

Claims

1. An oligonucleotide for reducing STAT3 expression, ~~the oligonucleotide comprising an antisense strand of 15 to 30 nucleotides in length comprising the nucleotide sequence of SEQ ID NO: 965 and a sense strand of 15 to 40 nucleotides in length comprising the nucleotide sequence of SEQ ID NO: 875, wherein the sense strand comprises a saturated C18 hydrocarbon chain conjugated to the 5' terminal nucleotide of the sense strand, and wherein each of the antisense strand form a duplex region, wherein the antisense strand has a region of complementarity to a target sequence of *STAT3* as set forth in SEQ ID NO: 85 or SEQ ID NO: 1217, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides and sense strands comprise at least one 2'-modified nucleotide and at least one modified internucleotide linkage.~~
2. The oligonucleotide of claim 1, ~~wherein comprising an antisense strand comprising the region of complementarity is fully complementary to nucleotide sequence of SEQ ID NO: 1145 and a sense strand comprising the target nucleotide sequence of *STAT3* SEQ ID NO: 1055.~~
3. ~~The oligonucleotide of claim 1 or 2, wherein the target sequence comprises any one of SEQ ID NOs: 89-280.~~
4. ~~The oligonucleotide of any one of claims 1-3, wherein the antisense strand is 19 to 27 nucleotides in length.~~
5. ~~The oligonucleotide of any one of claims 1-4, wherein the antisense strand is 21 to 27 nucleotides in length, optionally wherein the antisense strand is 22 nucleotides in length.~~
6. ~~The oligonucleotide of any one of claims 1-5, wherein the sense strand is 19 to 40 nucleotides in length, optionally wherein the sense strand is 36 nucleotides in length.~~
7. ~~The oligonucleotide of any one of claims 1-6, wherein the duplex region is at least 19 nucleotides in length.~~

8. ~~—The oligonucleotide of any one of claims 1-7, wherein the duplex region is at least 21 nucleotides in length, optionally wherein the duplex region is 20 nucleotides in length.~~

9. ~~—The oligonucleotide of any one of claims 1-8, wherein the region of complementarity to *STAT3* is at least 19 contiguous nucleotides in length.~~

10. ~~—The oligonucleotide of any one of claims 1-9, wherein the region of complementarity to *STAT3* is at least 21 contiguous nucleotides in length.~~

11. ~~—The oligonucleotide of any one of claims 1-2 and 4-10, wherein the antisense strand comprises a sequence as set forth in any one of SEQ ID NOs: 10, 38, 66, or 70.~~

12. ~~—The oligonucleotide of any one of claims 1-2 and 4-11, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 9, 37, 65, or 69.~~

13.3. ~~The oligonucleotide of any one of claims 1 to 12~~ claim 1 or 2, wherein the sense strand comprises at its 3' end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.

14. ~~—An oligonucleotide for reducing *STAT3* expression, the oligonucleotide comprising an antisense strand and a sense strand, wherein the antisense strand is 21 to 27 nucleotides in length and has a region of complementarity to a target sequence of *STAT3* as set forth in SEQ ID NO: 85 or SEQ ID NO: 1217, wherein the sense strand comprises at its 3' end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, and wherein the antisense strand and the sense strand form a duplex structure of at least 19 nucleotides in length.~~

15. ~~—An oligonucleotide for reducing *STAT3* expression, the oligonucleotide comprising an antisense strand and a sense strand, wherein the antisense strand is 21 to 27 nucleotides in~~

length and has a region of complementarity to a target sequence of *STAT3* as set forth in any one of SEQ ID NOs: 89-280, wherein the sense strand comprises at its 3' end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, and wherein the antisense strand and the sense strand form a duplex structure of at least 19 nucleotides in length.

16. — A double stranded oligonucleotide for reducing *STAT3* expression, the oligonucleotide comprising:

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

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

17. — The oligonucleotide of claims 14-16, wherein the region of complementarity is fully complementary to at least 19 contiguous nucleotides of *STAT3* mRNA.

18. — The oligonucleotide of claims 14-16, wherein the region of complementarity is fully complementary to at least 19 contiguous nucleotides of the *STAT3* mRNA target sequence.

19.4. The oligonucleotide of any one of claims 13-18 claim 3, wherein L is a tetraloop, optionally wherein L is 4 nucleotides in length.

20.5. The oligonucleotide of any one of the preceding claims 13-19, wherein L comprises a sequence set forth as GAAA.

~~21. — The oligonucleotide of any one of claims 1-20, wherein the antisense strand is 27 nucleotides in length and the sense strand is 25 nucleotides in length, optionally wherein the antisense strand is 22 nucleotides in length and the sense strand is 36 nucleotides in length.~~

~~22. — The oligonucleotide of claim 21, wherein the antisense strand and sense strand form a duplex region of 25 nucleotides in length, optionally wherein the duplex is 20 nucleotides in length.~~

~~23. — The oligonucleotide of any one of claims 1-22, wherein the antisense strand comprises a 3' overhang sequence of one or more nucleotides in length, optionally wherein the 3' overhang sequence is 2 nucleotides in length, optionally wherein the 3' overhang sequence is GG.~~

~~24. — The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleotide.~~

25.6. The oligonucleotide of claim 24_1, wherein the modified nucleotide comprises a 2'-modification; comprises 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro-β-d-arabinonucleic acid.

~~26. — The oligonucleotide of claim 25, wherein the 2' modification is a modification selected from 2' aminoethyl, 2' fluoro, 2' O methyl, 2' O methoxyethyl, and 2' deoxy 2' fluoro β d arabinonucleic acid.~~

~~27. — The oligonucleotide of any one of claims 24-26, wherein about 10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprise a 2' fluoro modification.~~

~~28. — The oligonucleotide of any one of claims 24-27, wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the antisense strand comprise a 2' fluoro modification.~~

~~29. The oligonucleotide of any one of claims 24-26, wherein about 25-35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the oligonucleotide comprise a 2'-fluoro modification.~~

~~30-7. The oligonucleotide of any one of claims 24-29 1 or 3-6, wherein the sense strand comprises 36 nucleotides with positions 1-36 from 5' to 3'-3', wherein:~~

~~_____ positions 8-11 a) one or more positions 8-11 comprise a 2'-fluoro modification, preferably all positions 8-11 comprises 2' fluoro modification; and/or~~

~~_____ b) one or more positions 1-7, 12-36 comprise 2'-O-methyl modification, preferably all positions 1-7, 12-36 comprise 2'-O-methyl modification.~~

~~31-8. The oligonucleotide of any one of claims 24-30 1 or 3-7, wherein the antisense strand comprises 22 nucleotides with positions 1-22 from 3'-to-5' to 3', and wherein:~~

~~_____ a) one or more positions 2, 3, 4, 5, 7, 10 and 14 comprise a 2'-fluoro modification, preferably all positions 2, 3, 4, 5, 7, 10 and 14 comprise 2'-fluoro modification; and/or~~

~~_____ b) one or more positions 1, 6, 8, 9, 11-13, 15-22 comprise 2'-O-methyl modification, preferably all positions 1, 6, 8, 9, 11-13, 15-22 comprise 2'-O-methyl modification.~~

~~32. The oligonucleotide of any one of claims 27-31, wherein the remaining nucleotides comprise a 2'-O-methyl modification.~~

~~33. The oligonucleotide of any one of claims 24-32, wherein all of the nucleotides of the oligonucleotide are modified.~~

~~34. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified internucleotide linkage.~~

~~35. The oligonucleotide of claim 31, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.~~

~~36.9.~~ The oligonucleotide of any one of the preceding claims, wherein ~~the~~ a 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog.

~~37.~~ The oligonucleotide of claim 36, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate.

~~38.10.~~ The oligonucleotide of any one of the preceding claims, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands, optionally, wherein the one or more targeting ligands is a saturated or unsaturated fatty acid moiety.

~~39.~~ The oligonucleotide of claim 38, wherein the nucleotide is conjugated to more than one targeting ligands, wherein the targeting ligands are the same or are different.

~~40.~~ The oligonucleotide of claim 38 or 39, wherein the one or more targeting ligands is selected from carbohydrate, amino sugar, cholesterol, polypeptide, or lipid.

~~41.~~ The oligonucleotide of claim 38 or 39, wherein the one or more targeting ligands is a saturated or unsaturated fatty acid moiety.

~~42.~~ The oligonucleotide of claim 38 or 39, wherein the targeting ligand is a saturated fatty acid moiety that ranges in size from C10 to C24 long.

~~43.~~ The oligonucleotide of claim 42, wherein the targeting ligand is a C16 saturated fatty acid moiety.

~~44.~~ The oligonucleotide of claim 42, wherein the targeting ligand is a C18 saturated fatty acid moiety.

~~45.~~ The oligonucleotide of claim 42, wherein the targeting ligand is a C22 saturated fatty acid moiety.

46. — ~~The oligonucleotide of 38 or 39, wherein the targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety.~~
47. — ~~The oligonucleotide of claim 46, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety or a tetravalent GalNAc moiety.~~
48. — ~~The oligonucleotide of any one of claims 13-47, wherein up to 4 nucleotides of L of the stem loop are each conjugated to a monovalent GalNAc moiety.~~
49. — ~~The oligonucleotide of any one of claims 1-10 and 13-48, wherein the sense strand comprises a sequence as set forth in SEQ ID NOs: 857-946.~~
50. — ~~The oligonucleotide of any one of claims 1-10 and 13-49, wherein the antisense strand comprises a sequence as set for in SEQ ID NOs: 947-1036.~~
51. — ~~The oligonucleotide of any one of claims 1-2, 4-14, and 17-48, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~
- ~~—— (a) SEQ ID NOs: 9 and 10, respectively;~~
 - ~~—— (b) SEQ ID NOs: 37 and 38, respectively;~~
 - ~~—— (c) SEQ ID NOs: 65 and 66, respectively; and~~
 - ~~—— (d) SEQ ID NOs: 69 and 70, respectively.~~
52. — ~~The oligonucleotide of any one of claims 1-10, and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~
- ~~(a) SEQ ID NOs: 861 and 951, respectively;~~
 - ~~(b) SEQ ID NOs: 857 and 947, respectively;~~
 - ~~(c) SEQ ID NOs: 858 and 948, respectively;~~
 - ~~(d) SEQ ID NOs: 859 and 949, respectively;~~
 - ~~(e) SEQ ID NOs: 860 and 950, respectively;~~

~~(f) SEQ ID NOs: 862 and 952, respectively;~~
~~(g) SEQ ID NOs: 863 and 953, respectively;~~
~~(h) SEQ ID NOs: 864 and 954, respectively;~~
~~(i) SEQ ID NOs: 865 and 955, respectively;~~
~~(j) SEQ ID NOs: 866 and 956, respectively;~~
~~(k) SEQ ID NOs: 867 and 957, respectively;~~
~~(l) SEQ ID NOs: 868 and 958, respectively;~~
~~(m) SEQ ID NOs: 869 and 959, respectively;~~
~~(n) SEQ ID NOs: 870 and 960, respectively;~~
~~(o) SEQ ID NOs: 871 and 961, respectively;~~
~~(p) SEQ ID NOs: 872 and 962, respectively;~~
~~(q) SEQ ID NOs: 873 and 963, respectively;~~
~~(r) SEQ ID NOs: 874 and 964, respectively;~~
~~(s) SEQ ID NOs: 875 and 965, respectively;~~
~~(t) SEQ ID NOs: 876 and 966, respectively;~~
~~(u) SEQ ID NOs: 877 and 967, respectively;~~
~~(v) SEQ ID NOs: 878 and 968, respectively;~~
~~(w) SEQ ID NOs: 879 and 969, respectively;~~
~~(x) SEQ ID NOs: 880 and 970, respectively;~~
~~(y) SEQ ID NOs: 881 and 971, respectively;~~
~~(z) SEQ ID NOs: 882 and 972, respectively;~~
~~(aa) SEQ ID NOs: 883 and 973, respectively;~~
~~(bb) SEQ ID NOs: 884 and 974, respectively;~~
~~(cc) SEQ ID NOs: 885 and 975, respectively;~~
~~(dd) SEQ ID NOs: 886 and 976, respectively;~~
~~(ee) SEQ ID NOs: 887 and 977, respectively;~~
~~(ff) SEQ ID NOs: 888 and 978, respectively;~~
~~(gg) SEQ ID NOs: 940 and 1030, respectively;~~
~~(hh) SEQ ID NOs: 896 and 986, respectively; and~~
~~(ii) SEQ ID NOs: 920 and 1010, respectively.~~

~~53. — The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 862 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 952.~~

~~54. — The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 875 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 965.~~

~~55. — The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 876 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 966.~~

~~56. — The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 920 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 1010.~~

~~57. — The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

- ~~(a) SEQ ID NOs: 901 and 991, respectively;~~
- ~~(b) SEQ ID NOs: 910 and 1000, respectively;~~
- ~~(c) SEQ ID NOs: 899 and 989, respectively;~~
- ~~(d) SEQ ID NOs: 896 and 986, respectively;~~
- ~~(e) SEQ ID NOs: 892 and 982, respectively;~~
- ~~(f) SEQ ID NOs: 890 and 980, respectively; and~~
- ~~(g) SEQ ID NOs: 889 and 979, respectively.~~

~~58. — The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

- ~~(a) SEQ ID NOs: 940 and 1030, respectively;~~
- ~~(b) SEQ ID NOs: 937 and 1027, respectively; and~~
- ~~(c) SEQ ID NOs: 939 and 1029, respectively.~~

59. — ~~The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

- ~~(a) SEQ ID NOs: 915 and 1005, respectively;~~
- ~~(b) SEQ ID NOs: 924 and 1014, respectively;~~
- ~~(c) SEQ ID NOs: 913 and 1003, respectively; and~~
- ~~(d) SEQ ID NOs: 920 and 1010, respectively.~~

60. — ~~The oligonucleotide of any one of claims, 1-2, 4-14, and 17-48, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 11, 39, 67 and 71.~~

61. — ~~The oligonucleotide of any one of claims 1-2, 4-14, 17-48, and 60, wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 12, 40, 68 and 72.~~

62. — ~~The oligonucleotide of any one of claims 1-2, 4-14, 17-48, and 60-61, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

- ~~—— (a) SEQ ID NOs: 11 and 12, respectively;~~
- ~~—— (b) SEQ ID NOs: 39 and 40, respectively;~~
- ~~—— (c) SEQ ID NOs: 67 and 68, respectively; and~~
- ~~—— (d) SEQ ID NOs: 71 and 72, respectively.~~

63. — ~~The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises a nucleotide sequence selected from SEQ ID NOs: 1042, 1055, 1056, and 1100.~~

64. — ~~The oligonucleotide of any one of claims 1-10 and 13-50, wherein the antisense strand comprises a nucleotide sequence selected from SEQ ID NOs: 1132, 1145, 1146, and 1190.~~

65. —The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:

- (a) SEQ ID NOs: 1041 and 1131, respectively;
- (b) SEQ ID NOs: 1037 and 1127, respectively;
- (c) SEQ ID NOs: 1038 and 1128, respectively;
- (d) SEQ ID NOs: 1039 and 1129, respectively;
- (e) SEQ ID NOs: 1040 and 1130, respectively;
- (f) SEQ ID NOs: 1042 and 1132, respectively;
- (g) SEQ ID NOs: 1043 and 1133, respectively;
- (h) SEQ ID NOs: 1044 and 1134, respectively;
- (i) SEQ ID NOs: 1045 and 1135, respectively;
- (j) SEQ ID NOs: 1046 and 1136, respectively;
- (k) SEQ ID NOs: 1047 and 1137, respectively;
- (l) SEQ ID NOs: 1048 and 1138, respectively;
- (m) SEQ ID NOs: 1049 and 1139, respectively;
- (n) SEQ ID NOs: 1050 and 1140, respectively;
- (o) SEQ ID NOs: 1051 and 1141, respectively;
- (p) SEQ ID NOs: 1052 and 1142, respectively;
- (q) SEQ ID NOs: 1053 and 1143, respectively;
- (r) SEQ ID NOs: 1054 and 1144, respectively;
- (s) SEQ ID NOs: 1055 and 1145, respectively;
- (t) SEQ ID NOs: 1056 and 1146, respectively;
- (u) SEQ ID NOs: 1057 and 1147, respectively;
- (v) SEQ ID NOs: 1058 and 1148, respectively;
- (w) SEQ ID NOs: 1059 and 1149, respectively;
- (x) SEQ ID NOs: 1060 and 1150, respectively;
- (y) SEQ ID NOs: 1061 and 1151, respectively;
- (z) SEQ ID NOs: 1062 and 1152, respectively;
- (aa) SEQ ID NOs: 1063 and 1153, respectively;
- (bb) SEQ ID NOs: 1064 and 1154, respectively;
- (cc) SEQ ID NOs: 1065 and 1155, respectively;

- ~~(dd) SEQ ID NOs: 1066 and 1156, respectively;~~
- ~~(ee) SEQ ID NOs: 1067 and 1157, respectively;~~
- ~~(ff) SEQ ID NOs: 1068 and 1158, respectively;~~
- ~~(gg) SEQ ID NOs: 1120 and 1210, respectively;~~
- ~~(hh) SEQ ID NOs: 1076 and 1166, respectively; and~~
- ~~(ii) SEQ ID NOs: 1100 and 1190, respectively.~~

~~66. — The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 1042 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 1132.~~

~~67. — The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 1055 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 1145.~~

~~68. — The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 1056 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 1146.~~

~~69. — The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO: 1100 and the antisense strand comprises the nucleotide sequence of SEQ ID NO: 1190.~~

~~70. — The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

- ~~(a) SEQ ID NOs: 1081 and 1171, respectively;~~
- ~~(b) SEQ ID NOs: 1090 and 1180, respectively;~~
- ~~(c) SEQ ID NOs: 1079 and 1169, respectively;~~
- ~~(d) SEQ ID NOs: 1076 and 1166, respectively;~~
- ~~(e) SEQ ID NOs: 1072 and 1162, respectively;~~
- ~~(f) SEQ ID NOs: 1070 and 1160, respectively; and~~

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

~~71. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

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

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

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

~~72. The oligonucleotide of any one of claims 1-10 and 13-50, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

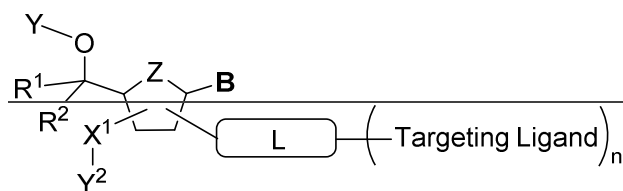
~~(a) SEQ ID NOs: 1095 and 1185, respectively;~~

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

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

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

~~73. An oligonucleotide-ligand conjugate comprising a nucleotide sequence that reduces expression of *STAT3* mRNA in an immune cell associated with a tumor microenvironment and one or more targeting ligands, wherein one or more nucleosides of the nucleotide sequence conjugated with one or more targeting ligands is represented by formula I-a:~~



~~I-a;~~

~~or a pharmaceutically acceptable salt thereof, wherein:~~

~~B is a nucleobase or hydrogen;~~

~~R¹ and R² are independently hydrogen, halogen, R^A, CN, S(O)R, S(O)₂R, Si(OR)₂R, Si(OR)R₂, or SiR₃; or~~

~~R¹ and R² on the same carbon are taken together with their intervening atoms to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur;~~

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

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

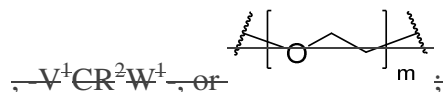
two R groups on the same atom are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, silicon, and sulfur;

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

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

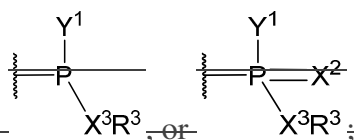
n is 1-10;

~~L is a covalent bond or a bivalent saturated or unsaturated, straight or branched C₁₋₅₀ 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~~



~~m is 1-50;~~

~~X¹, V¹ and W¹ are independently C(R)₂, OR, O, S, Se, or NR;~~



~~Y is hydrogen, a suitable hydroxyl protecting group,~~

~~R³ is hydrogen, a suitable protecting group, a suitable prodrug, or an optionally substituted group selected from C₁₋₆-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;~~

~~X² is O, S, or NR;~~

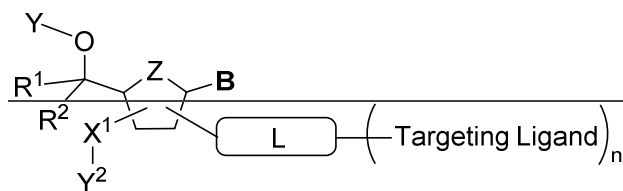
~~X³ is O, S, BH₂, or a covalent bond;~~

~~Y¹ is a linking group attaching to the 2' or 3' terminal of a nucleoside, a nucleotide, or an oligonucleotide;~~

~~Y² 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 CR₂.~~

74. — An oligonucleotide ligand conjugate comprising a nucleotide sequence that reduces expression of a target mRNA in an immune cell associated with a tumor microenvironment and one or more targeting ligands, wherein one or more nucleosides of the nucleotide sequence conjugated with one or more targeting ligands is represented by formula **I-a**:



I-a;

or a pharmaceutically acceptable salt thereof, wherein:

B is a nucleobase or hydrogen;

~~R¹ and R² are independently hydrogen, halogen, R^A, CN, S(O)R, S(O)₂R, Si(OR)₂R, Si(OR)R₂, or SiR₃; or~~

~~R¹ and R² 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 C₁₋₆ 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 C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or~~

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

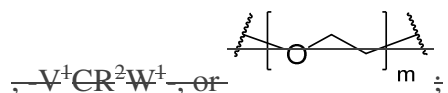
~~each targeting ligand is selected from lipid conjugate moiety (LC), carbohydrate, amino sugar or GalNAc; and wherein LC is independently a lipid conjugate moiety comprising a saturated or unsaturated, straight, or branched C₁₋₅₀ hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain 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 arylene, a 4-7 membered saturated or partially unsaturated~~

carboicyclic, a 4-11 membered saturated or partially unsaturated spiro-carboicyclic, an 8-10 membered bicyclic saturated or partially unsaturated carboicyclic, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro-heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

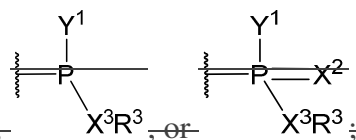
n is 1-10;

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, $C(O)$, $C(O)O$, $S(O)$, $S(O)_2$, $P(O)OR$, $P(S)OR$,



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,

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

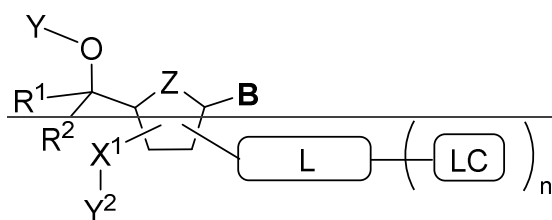
X^2 is O, S, or NR;

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

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

Y^2 is hydrogen, a suitable protecting group, a phosphoramidite analogue, an internucleotide linking group attaching to the 5' terminal of a nucleoside, a nucleotide, or an oligonucleotide, or a linking group attaching to a solid support; and
 Z is O , S , NR , or CR_2 .

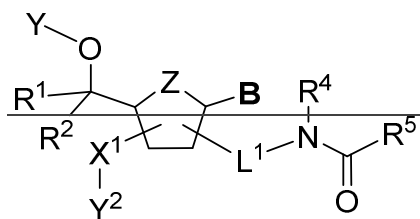
75. — The oligonucleotide ligand conjugate of claim 73 or 74, wherein the one or more nucleosides is represented by formula **H-a**:



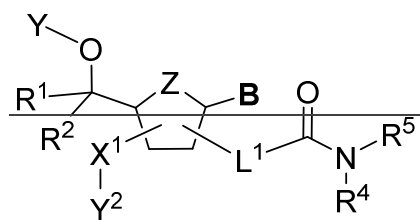
H-a.

or a pharmaceutically acceptable salt thereof.

76. — The oligonucleotide ligand conjugate of any one of claims 73-76, wherein the one or more nucleosides is represented by formula **H-b** or **H-c**:



H-b



H-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),~~



~~R⁴ is hydrogen, R^A, or a suitable amine protection group; and~~

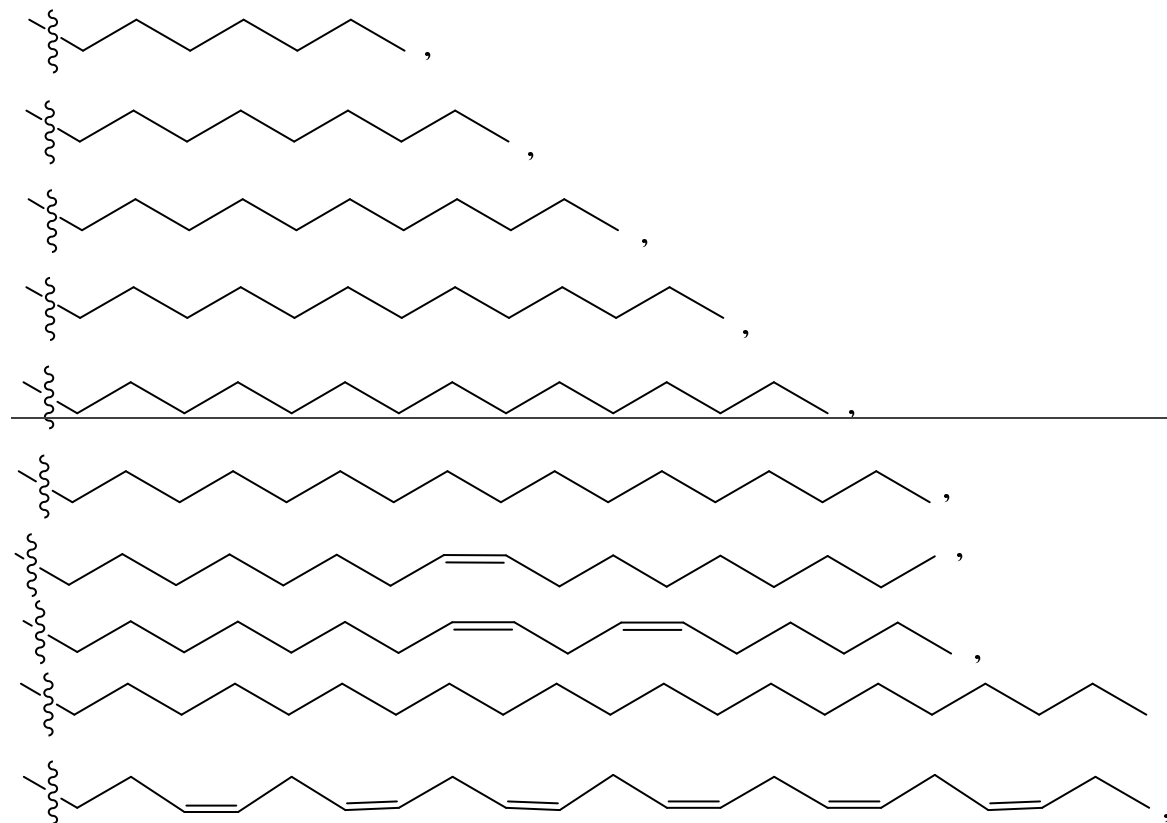
~~R⁵ is adamantyl, or a saturated or unsaturated, straight, or branched C₁₋₅₀ hydrocarbon chain,~~

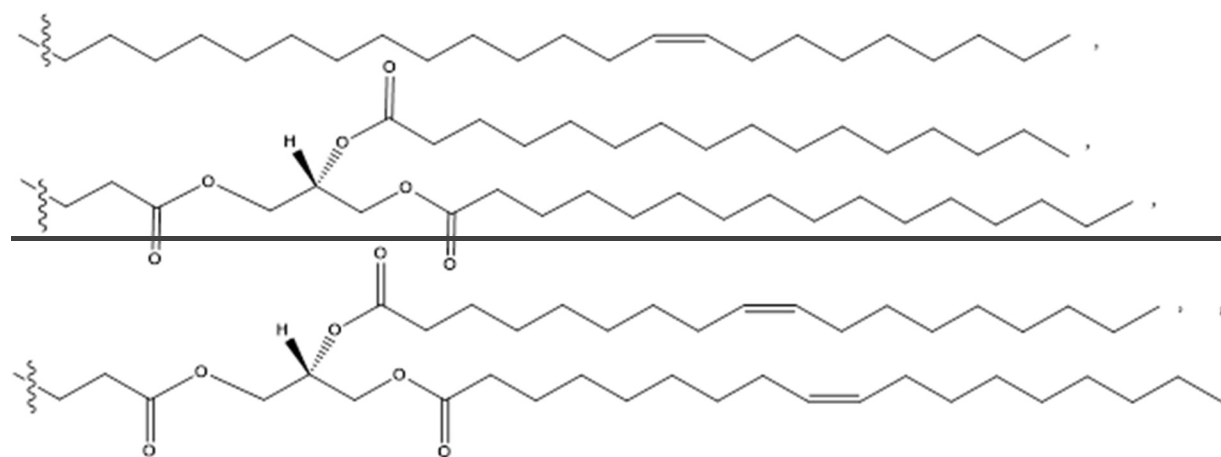
~~wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by~~

~~O, C(O)NR, NR, S, C(O), C(O)O, S(O), S(O)₂, P(O)OR, or P(S)OR.~~

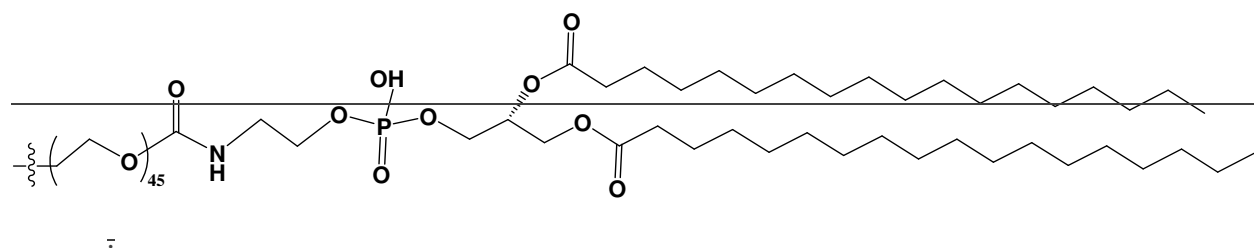
~~77. The oligonucleotide ligand conjugate of claim 76, wherein:~~

~~R⁵ is selected from~~



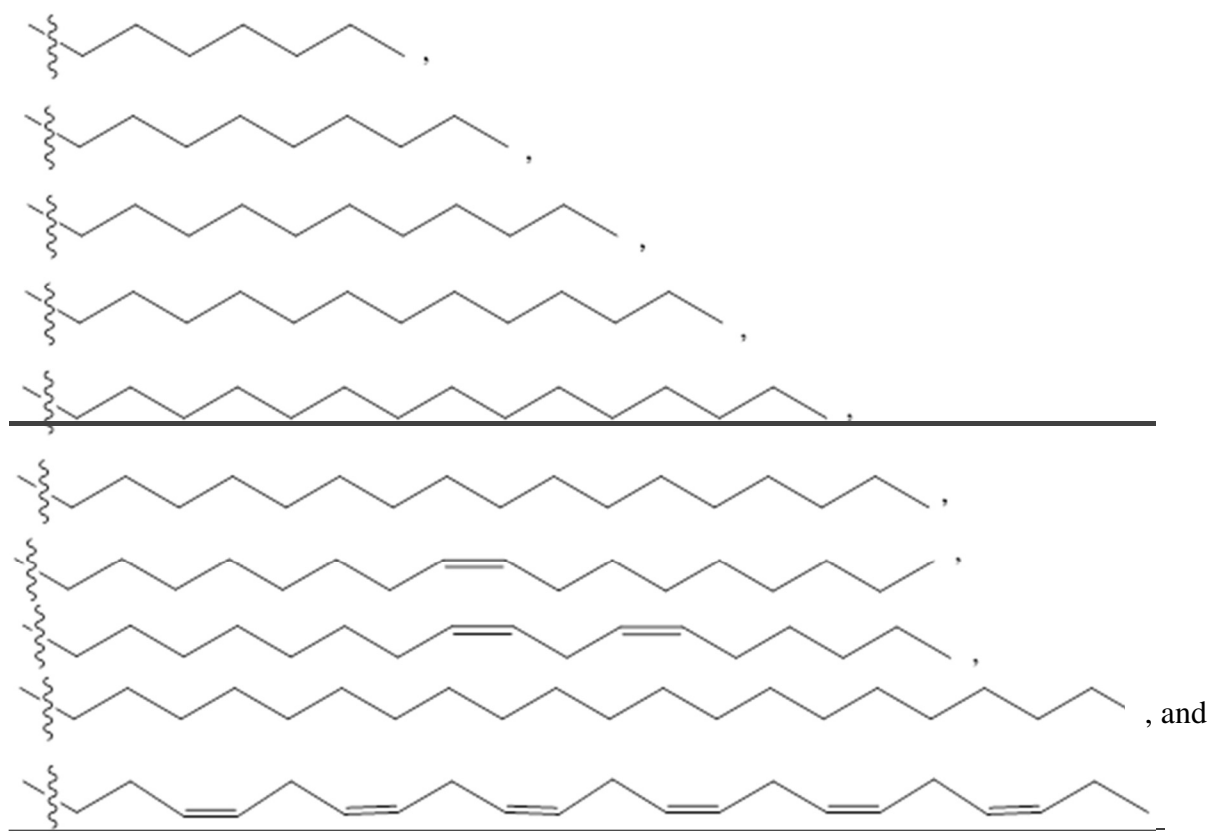


and,

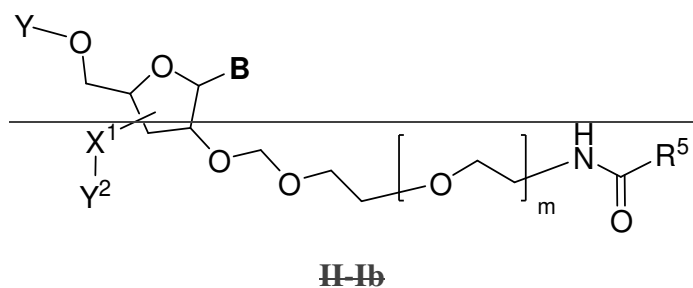
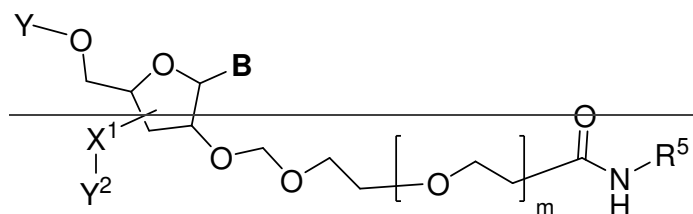


78. The oligonucleotide-ligand conjugate of claim 75, wherein:

R^5 is selected from



79. — An oligonucleotide-ligand conjugate comprising a nucleotide sequence that reduces expression of *STAT3* mRNA in an immune cell associated with a tumor microenvironment and one or more targeting ligands, wherein one or more nucleosides of the nucleotide sequence conjugated with one or more targeting ligands is represented by formula **II-Ib** or **II-Ic**:



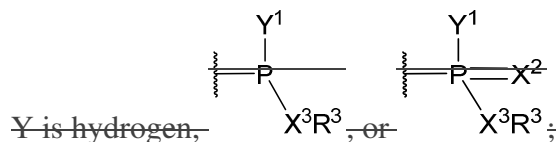
II-Ic

or a pharmaceutically acceptable salt thereof; wherein

B is a nucleobase or hydrogen;

m is 1-50;

X¹ is O, or S;



R³ is hydrogen, or a suitable protecting group;

X² is O, or S;

X³ is O, S, or a covalent bond;

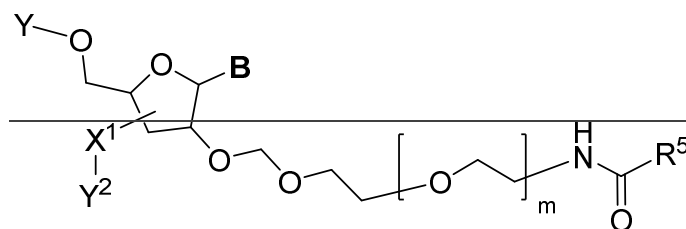
Y¹ is a linking group attaching to the 2' or 3' terminal of a nucleoside, a nucleotide, or an oligonucleotide;

Y² 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;

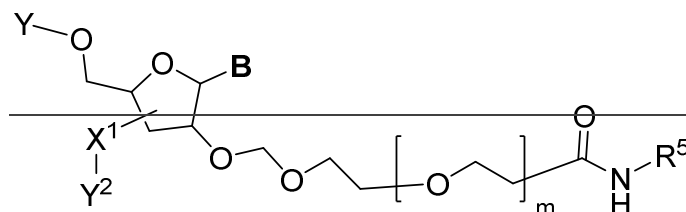
R⁵ is adamantyl, or a saturated or unsaturated, straight, or branched C₁₋₅₀ hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by O, C(O)NR, NR, S, C(O), C(O)O, S(O), S(O)₂, P(O)OR, or P(S)OR; and

R is hydrogen, a suitable protecting group, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

80. An oligonucleotide ligand conjugate comprising a nucleotide sequence that reduces expression of a target mRNA in an immune cell associated with a tumor microenvironment and one or more targeting ligands, wherein one or more nucleosides of the nucleotide sequence conjugated with the targeting ligand is represented by formula II-Ib or II-Ic:



II-Ib



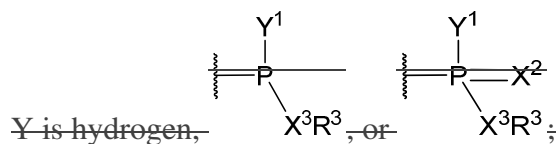
II-Ic

or a pharmaceutically acceptable salt thereof; wherein

B is a nucleobase or hydrogen;

m is 1-50;

X¹ is O, or S;



R³ is hydrogen, or a suitable protecting group;

X² is O, or S;

X³ is O, S, or a covalent bond;

Y¹ is a linking group attaching to the 2' or 3' terminal of a nucleoside, a nucleotide, or an oligonucleotide;

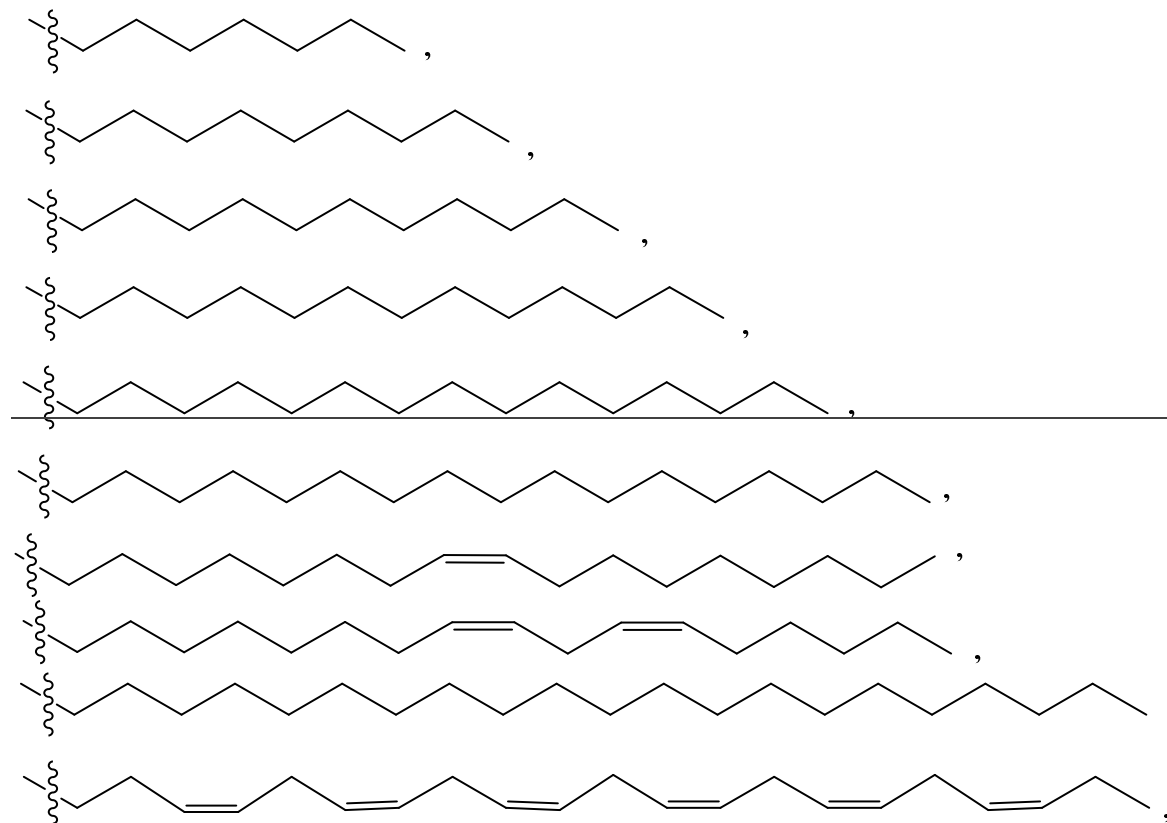
Y² is hydrogen, a phosphoramidite analogue, an internucleotide linking group attaching to the 5' terminal of a nucleoside, a nucleotide, or an oligonucleotide, or a linking group attaching to a solid support;

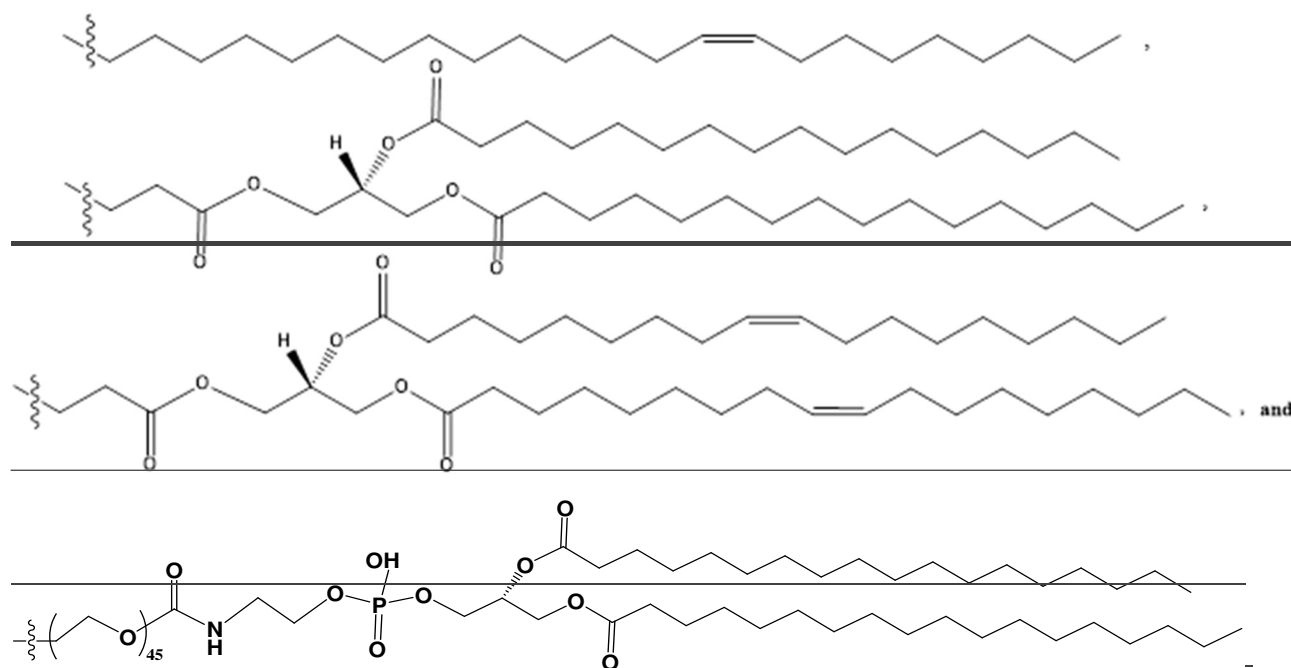
R⁵ is adamantyl, or a saturated or unsaturated, straight, or branched C₁₋₅₀ hydrocarbon chain, wherein 0-10 methylene units of the hydrocarbon chain are independently replaced by O, -C(O)NR, NR, S, C(O), C(O)O, S(O), S(O)₂, P(O)OR, or P(S)OR; and

~~R is hydrogen, a suitable protecting group, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.~~

81.—~~The oligonucleotide-ligand conjugate of claim 79 or 80, wherein:~~

~~R⁵ is selected from~~





82. — The oligonucleotide-ligand conjugate of any one of claims 73-81, wherein the nucleotide sequence comprises 1-10 targeting ligands.

83. — The oligonucleotide-ligand conjugate of any one of claims 73-82, wherein the nucleotide sequence comprises 1, 2 or 3 targeting ligands.

84. — The oligonucleotide-ligand conjugate of any one of claims 73, 75-79 and 81-83, wherein the oligonucleotide comprises a sense strand of 10-53 nucleotides in length and an antisense strand of 15-53 nucleotides in length, wherein the antisense strand has a region of complementarity to the *STAT3* mRNA, wherein the region of complementarity is at least 15 nucleotides in length differing by no more than 3 nucleotides from the *STAT3* mRNA.

85. — The oligonucleotide of claim 84, wherein the region of complementarity is selected from SEQ ID NOs: 89-280.

86. — The oligonucleotide-ligand conjugate of any one of claims 74-78 and 80-83, wherein the oligonucleotide comprises a sense strand of 10-53 nucleotides in length and an antisense strand of 15-53 nucleotides in length, wherein the antisense strand has a region of complementarity to

the *STAT3* mRNA, wherein the region of complementarity is at least 15 nucleotides in length differing by no more than 3 nucleotides from the *STAT3* mRNA.

87. — The oligonucleotide ligand conjugate of any one of claims 74-78, 80-83 and 86, wherein the target mRNA encodes a regulator of immune suppression.

88. — The oligonucleotide ligand conjugate of claim 87, wherein the regulator of immune suppression is a transcription factor.

89. — The oligonucleotide ligand conjugate of any one of claims 73-88, wherein the immune cell associated with the tumor microenvironment is a myeloid cell

90. — The oligonucleotide conjugate of any one of claims 73-88, wherein the immune cell associated with the tumor microenvironment is a T cell.

91. — The oligonucleotide ligand conjugate of any one of claims 73-88, wherein the nucleotide sequence reduces expression of the target mRNA or *STAT3* mRNA in more than one immune cell associated with the tumor microenvironment.

92. — The oligonucleotide ligand conjugate of claim 91, wherein the immune cell is a myeloid cell.

93. — The oligonucleotide ligand conjugate of claim 91, wherein the immune cell is a T cell.

94. — The oligonucleotide ligand conjugate of claim 90 or 93, wherein the myeloid cell is a myeloid derived suppressor cell (MDSC).

95. — The oligonucleotide ligand conjugate of claim 94, wherein the MDSC is a granulocytic MDSC (G-MDSC) or monocytic MDSC (M-MDSC).

96. — ~~The oligonucleotide ligand conjugate of claim 95, wherein the nucleotide sequence reduces expression of the target mRNA in G-MDSCs and M-MDSCs.~~

97. — ~~The oligonucleotide ligand conjugate of any one of claims 91 and 93-96, wherein the T cell is a CD8⁺T cell or Treg cell.~~

98. — ~~The oligonucleotide ligand conjugate of any one of claims 73-83 and 87-97, wherein the oligonucleotide is single stranded, optionally wherein the single stranded oligonucleotide is 15-30 nucleotides in length.~~

99. — ~~The oligonucleotide ligand conjugate of any one of claims 73-83 and 87-97, wherein the oligonucleotide is double stranded.~~

100. — ~~The oligonucleotide ligand conjugate of claim 99, wherein the oligonucleotide comprises an antisense strand of 15 to 30 nucleotides in length and a sense strand of 15 to 40 nucleotides in length, wherein the sense strand and antisense strand form a duplex region, wherein the antisense strand has a region of complementarity to the target mRNA or *STAT3* mRNA, and wherein the region of complementarity is at least 15 contiguous nucleotides in length differing by no more than 3 nucleotides from the target mRNA or *STAT3* mRNA.~~

101. — ~~The oligonucleotide ligand conjugate of claim 100, wherein the antisense strand is 19 to 27 nucleotides in length.~~

102. — ~~The oligonucleotide ligand conjugate of claim 100 or 101, wherein the antisense strand is 21 to 27 nucleotides in length, optionally wherein the antisense strand is 22 nucleotides in length.~~

103. — ~~The oligonucleotide ligand conjugate of claim 100 or 102, wherein the sense strand is 19 to 40 nucleotides in length, optionally wherein the sense strand is 36 nucleotides in length.~~

104. — ~~The oligonucleotide ligand conjugate of any one of claims 100-103, wherein the duplex region is at least 19 nucleotides in length.~~

~~105. —The oligonucleotide-ligand conjugate of any one of claims 100-104, wherein the duplex region is at least 21 nucleotides in length, optionally wherein the duplex region is 20 nucleotides in length.~~

~~106. —The oligonucleotide-ligand conjugate of any one of claims 100-105, wherein the region of complementarity to the target mRNA is at least 19 contiguous nucleotides in length.~~

~~107. —The oligonucleotide-ligand conjugate of any one of claims 100-106, wherein the region of complementarity to the target mRNA is at least 21 contiguous nucleotides in length.~~

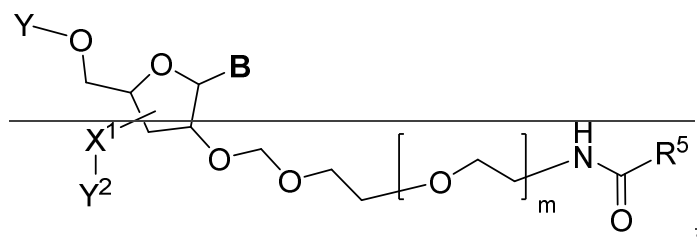
~~108. —The oligonucleotide-ligand conjugate of any one of claims 100-107, wherein the sense strand comprises at its 3' end a stem-loop set forth as: S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.~~

~~109. —The oligonucleotide-ligand conjugate of claim 108, wherein L is a tetraloop.~~

~~110. —The oligonucleotide-ligand conjugate of any one of claims 108-109, wherein L comprises a sequence set forth as GAAA.~~

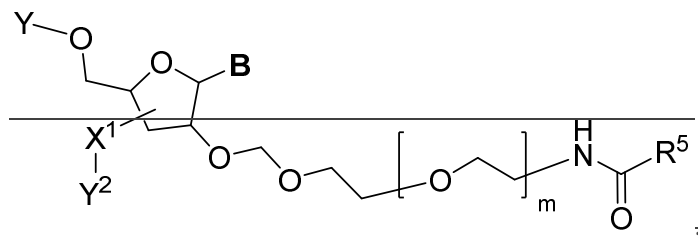
~~111. —The oligonucleotide-ligand conjugate of any one of claims 100-110, wherein the antisense strand comprises a 3' overhang sequence of one or more nucleotides in length, optionally wherein the 3' overhang sequence is 2 nucleotides in length, optionally wherein the 3' overhang sequence is GG.~~

~~112. —An oligonucleotide-ligand conjugate comprising an antisense strand of 15 to 30 nucleotides and a sense strand of 15 to 40 nucleotide, wherein the sense and antisense strands form a duplex region, wherein the antisense strand comprises a region of complementarity to a human *STAT3* mRNA target sequence expressed in an immune cell associated with a tumor microenvironment, wherein the sense strand comprises at its 3' end a stem-loop comprising a tetraloop comprising 4 nucleosides, wherein one or more of the 4 nucleosides conjugated with one or more targeting ligands is represented by formula II-Ib:~~



wherein B is selected from an adenine and a guanine nucleobase, and wherein R⁵ is a hydrocarbon chain.

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

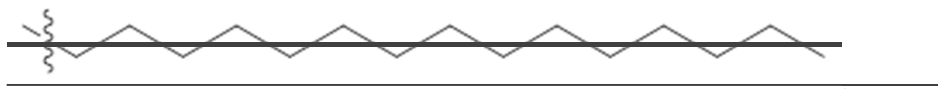


wherein B is selected from an adenine and a guanine nucleobase, and wherein R⁵ is a hydrocarbon chain.

114. ~~The oligonucleotide ligand conjugate of claim 112 or 113, wherein the hydrocarbon chain is a C8-C30 hydrocarbon chain.~~

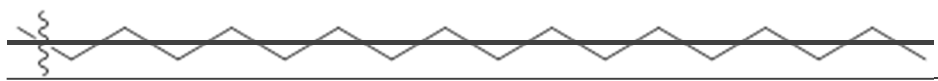
115. ~~The oligonucleotide ligand conjugate of any one of claims 112-114, wherein the hydrocarbon chain is a C16 hydrocarbon chain.~~

116. ~~The oligonucleotide ligand conjugate of claim 115, wherein the C16 hydrocarbon chain is represented by~~



117. The oligonucleotide ligand conjugate of any one of claims 112-114, wherein the hydrocarbon chain is a C18 hydrocarbon chain.

118. The oligonucleotide ligand conjugate of claim 117, wherein the C18 hydrocarbon chain is represented by



119. The oligonucleotide ligand conjugate of any one of claims 112-118, wherein the 4 nucleosides of the tetraloop are numbered 1-4 from 5' to 3', and wherein position 1 is represented by formula II-Ib.

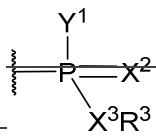
120. The oligonucleotide ligand conjugate of any one of claims 112-118, wherein the 4 nucleosides of the tetraloop are numbered 1-4 from 5' to 3', and wherein position 2 is represented by formula II-Ib.

121. The oligonucleotide ligand conjugate of any one of claims 112-118, wherein the 4 nucleosides of the tetraloop are numbered 1-4 from 5' to 3', and wherein position 3 is represented by formula II-Ib.

122. The oligonucleotide ligand conjugate of any one of claims 112-118, wherein the 4 nucleosides of the tetraloop are numbered 1-4 from 5' to 3', and wherein position 4 is represented by formula II-Ib.

123. The oligonucleotide ligand conjugate of any one of claims 112-122, wherein the sense strand is 36 nucleotides with positions numbered 1-36 from 5' to 3', wherein the stem-loop comprises nucleotides at positions 21-36, and wherein one or more nucleosides at positions 27-30 are represented by formula II-Ib.

124. ~~The oligonucleotide-ligand conjugate of any one of claims 112-123, wherein~~
~~— m is 1,~~
~~— X1 is O,~~
~~— Y2 is an internucleotide linking group attaching to the 5' terminal of a nucleoside,~~



~~— Y is represented by~~ ~~X³R³, Y1 is a linking group attaching to the 2' or 3'~~
~~terminal of a nucleotide,~~
~~— X2 is O,~~
~~— X3 is O, and~~
~~— R3 is H.~~

125. ~~The oligonucleotide-ligand conjugate of any one of claims 112-124, wherein the~~
~~antisense strand is 22 nucleotides.~~

126. ~~The oligonucleotide-ligand conjugate of claims 73-125, wherein the oligonucleotide~~
~~comprises at least one modified nucleotide.~~

127. ~~The oligonucleotide-ligand conjugate of claim 126, wherein the modified nucleotide~~
~~comprises a 2' modification.~~

128. ~~The oligonucleotide-ligand conjugate of claim 126, wherein the 2' modification is a~~
~~modification selected from 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-~~
~~deoxy 2'-fluoro β-D-arabinonucleic acid.~~

129. ~~The oligonucleotide-ligand conjugate of any one of claims 126-128, wherein about~~
~~10-15%, 10%, 11%, 12%, 13%, 14% or 15% of the nucleotides of the sense strand comprise~~
~~a 2'-fluoro modification.~~

~~130. — The oligonucleotide ligand conjugate of any one of claims 126–129, wherein about 25–35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the antisense strand comprise a 2' fluoro modification.~~

~~131. — The oligonucleotide ligand conjugate of any one of claims 126–130, wherein about 25–35%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34% or 35% of the nucleotides of the oligonucleotide comprise a 2' fluoro modification.~~

~~132. — The oligonucleotide ligand conjugate of any one of claims 126–131, wherein the sense strand comprises 36 nucleotides with positions 1–36 from 5' to 3', wherein positions 8–11 comprise a 2' fluoro modification.~~

~~133. — The oligonucleotide ligand conjugate of any one of claims 126–132, wherein the antisense strand comprises 22 nucleotides with positions 1–22 from 5' to 3', and wherein positions 2, 3, 4, 5, 7, 10 and 14 comprise a 2' fluoro modification.~~

~~134. — The oligonucleotide ligand conjugate of any one of claims 129–133, wherein the remaining nucleotides comprise a 2' O-methyl modification.~~

~~135. — The oligonucleotide ligand of any one of claims 129–133, wherein all of the nucleotides of the oligonucleotide are modified.~~

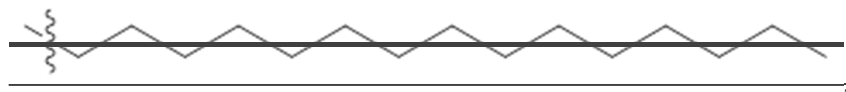
~~136. — The oligonucleotide ligand conjugate of any one of claims 73–135, wherein the oligonucleotide comprises at least one modified internucleotide linkage.~~

~~137. — The oligonucleotide ligand conjugate of claim 136, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.~~

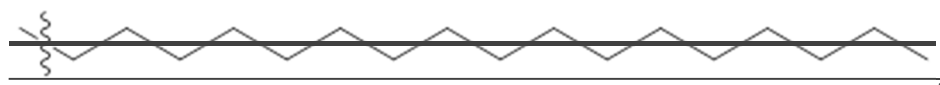
~~138. — The oligonucleotide ligand conjugate of any one of claims 100–137, wherein the 4'-carbon of the sugar of the 5' nucleotide of the antisense strand comprises a phosphate analog.~~

~~139. The oligonucleotide ligand conjugate of claim 138, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate.~~

~~140. The oligonucleotide ligand conjugate of any one of claims 76 113 and 119 139, wherein R5 is~~



~~141. The oligonucleotide ligand conjugate of any one of claims 76 113 and 119 139, wherein R5 is~~



~~142. The oligonucleotide ligand conjugate of any one of claims 100 141, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

- ~~—— (a) SEQ ID NOs: 9 and 10, respectively;~~
- ~~—— (b) SEQ ID NOs: 37 and 38, respectively;~~
- ~~—— (c) SEQ ID NOs: 65 and 66, respectively; and~~
- ~~—— (d) SEQ ID NOs: 69 and 70, respectively.~~

~~143. The oligonucleotide of any one of claims 100 141, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

- ~~(a) SEQ ID NOs: 861 and 951, respectively;~~
- ~~(b) SEQ ID NOs: 857 and 947, respectively;~~
- ~~(c) SEQ ID NOs: 858 and 948, respectively;~~
- ~~(d) SEQ ID NOs: 859 and 949, respectively;~~
- ~~(e) SEQ ID NOs: 860 and 950, respectively;~~
- ~~(f) SEQ ID NOs: 862 and 952, respectively;~~
- ~~(g) SEQ ID NOs: 863 and 953, respectively;~~
- ~~(h) SEQ ID NOs: 864 and 954, respectively;~~
- ~~(i) SEQ ID NOs: 865 and 955, respectively;~~

~~(j) SEQ ID NOs: 866 and 956, respectively;~~
~~(k) SEQ ID NOs: 867 and 957, respectively;~~
~~(l) SEQ ID NOs: 868 and 958, respectively;~~
~~(m) SEQ ID NOs: 869 and 959, respectively;~~
~~(n) SEQ ID NOs: 870 and 960, respectively;~~
~~(o) SEQ ID NOs: 871 and 961, respectively;~~
~~(p) SEQ ID NOs: 872 and 962, respectively;~~
~~(q) SEQ ID NOs: 873 and 963, respectively;~~
~~(r) SEQ ID NOs: 874 and 964, respectively;~~
~~(s) SEQ ID NOs: 875 and 965, respectively;~~
~~(t) SEQ ID NOs: 876 and 966, respectively;~~
~~(u) SEQ ID NOs: 877 and 967, respectively;~~
~~(v) SEQ ID NOs: 878 and 968, respectively;~~
~~(w) SEQ ID NOs: 879 and 969, respectively;~~
~~(x) SEQ ID NOs: 880 and 970, respectively;~~
~~(y) SEQ ID NOs: 881 and 971, respectively;~~
~~(z) SEQ ID NOs: 882 and 972, respectively;~~
~~(aa) SEQ ID NOs: 883 and 973, respectively;~~
~~(bb) SEQ ID NOs: 884 and 974, respectively;~~
~~(cc) SEQ ID NOs: 885 and 975, respectively;~~
~~(dd) SEQ ID NOs: 886 and 976, respectively;~~
~~(ee) SEQ ID NOs: 887 and 977, respectively;~~
~~(ff) SEQ ID NOs: 888 and 978, respectively;~~
~~(gg) SEQ ID NOs: 940 and 1030, respectively;~~
~~(hh) SEQ ID NOs: 896 and 986, respectively; and~~
~~(ii) SEQ ID NOs: 920 and 1010, respectively.~~

144. — ~~The oligonucleotide of any one of claims 100–141, wherein the sense strand comprises a nucleotide sequence of SEQ ID NO: 862 and the antisense strand comprises a nucleotide sequence of SEQ ID NO: 952.~~

~~145.—The oligonucleotide of any one of claims 100–141, wherein the sense strand comprises a nucleotide sequence of SEQ ID NO: 875 and the antisense strand comprises a nucleotide sequence of SEQ ID NO: 965.~~

~~146.—The oligonucleotide of any one of claims 100–141, wherein the sense strand comprises a nucleotide sequence of SEQ ID NO: 876 and the antisense strand comprises a nucleotide sequence of SEQ ID NO: 966.~~

~~147.—The oligonucleotide of any one of claims 100–141, wherein the sense strand comprises a nucleotide sequence of SEQ ID NO: 920 and the antisense strand comprises a nucleotide sequence of SEQ ID NO: 1010.~~

~~148.—The oligonucleotide of any one of claims 100–141, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

- ~~(a) SEQ ID NOs: 901 and 991, respectively;~~
- ~~(b) SEQ ID NOs: 910 and 1000, respectively;~~
- ~~(c) SEQ ID NOs: 899 and 989, respectively;~~
- ~~(d) SEQ ID NOs: 896 and 986, respectively;~~
- ~~(e) SEQ ID NOs: 892 and 982, respectively;~~
- ~~(f) SEQ ID NOs: 890 and 980, respectively; and~~
- ~~(g) SEQ ID NOs: 889 and 979, respectively.~~

~~149.—The oligonucleotide of any one of claims 100–141, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

- ~~(a) SEQ ID NOs: 940 and 1030, respectively;~~
- ~~(b) SEQ ID NOs: 937 and 1027, respectively; and~~
- ~~(c) SEQ ID NOs: 939 and 1029, respectively.~~

~~150.—The oligonucleotide of any one of claims 100–141, wherein the sense strand and antisense strand comprise nucleotide sequences selected from the group consisting of:~~

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

- (b) ~~SEQ ID NOs: 924 and 1014, respectively;~~
(c) ~~SEQ ID NOs: 913 and 1003, respectively; and~~
(d) ~~SEQ ID NOs: 920 and 1010, respectively.~~

11. An oligonucleotide for reducing STAT3 expression, the oligonucleotide comprising an antisense of SEQ ID NO: 1145 and further comprising a sense strand of SEQ ID NO: 1055, wherein:

the antisense strand comprises

[MePhosphonate-4O-

mUs][fUs][fAs][fA][fU][mU][fU][mU][mA][fA][mG][mC][mU][fG][mA][mU][mA][mA][mU][mUs][mGs][mG]

and the sense strand comprises

[mAs][mA][mU][mU][mA][mU][mC][fA][fG][fC][fU][mU][mA][mA][mA][mA][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC].

~~151.12.~~ A pharmaceutical composition comprising the oligonucleotide or oligonucleotide-ligand conjugate of any one of the preceding claims and a pharmaceutically acceptable carrier, delivery agent or excipient.

~~152.13.~~ A method composition for ~~delivering an oligonucleotide to an immune cell associated with a tumor microenvironment, comprising administering use in treating a disorder or condition associated with STAT3 expression in a patient in need thereof, wherein the composition comprises the oligonucleotide or oligonucleotide-ligand conjugate of any one of the preceding claims, 1-150, or the composition of claim 151, thereby delivering the oligonucleotide to the immune cell.~~

~~153.~~ A method of reducing expression of a target mRNA in an immune cell associated with a tumor microenvironment in a subject, comprising administering the oligonucleotide-ligand conjugate of any one of claims 1-150, or the composition of claim 151, thereby reducing expression of the target mRNA in the subject.

154. — ~~The method of claim 152 or 153, wherein the immune cell is a myeloid cell and/or a T cell.~~

155. — ~~The method of claim 154, wherein the myeloid cell is a myeloid derived suppressor cell (MDSC).~~

156. — ~~The method of claim 155, wherein the MDSC is a granulocytic MDSC (G-MDSC) or monocytic MDSC (M-MDSC).~~

157. — ~~The method of any one of claims 154-156, wherein the T cell is a CD8⁺T cell or Treg cell.~~

158. — ~~A method for increasing an immune response in a subject in need thereof, comprising administering the oligonucleotide ligand conjugate of any one of claims 1-150, or the composition of claim 151, thereby increasing the immune response in the subject.~~

159. — ~~The method of claim 158, wherein the subject has cancer.~~

160. — ~~The method of any one of claims 158-159, comprising administering a second composition or therapeutic agent.~~

161. — ~~The method of claim 160, wherein the second composition or therapeutic agent is selected from the group consisting of: a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy, or a combination thereof.~~

162. — ~~Use of the oligonucleotide ligand conjugate of any one of claims 1-150, or the composition of claim 151, for delivering an oligonucleotide to an immune cells associated with a tumor microenvironment in a subject, comprising administering the oligonucleotide ligand conjugate to the subject.~~

~~163. Use of the oligonucleotide-ligand conjugate of any one of claims 1-150, or the composition of claim 151, for reducing expression of a target mRNA in an immune cell associated with a tumor microenvironment in a subject, comprising administering the oligonucleotide-ligand conjugate to the subject.~~

~~164. Use of the oligonucleotide-ligand conjugate of any one of claims 1-150, or the composition of claim 151, for increasing an immune response in a subject in need thereof, comprising administering the oligonucleotide-ligand conjugate to the subject.~~

~~165. The use of the oligonucleotide-ligand conjugate of any one of claims 162-164, wherein the subject has cancer.~~

~~166. A kit comprising the oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with STAT3 expression.~~

~~167.14. A method for treating a subject having a disease, The composition of claim 13 wherein the disorder or condition associated with STAT3 expression, the method comprising administering to the subject a therapeutically effective amount of the oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1 to 150 or the pharmaceutical composition of claim 151 is cancer.~~

~~168.15. The method composition of claim 167.14, wherein the disease, disorder or condition associated with STAT3 expression is selected from the group consisting of cancer; comprises a carcinoma, sarcoma, melanoma, lymphoma, and leukemia, prostate cancer, breast cancer, hepatocellular carcinoma (HCC), colorectal cancer, pancreatic cancer and or a glioblastoma.~~

~~169. The method of claim 167, wherein the disease, disorder or condition associated with STAT3 expression is prostate cancer, breast cancer, hepatocellular carcinoma (HCC), colorectal cancer, and glioblastoma.~~

~~170. — The method of any one of claims 167–169, wherein the oligonucleotide, or pharmaceutical composition, is administered in combination with a second composition or therapeutic agent.~~

~~171. — The method of claim 170 wherein the second composition or therapeutic agent is selected from the group consisting of: a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy, or a combination thereof.~~

~~172. — The method of any one of claims 167–169 wherein the oligonucleotide, or pharmaceutical composition, is administered in combination with at least 2 additional therapeutic agents.~~

~~173. — A method of inhibiting tumor growth in a subject, comprising administering to the subject the oligonucleotide or oligonucleotide ligand conjugate of any one of claims 1–150 or the pharmaceutical composition of claim 151.~~

~~174. A method of treating cancer, or preventing metastasis of cancer, in a subject, comprising administering to the subject the oligonucleotide or oligonucleotide ligand conjugate of any one of claims 1–150 or the pharmaceutical composition of claim 151, wherein tumor associated cells express STAT3.~~

~~175. — A pharmaceutical composition comprising a therapeutically effective amount of the oligonucleotide or oligonucleotide ligand conjugate of any one of claims 1–150, wherein the oligonucleotide decreases the expression, production, or activity of STAT3.~~

~~176. — Use of the oligonucleotide or oligonucleotide ligand conjugate of any one of claims 1–150, or the pharmaceutical composition of claim 151, for reducing STAT3 expression in an immune cell associated with a tumor microenvironment in a subject.~~

~~177. — The oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150, for use in reducing STAT3 expression in an immune cell associated with a tumor microenvironment in a subject.~~

~~178. — Use of the oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150, or the pharmaceutical composition of claim 151, for reducing STAT3 expression in a subject having a disease, disorder or condition associated with STAT3 expression.~~

~~179. — The use of claim 178, wherein the disease, disorder or condition associated with STAT3 expression is selected from the group consisting of cancer, carcinoma, sarcoma, melanoma, lymphoma, and leukemia, prostate cancer, breast cancer, hepatocellular carcinoma (HCC), colorectal cancer, pancreatic cancer and glioblastoma.~~

~~180. — The use of claim 178-179, wherein tumor growth is reduced or inhibited.~~

~~181. — The oligonucleotide or oligonucleotide-ligand conjugate of any one of claims 1-150, for use in reducing STAT3 expression in a subject having a disease, disorder or condition associated with STAT3 expression.~~

~~182. — The oligonucleotide or oligonucleotide-ligand conjugate of claim 181, wherein the disease, disorder or condition associated with STAT3 expression is selected from the group consisting of cancer, carcinoma, sarcoma, melanoma, lymphoma, and leukemia, prostate cancer, breast cancer, hepatocellular carcinoma (HCC), colorectal cancer, pancreatic cancer and glioblastoma.~~

~~183. — The oligonucleotide or oligonucleotide-ligand conjugate of claim 181 or 182, wherein tumor growth is reduced or inhibited.~~