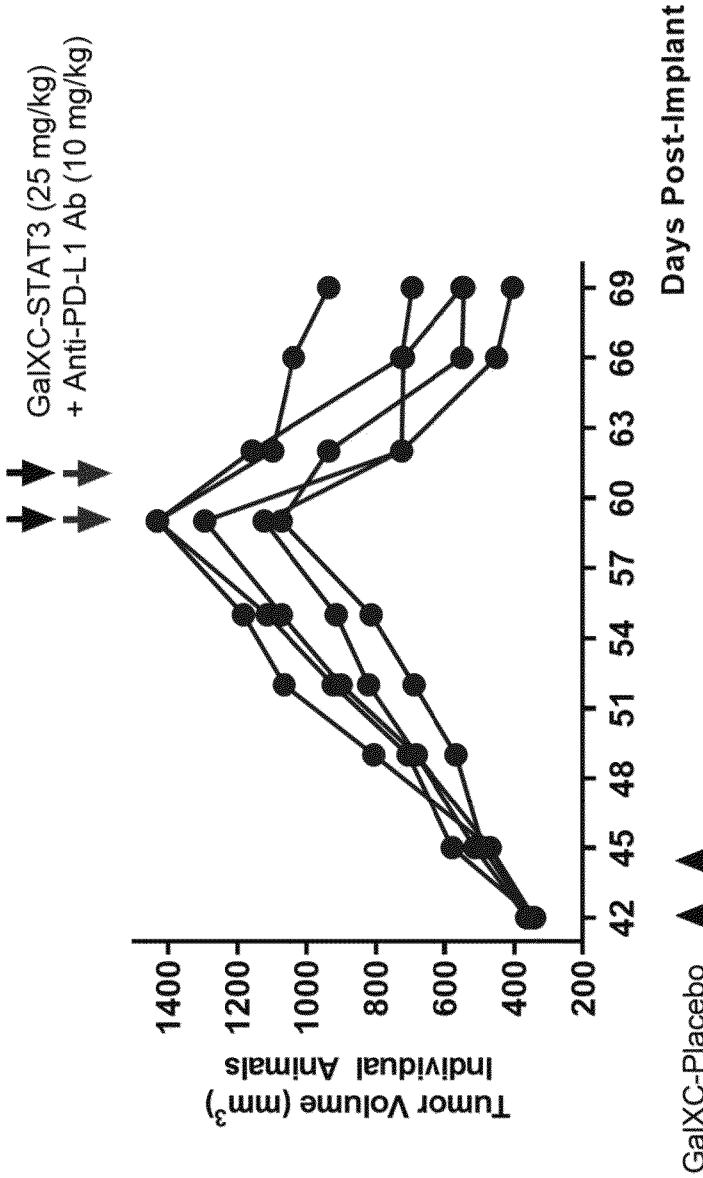
GalXC-STAT3 (25 mg/kg)
+ Anti-PD-L1 Ab (10 mg/kg)
Tumor Volume (mm3)
Individual Animals
1400
1200
1000
800
600
400
200
42
45
48
51
54
57
60
63
66
69
Days Post-Implant
GalXC-Placebo
25 mg/kg

FIG. 18B

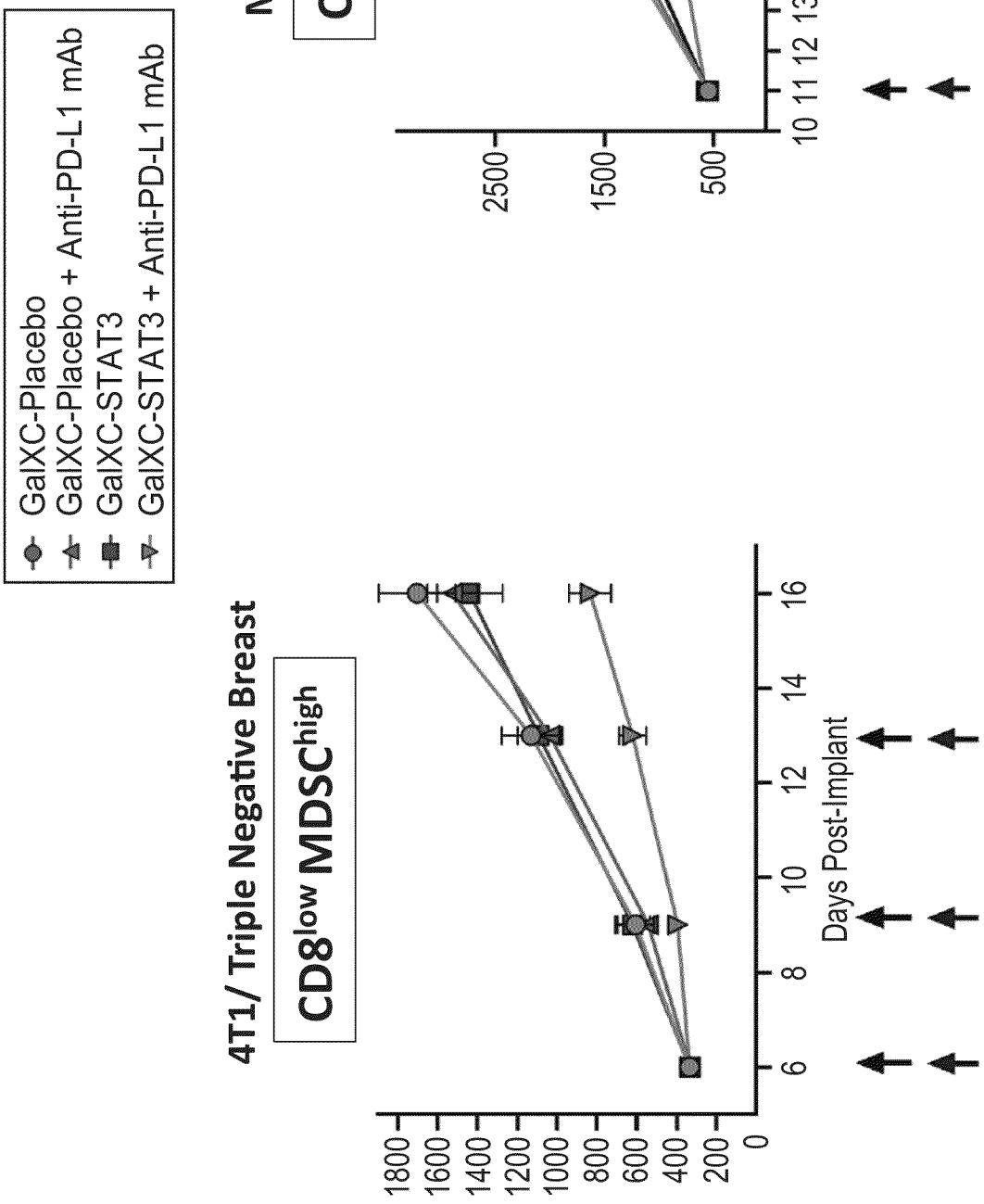

FIG. 19A

FIG. 19B

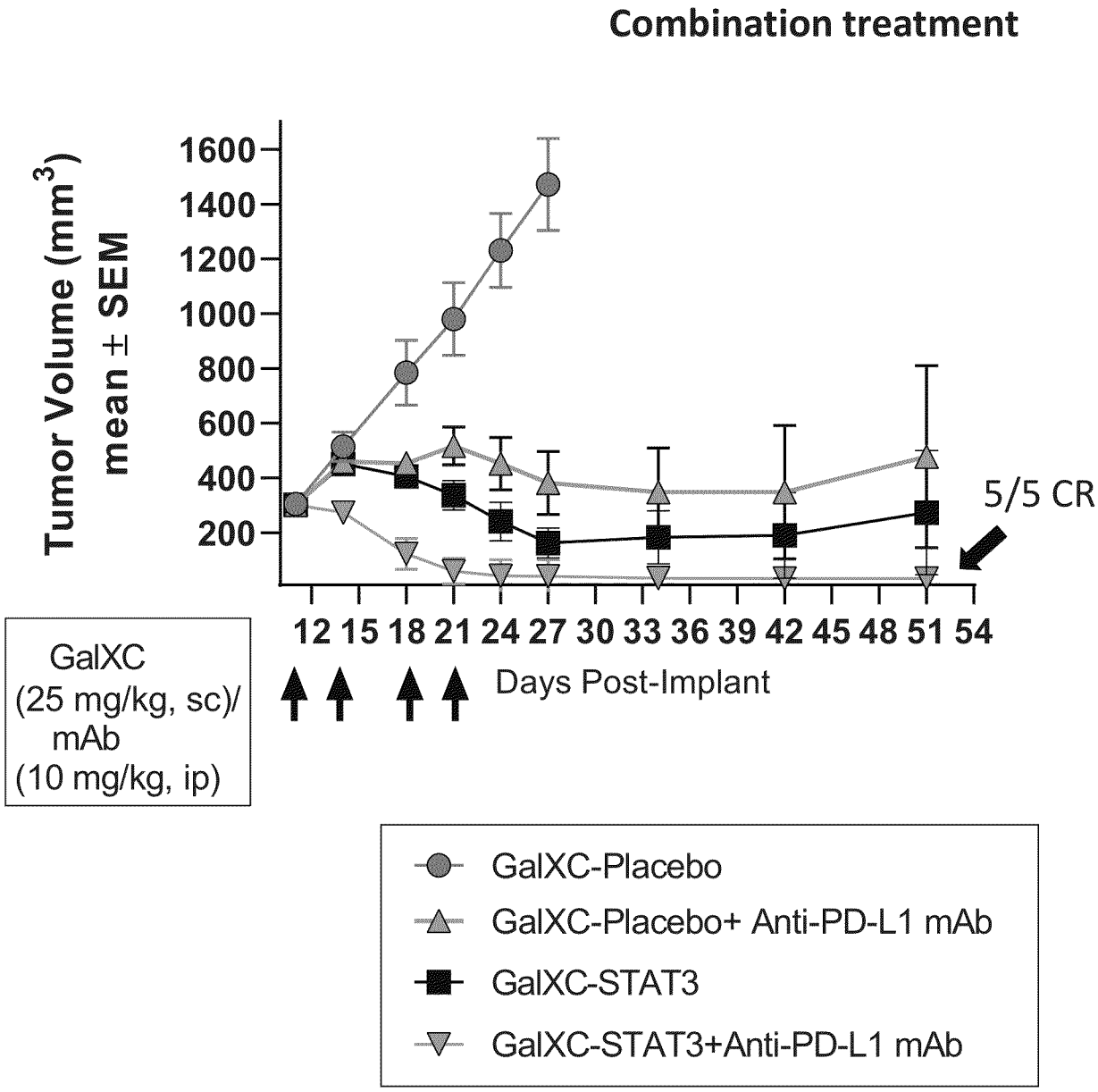
Combination treatment
Tumor Volume (mm^3)
mean ± SEM
1600
1400
1200
1000
800
600
400
200
5/5 CR
12 15 18 21 24 27 30 33 36 39 42 45 48 51 54
Days Post-Implant
GalXC
(25 mg/kg, sc)/
mAb
(10 mg/kg, ip)
GalXC-Placebo
GalXC-Placebo+ Anti-PD-L1 mAb
GalXC-STAT3
GalXC-STAT3+Anti-PD-L1 mAb

FIG. 19C

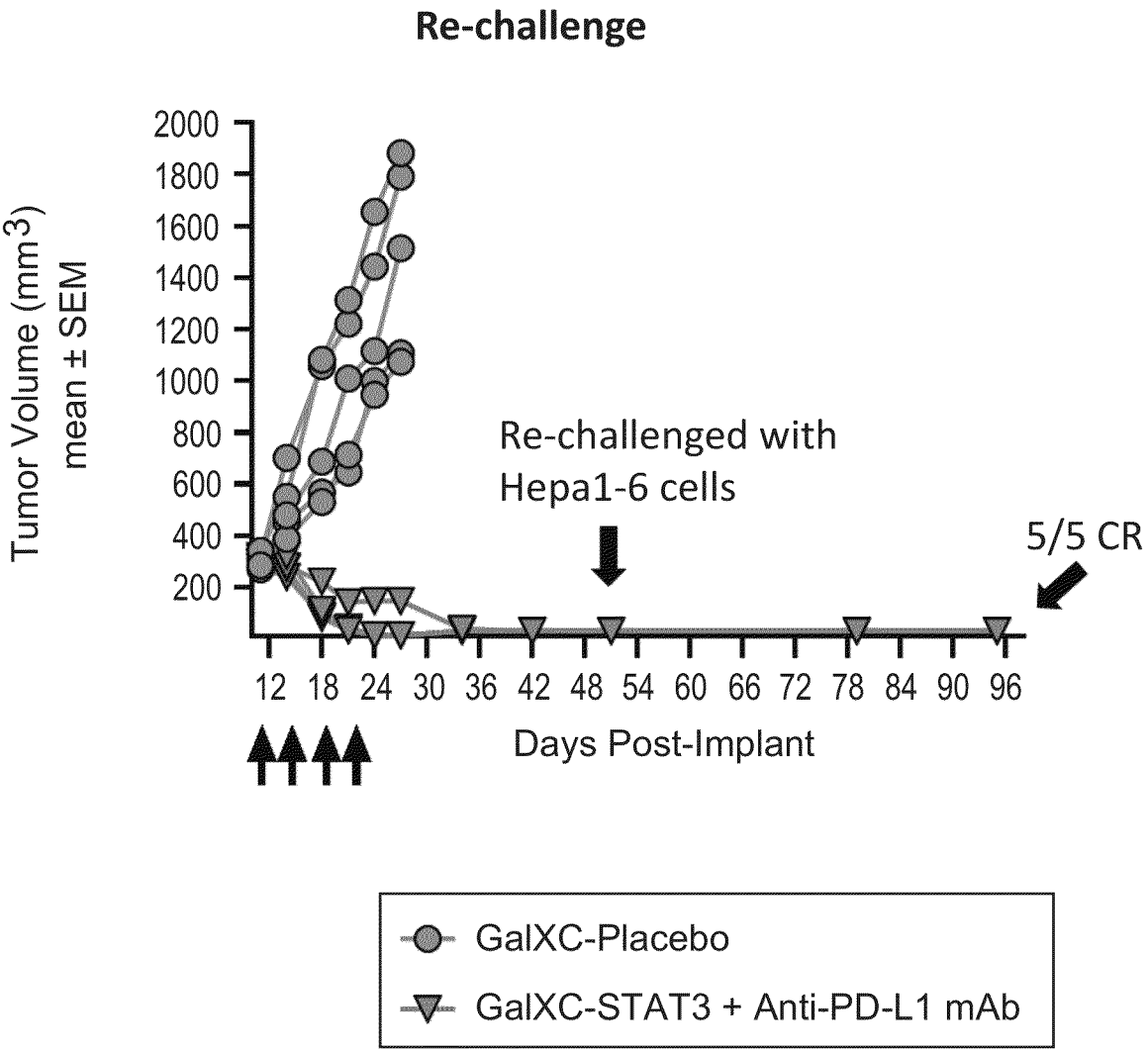
Re-challenge
Tumor Volume (mm3)
mean ± SEM
2000
1800
1600
1400
1200
1000
800
600
400
200
Re-challenged with
Hepa1-6 cells
5/5 CR
12 18 24 30 36 42 48 54 60 66 72 78 84 90 96
Days Post-Implant
GalXC-Placebo
GalXC-STAT3 + Anti-PD-L1 mAb

FIG. 20

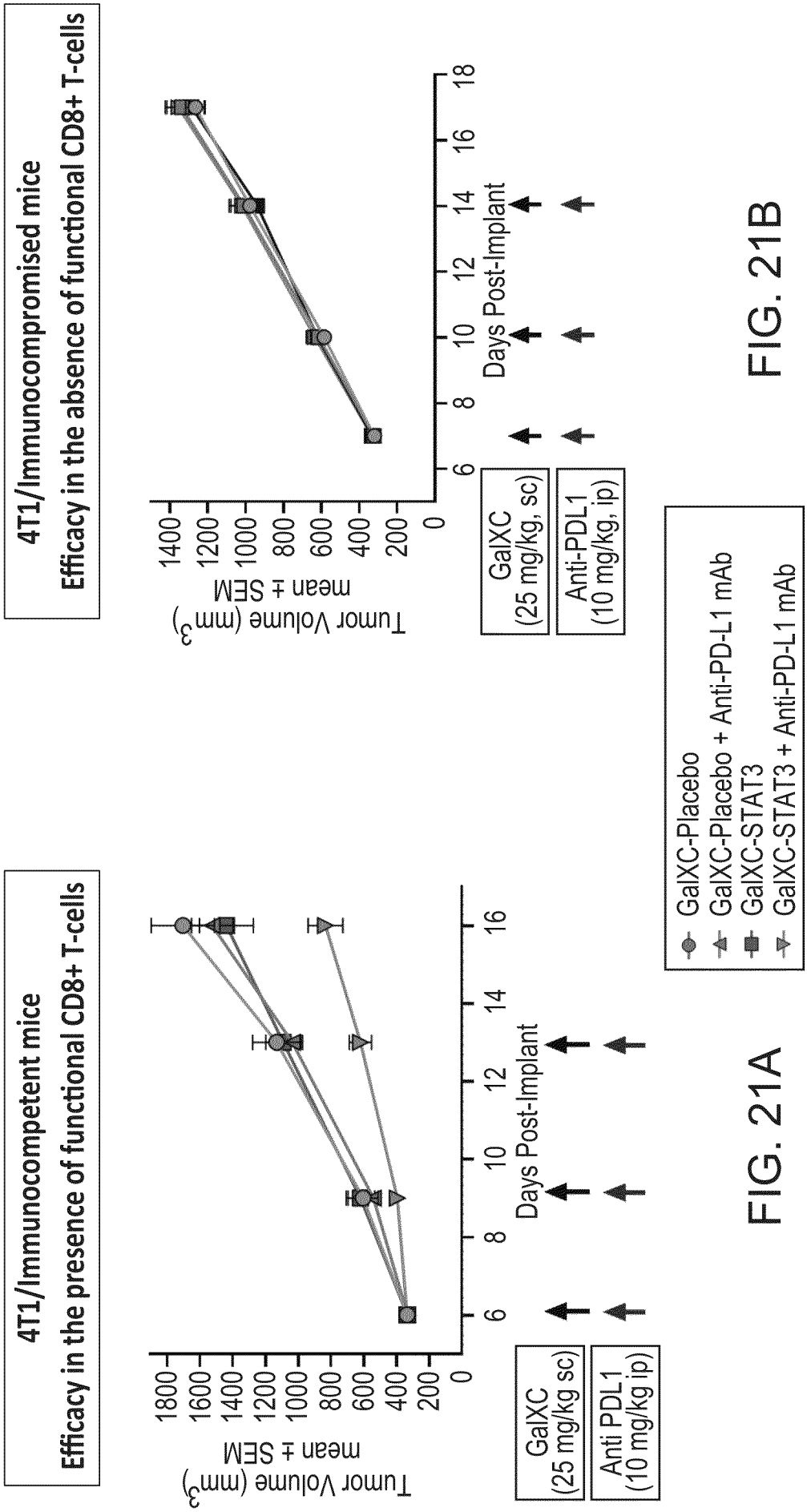

FIG. 21A

FIG. 21B

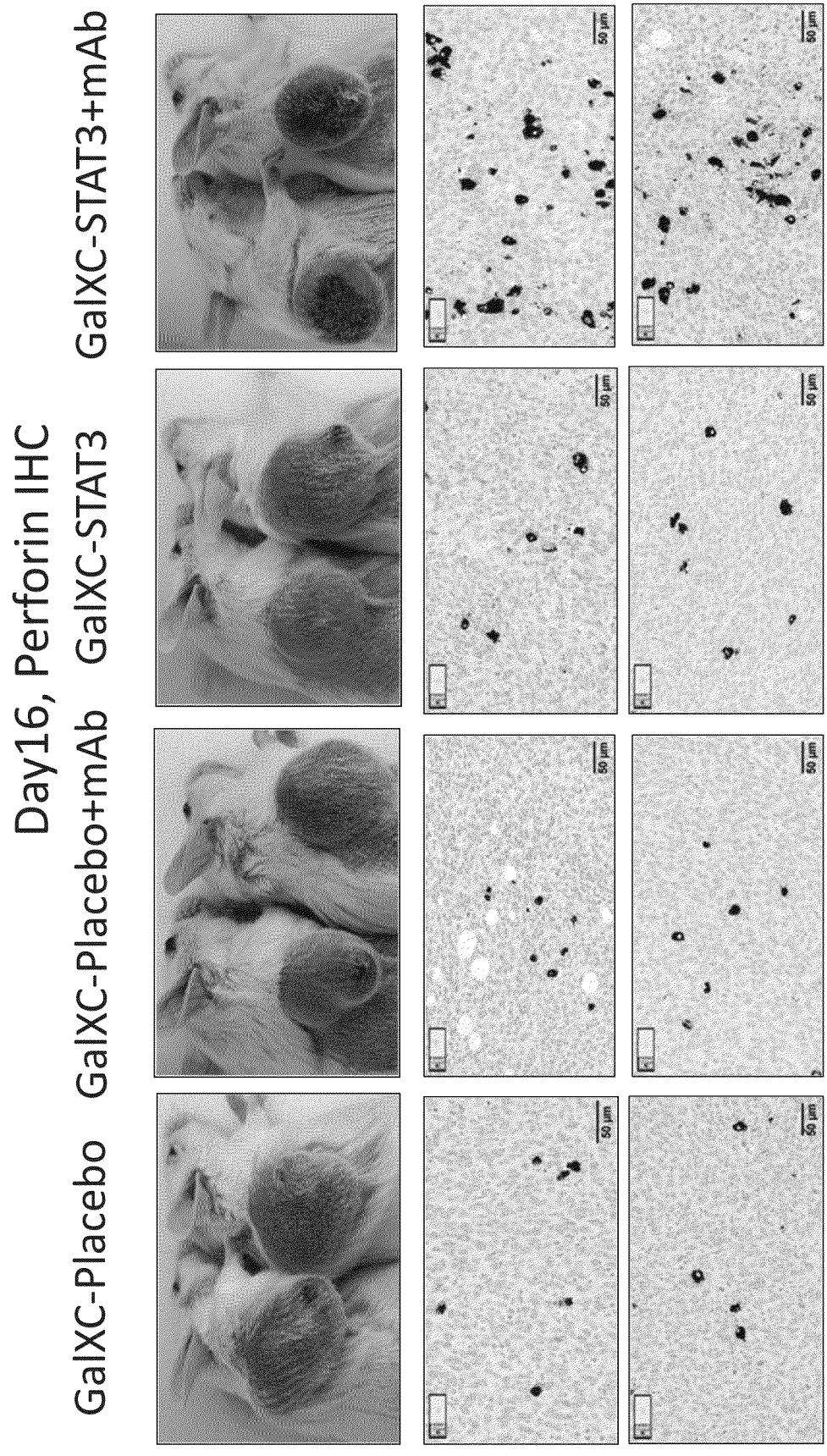
Day16, Perforin IHC
GalXC-Placebo
GalXC-Placebo+mAb
GalXC-STAT3
GalXC-STAT3+mAb
50 μm
GalXC-Placebo
GalXC-Placebo + Anti-PD-L1 mAb
GalXC-STAT3
GalXC-STAT3 + Anti-PD-L1 mAb

FIG. 22

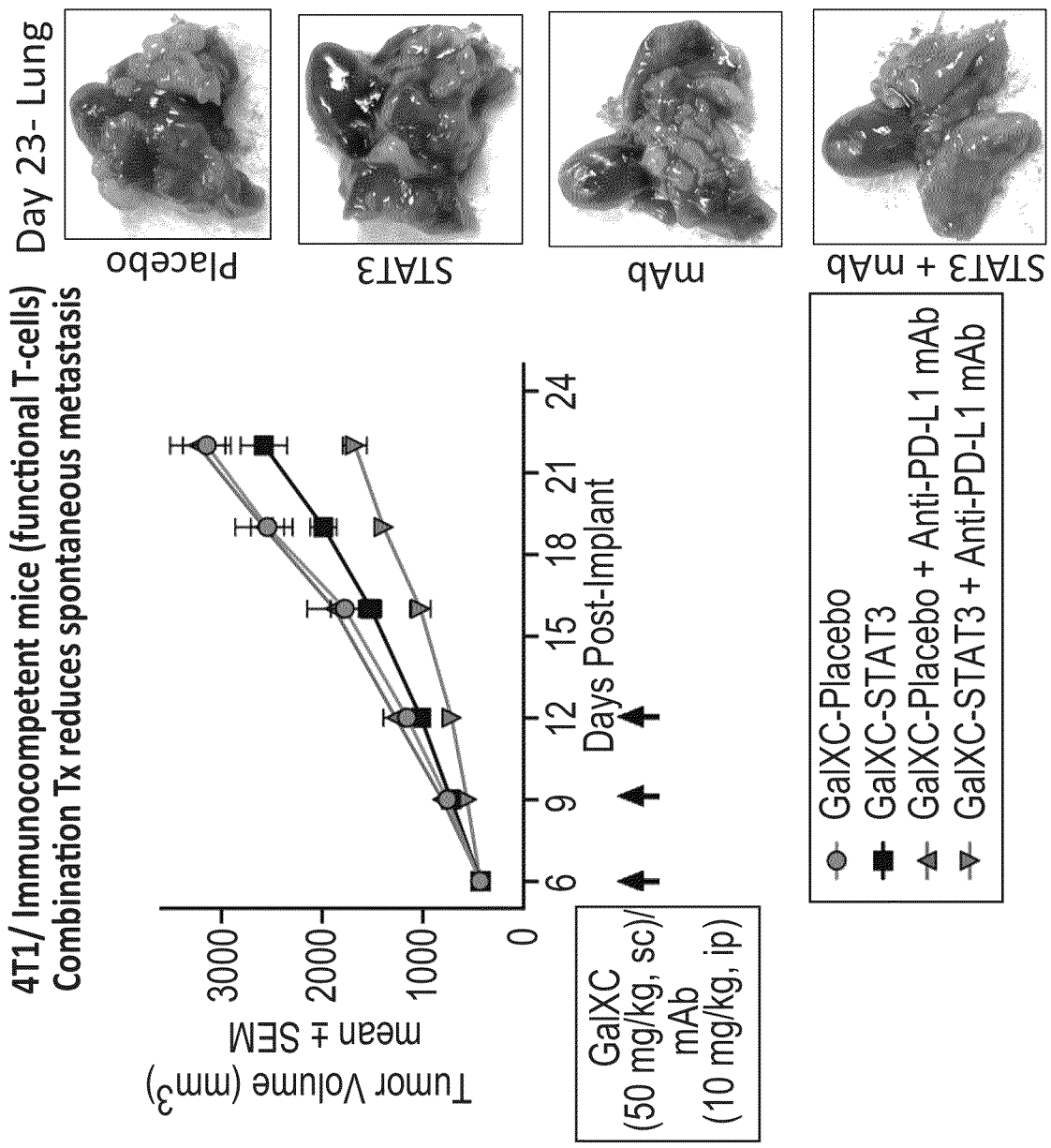
4T1/ Immunocompetent mice (functional T-cells)
Combination Tx reduces spontaneous metastasis
Tumor Volume (mm3)
mean ± SEM
3000
2000
1000
0
6
9
12
15
18
21
24
Days Post-Implant
GalXC
(50 mg/kg, sc)/
mAb
(10 mg/kg, ip)
GalXC-Placebo
GalXC-STAT3
GalXC-Placebo + Anti-PD-L1 mAb
GalXC-STAT3 + Anti-PD-L1 mAb
Day 23- Lung
Placebo
STAT3
mAb
STAT3 + mAb

FIG. 23

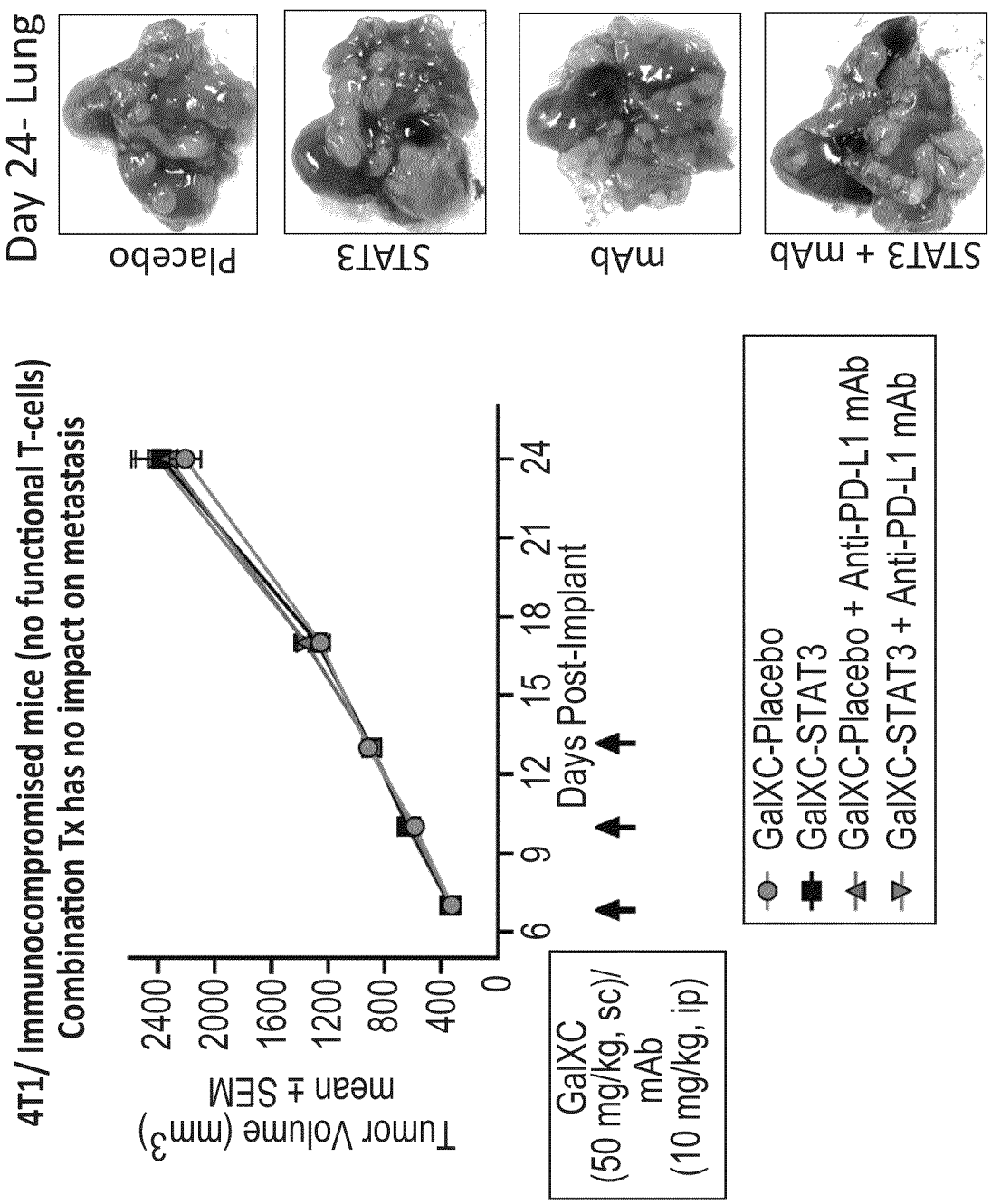
Day 24- Lung
Placebo
STAT3
mAb
STAT3 + mAb
4T1/ Immunocompromised mice (no functional T-cells)
Combination Tx has no impact on metastasis
Tumor Volume (mm3)
mean ± SEM
2400
2000
1600
1200
800
400
0
6
9
12
15
18
21
24
Days Post-Implant
GalXC
(50 mg/kg, sc)/
mAb
(10 mg/kg, ip)
GalXC-Placebo
GalXC-STAT3
GalXC-Placebo + Anti-PD-L1 mAb
GalXC-STAT3 + Anti-PD-L1 mAb

FIG. 23 (cont.)

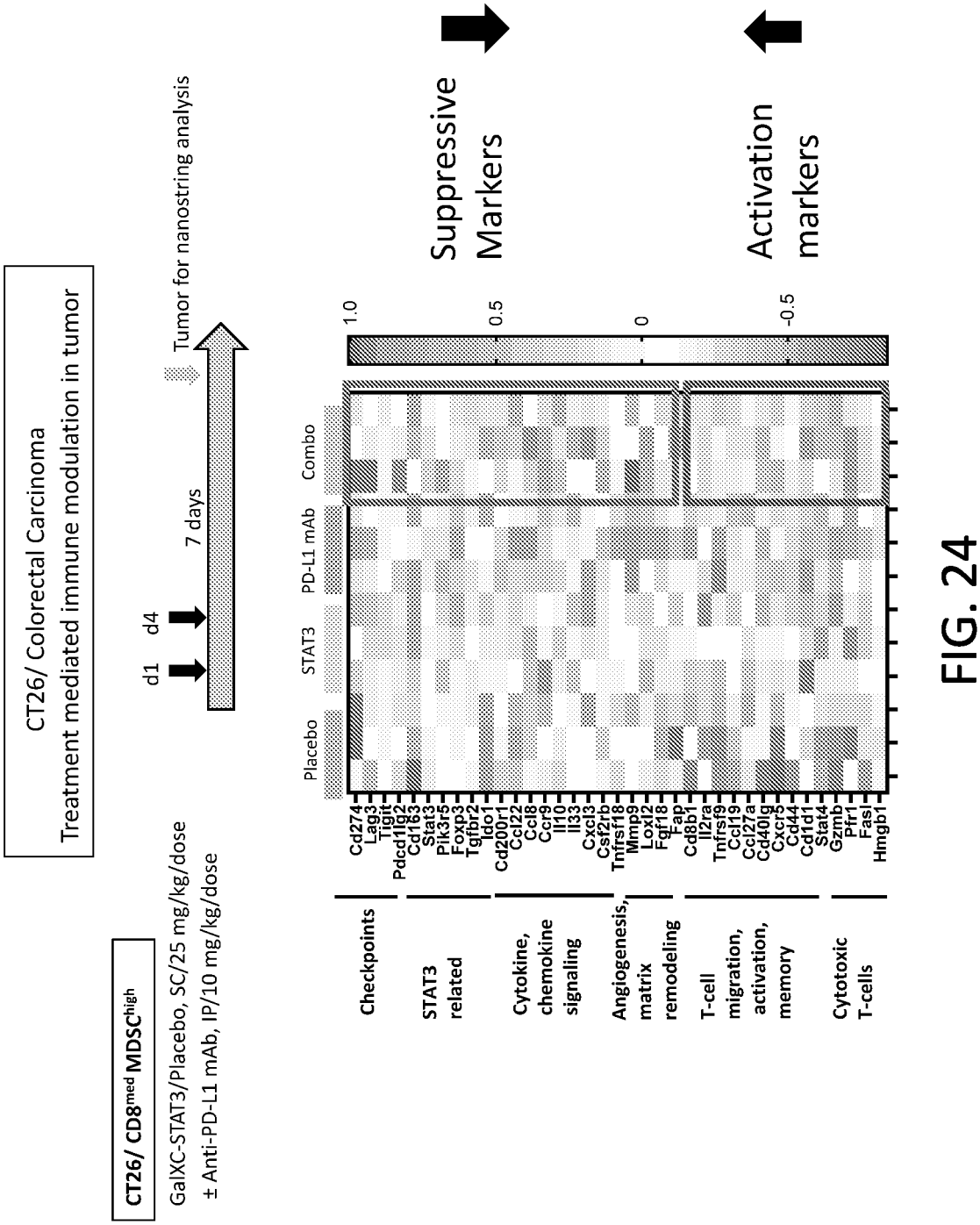
CT26/ Colorectal Carcinoma
Treatment mediated immune modulation in tumor
CT26/ CD8med MDSChigh
GalXC-STAT3/Placebo, SC/25 mg/kg/dose
± Anti-PD-L1 mAb, IP/10 mg/kg/dose
d1
d4
7 days
Tumor for nanostring analysis
Placebo
STAT3
PD-L1 mAb
Combo
Checkpoints
Cd274
Lag3
Tigit
Pdcd1lg2
STAT3 related
Cd163
Stat3
Pik3r5
Foxp3
Tgfbr2
Ido1
Cytokine, chemokine signaling
Cd200r1
Ccl22
Ccl8
Ccr9
Il10
Il33
Cxcl3
Csf2rb
Angiogenesis, matrix remodeling
Tnfrsf18
Mmp9
Loxl2
Fgf18
Fap
T-cell migration, activation, memory
Cd8b1
Il2ra
Tnfrsf9
Ccl19
Ccl27a
Cd40lg
Cxcr5
Cd44
Cytotoxic T-cells
Cd1d1
Stat4
Gzmb
Ptr1
Fasl
Hmgb1
1.0
0.5
0
-0.5
Suppressive Markers
Activation markers

FIG. 24

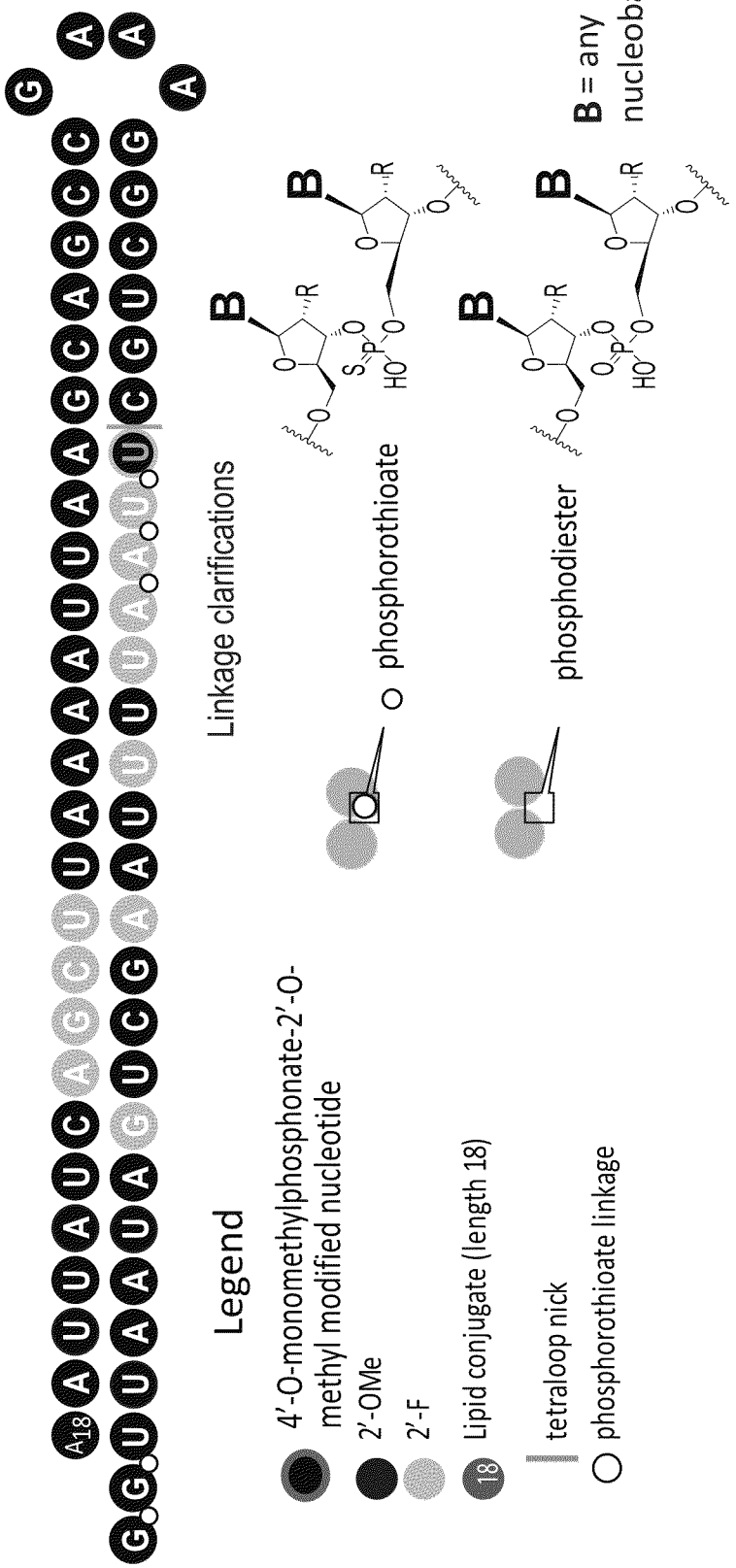
Legend
4'-O-monomethylphosphonate-2'-O-methyl modified nucleotide
2'-OMe
2'-F
Lipid conjugate (length 18)
tetraloop nick
phosphorothioate linkage
Linkage clarifications
phosphorothioate
phosphodiester
B = any nucleobase

FIG. 25

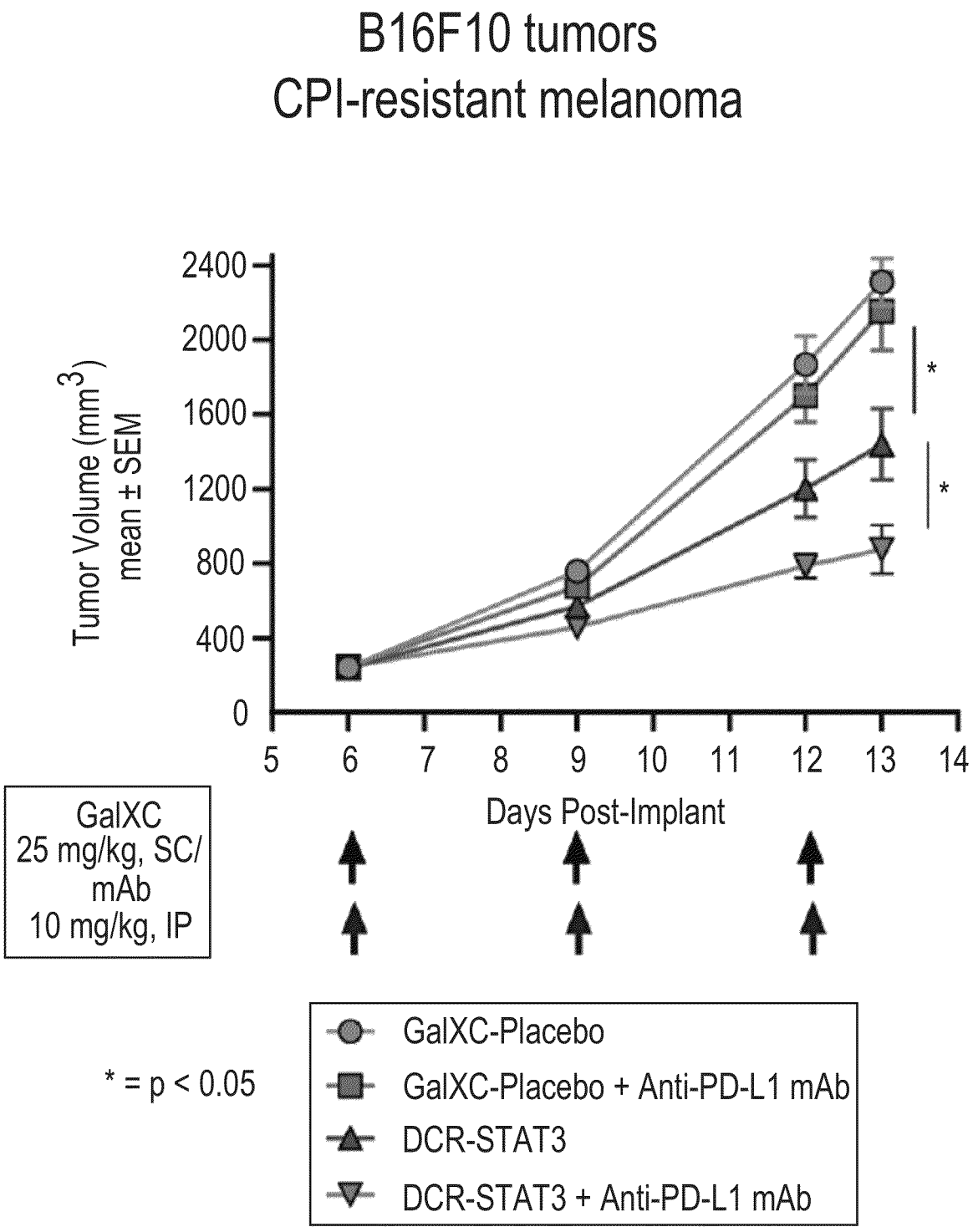
B16F10 tumors
CPI-resistant melanoma
Tumor Volume (mm3)
mean ± SEM
2400
2000
1600
1200
800
400
0
5
6
7
8
9
10
11
12
13
14
Days Post-Implant
*
*
GalXC
25 mg/kg, SC/
mAb
10 mg/kg, IP
* = p < 0.05
GalXC-Placebo
GalXC-Placebo + Anti-PD-L1 mAb
DCR-STAT3
DCR-STAT3 + Anti-PD-L1 mAb

FIG. 26A

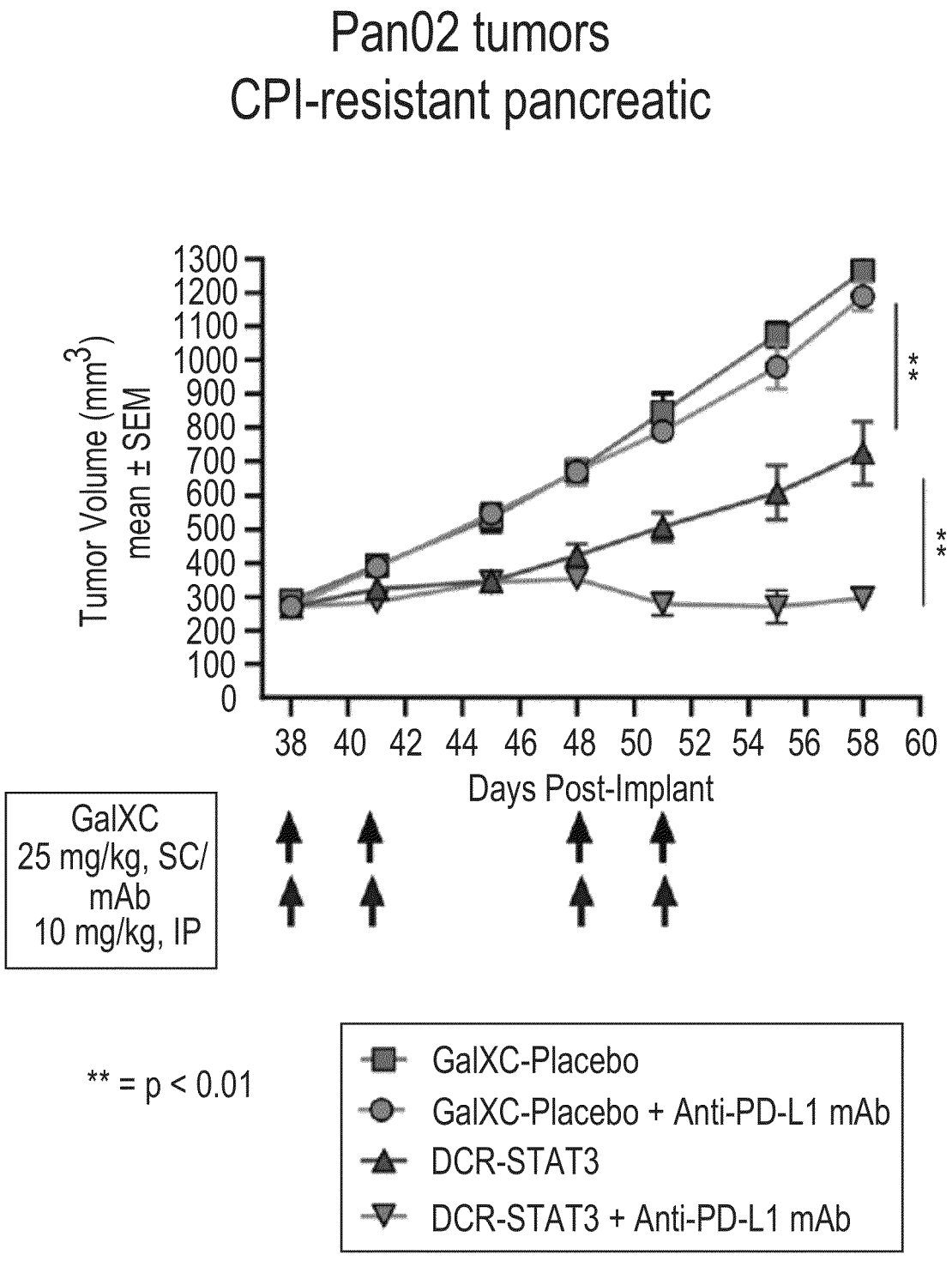
Pan02 tumors
CPI-resistant pancreatic
Tumor Volume (mm3)
mean ± SEM
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
38 40 42 44 46 48 50 52 54 56 58 60
Days Post-Implant
**
**
GalXC
25 mg/kg, SC/
mAb
10 mg/kg, IP
** = p < 0.01
GalXC-Placebo
GalXC-Placebo + Anti-PD-L1 mAb
DCR-STAT3
DCR-STAT3 + Anti-PD-L1 mAb

FIG. 26B

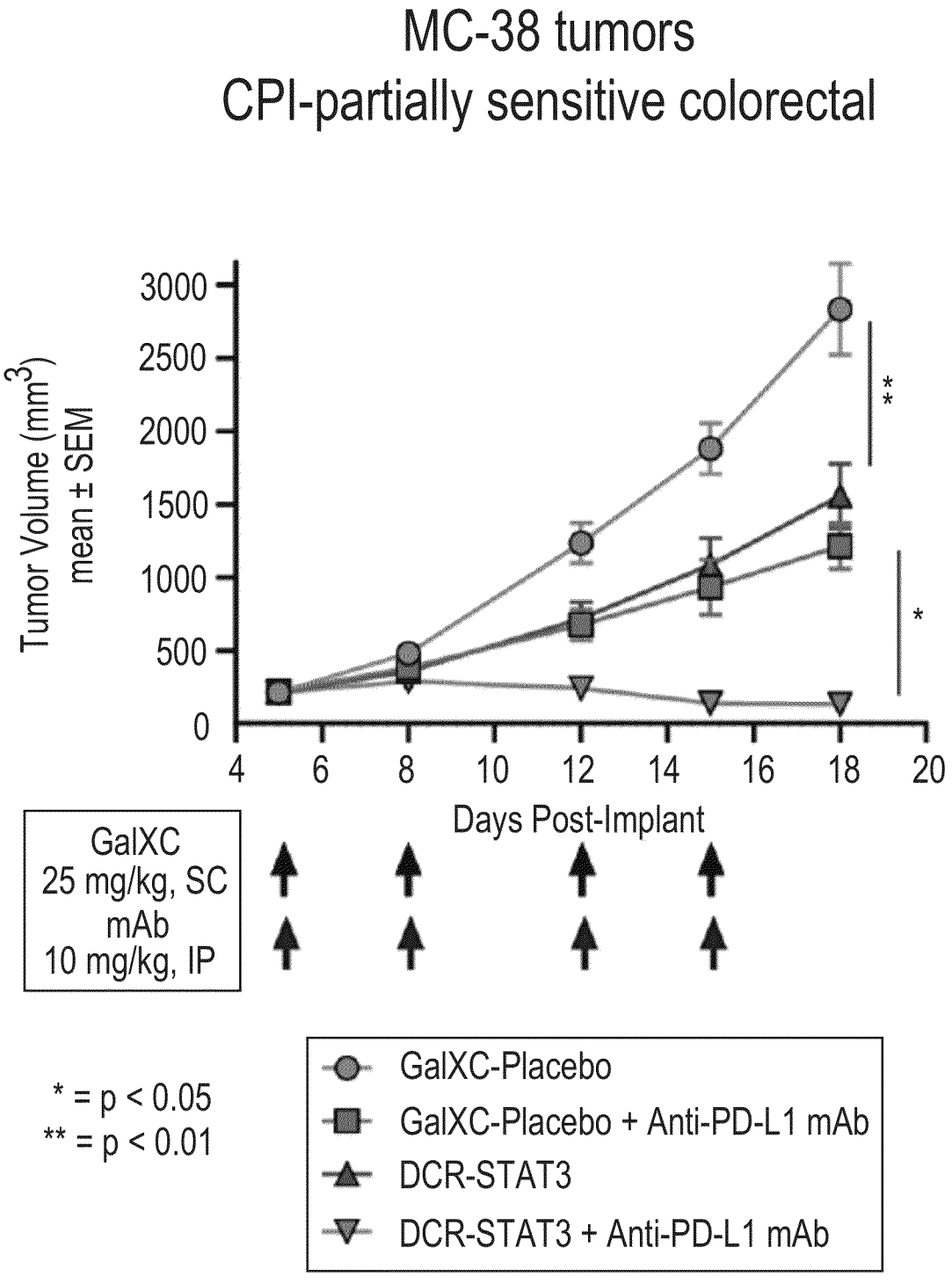
MC-38 tumors
CPI-partially sensitive colorectal
Tumor Volume (mm3)
mean ± SEM
3000
2500
2000
1500
1000
500
0
4
6
8
10
12
14
16
18
20
Days Post-Implant
**
*
GalXC
25 mg/kg, SC
mAb
10 mg/kg, IP
* = p < 0.05
** = p < 0.01
GalXC-Placebo
GalXC-Placebo + Anti-PD-L1 mAb
DCR-STAT3
DCR-STAT3 + Anti-PD-L1 mAb

FIG. 26C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/080076

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/187622 A1 (DICERNA PHARMACEUTICALS, INC. [US]) 9 September 2022 (2022-09-09) sequences 140, 332, 965, 1145, 1226, 524, 716, 875, 1055 sequences 141, 333, 1227, 966, 1146, 525, 717, 876, 1056, sequences 139, 331, 964, 1144, 523, 715, 874, 1054, 138, 330 sequences 521, 522, 713, 714, 137, 329, 38, 963, 1143, 40 sequences 520, 712, 37, 39, 1053, page 178 - page 180 the whole document ----- -/--	1-95

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2024	15/05/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Macchia, Giovanni

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/080076

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GUHA PRAJNA ET AL.: "STAT3 inhibition induces Bax-dependent apoptosis in liver tumor myeloid-derived suppressor cells", ONCOGENE, NATURE PUBLISHING GROUP UK, LONDON, vol. 38, no. 4, 29 August 2018 (2018-08-29), pages 533-548, XP036847014, ISSN: 0950-9232, DOI: 10.1038/S41388-018-0449-Z [retrieved on 2018-08-29] the whole document ----- BASTAKI SHIMA ET AL.: "Codelivery of STAT3 and PD-L1 siRNA by hyaluronate-TAT trimethyl/thiolated chitosan nanoparticles suppresses cancer progression in tumor-bearing mice", LIFE SCIENCE, PERGAMON PRESS, OXFORD, GB, vol. 266, 9 December 2020 (2020-12-09), XP086463054, ISSN: 0024-3205, DOI: 10.1016/J.LFS.2020.118847 [retrieved on 2020-12-09] the whole document -----	1 55

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/080076

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed.

   b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      ☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/080076

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

1-81, 95(completely); 82-94(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-81, 95(completely); 82-94(partially)

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: 140, wherein the sense strand comprises at least one lipid moiety conjugated to the 5'-terminal nucleotide of the sense strand.
Products and methods related thereto.

---

2. claims: 82-94(partially)

A method of determining responsiveness in a subject with cancer who has received or is receiving a treatment, the method comprising detecting the presence of myeloid-derived suppressor cells (MDSCs) or a marker of MDSC activity in a biological sample of the subject, wherein the treatment is administration of an oligonucleotide targeting STAT3, and wherein a reduction of MDSCs or a reduction in a marker of MDSC activity in the biological sample indicates the subject is responding to the treatment.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/080076

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022187622 A1	09-09-2022	AU 2022228341 A1	07-09-2023
		BR 112023017961 A2	14-11-2023
		CA 3209281 A1	09-09-2022
		CL 2023002484 A1	26-01-2024
		CO 2023011779 A2	18-09-2023
		EP 4301376 A1	10-01-2024
		IL 305634 A	01-11-2023
		JP 2024508119 A	22-02-2024
		KR 20230160828 A	24-11-2023
		TW 202302850 A	16-01-2023
		US 2024124875 A1	18-04-2024
		WO 2022187622 A1	09-09-2022