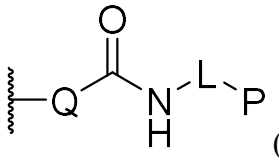
CLAIMS

What is claimed is:

1. A conjugate comprising (i) an antibody or antigen-binding fragment thereof that specifically binds an extracellular domain of a human SIRP-α polypeptide and (ii) one or more immunomodulating oligonucleotides (P), wherein the antibody or antigen-binding fragment is linked to one or more Q-tag peptides (Q) comprising at least one glutamine residue, and wherein each immunomodulating oligonucleotide is linked to a Q-tag peptide via an amide bond with the glutamine residue of the Q-tag peptide and a linker (L) as shown in Formula (A):

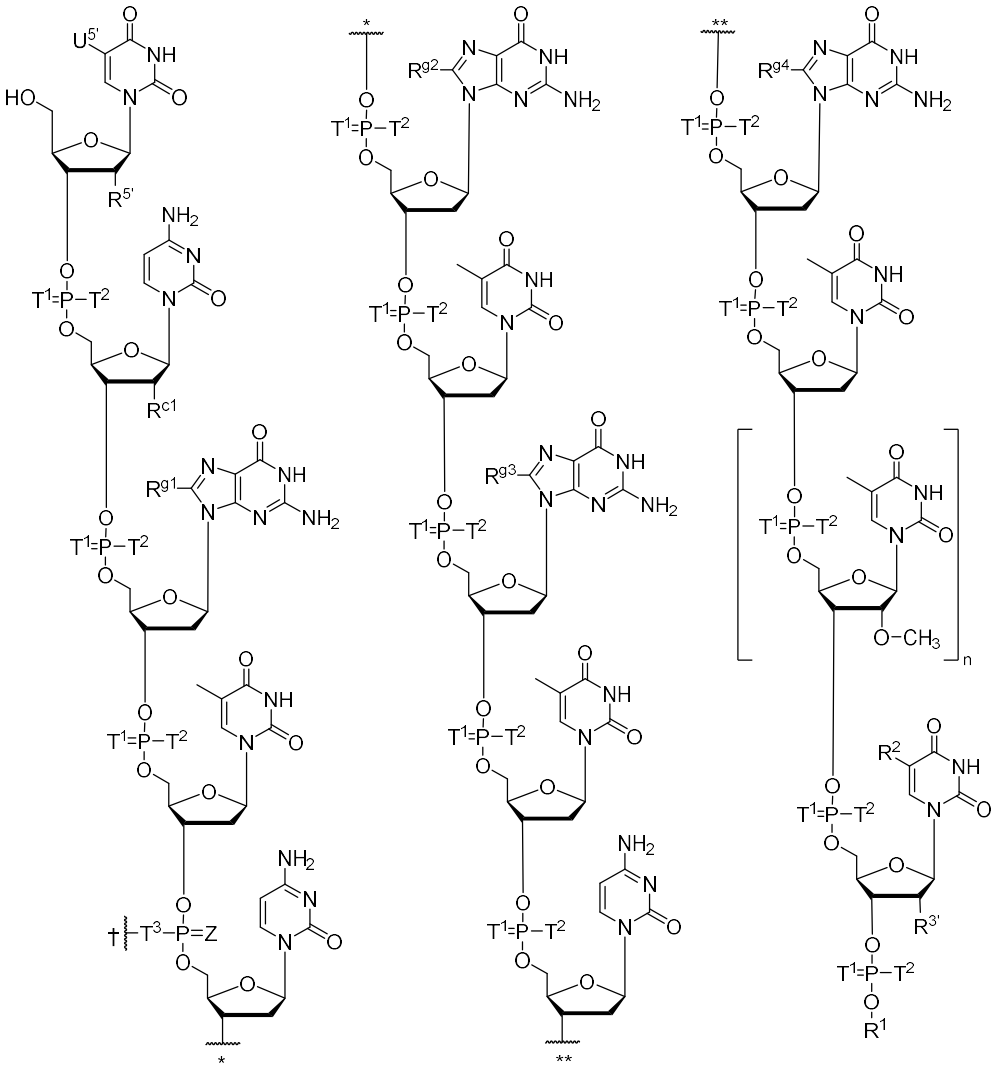


(A);

wherein ~~~ indicates the point of attachment of each Q to the antibody or antigen-binding fragment thereof (Ab);

wherein the antibody or antigen-binding fragment thereof (Ab) comprises: (a) a heavy chain variable (VH) domain that comprises a CDR-H1 comprising the amino acid sequence of SNAMS (SEQ ID NO:56), a CDR-H2 comprising the amino acid sequence of GISAGGSDTYYPASVKG (SEQ ID NO:57), and a CDR-H3 comprising the amino acid sequence of ETWNHLFDY (SEQ ID NO:58), and (b) a light chain variable (VL) domain that comprises a CDR-L1 comprising the amino acid sequence of SGGSYSSYYYA (SEQ ID NO:59), a CDR-L2 comprising the amino acid sequence of SDDKRPS (SEQ ID NO:60), and a CDR-L3 comprising the amino acid sequence of GGYDQSSYTNP (SEQ ID NO:61);

wherein each P is independently an immunomodulating oligonucleotide comprising the structure

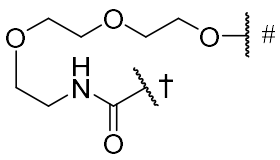


wherein

~~~ * and ~~~ ** indicate the points of attachment within the oligonucleotide, and wherein ~~~ † indicates the point of attachment to the linker L;

each T^1 is independently O or S;

each T^2 is S^-;



T^3 is a group , wherein ~~~ † indicates the point of attachment to L and wherein ~~~ # indicates the point of attachment to the rest of the oligonucleotide;

Z is O or S;
~~~

$U^{5'}$ is –H or halogen;

$R^{5'}$ is -H or methoxy;

R^{c1} is -H or methoxy;

R^{g1}, R^{g2}, R^{g3}, and R^{g4} are H;

$R^{3'}$ is methoxy;

R^{1} is -$(CH_2)_3$-OH;

R^{2} is -H or methyl; and

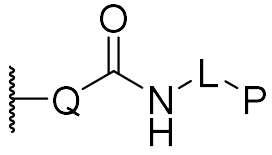
n is an integer from 0 to 2.

2. A conjugate comprising (i) an antibody or antigen-binding fragment thereof that specifically binds an extracellular domain of a human SIRP-α polypeptide and (ii) one or more immunomodulating oligonucleotides (P),

wherein the antibody or antigen-binding fragment is linked to one or more Q-tag peptides (Q) that comprise the amino acid sequence RPQGF (SEQ ID NO:47);

wherein the antibody or antigen-binding fragment thereof (Ab) comprises: (a) a heavy chain variable (VH) domain that comprises a CDR-H1 comprising the amino acid sequence of SNAMS (SEQ ID NO:56), a CDR-H2 comprising the amino acid sequence of GISAGGSDTYYPASVKG (SEQ ID NO:57), and a CDR-H3 comprising the amino acid sequence of ETWNHLFDY (SEQ ID NO:58), and (b) a light chain variable (VL) domain that comprises a CDR-L1 comprising the amino acid sequence of SGGSYSSYYYA (SEQ ID NO:59), a CDR-L2 comprising the amino acid sequence of SDDKRPS (SEQ ID NO:60), and a CDR-L3 comprising the amino acid sequence of GGYDQSSYTNP (SEQ ID NO:61);

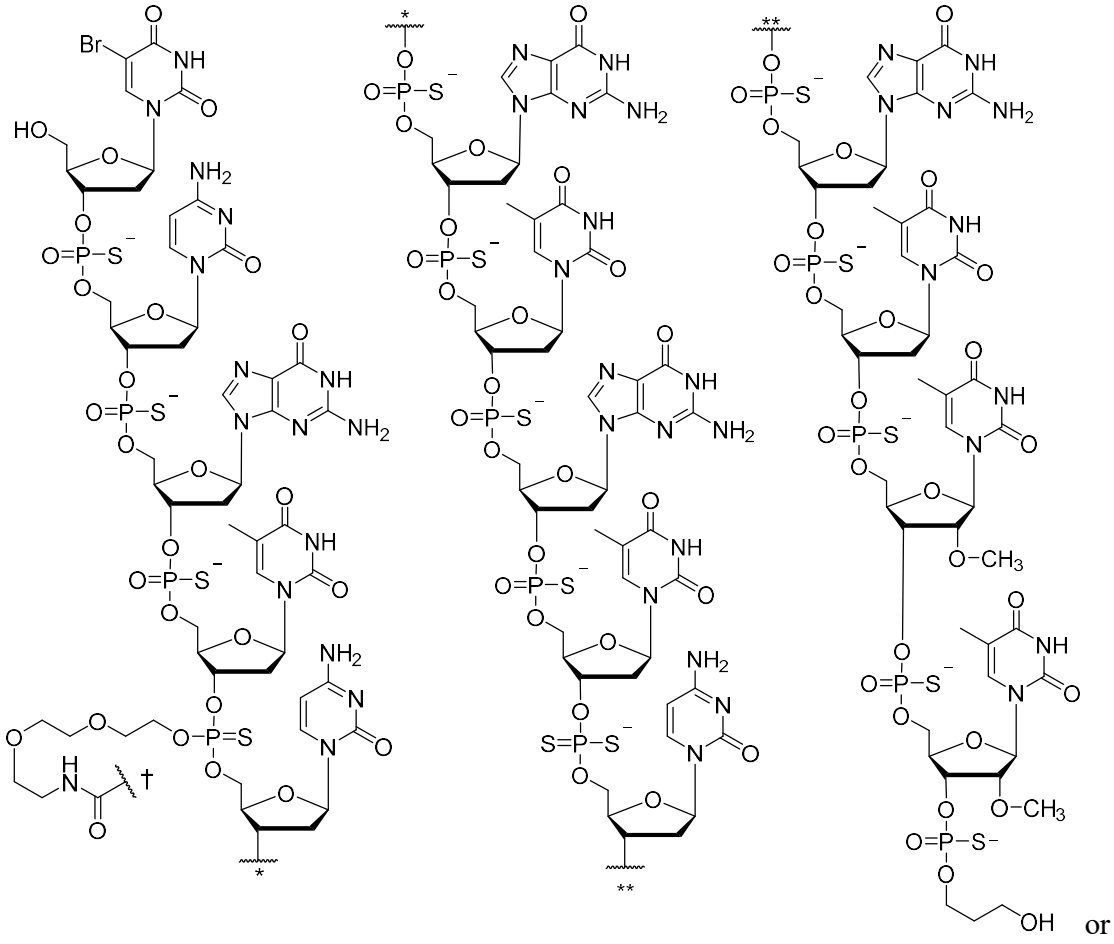
and wherein each immunomodulating oligonucleotide (P) is linked to a Q-tag peptide via an amide bond with the glutamine residue of the Q-tag peptide and a linker (L) as shown in Formula (A):



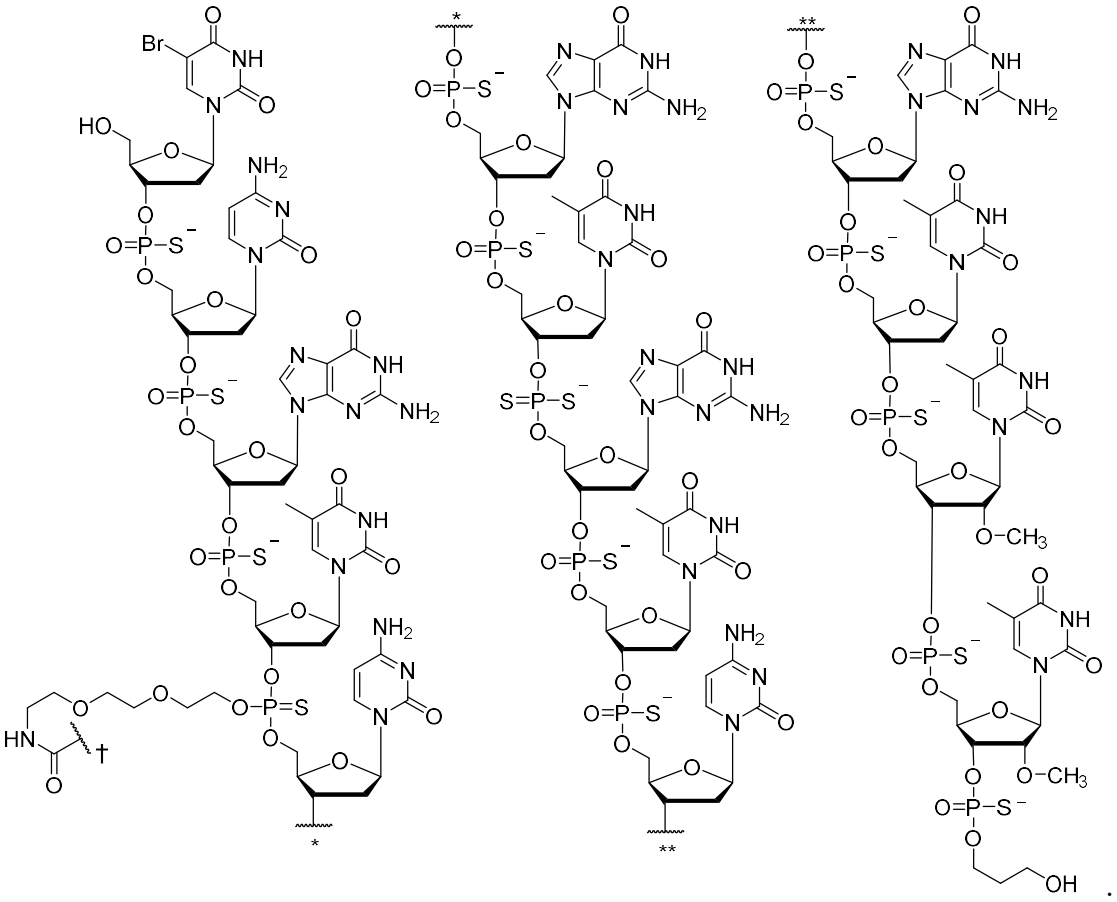
(A),

wherein 〰 indicates the point of attachment of each Q to the antibody or antigen-binding fragment thereof (Ab).

3. The conjugate of claim 1 or claim 2, wherein each P is independently an immunomodulating oligonucleotide comprising the structure



or



4. The conjugate of any one of claims 1-3, wherein the VH domain comprises the amino acid sequence of EVQLVESGGGVVQPGGSLRLSCAASGFTFSSNAMSWVRQAPGKGLEWVAGISAGGSDT YYPASVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARETWNHLFDYWGQGTLVT VSS (SEQ ID NO:62), and wherein:

(a) the VL domain comprises the amino acid sequence of SYELTQPPSVSVSPGQTARITCSGGSYSSYYYAWYQQKPGQAPVTLIYSDDKRPSNIPER FSGSSSGTTVTLTISGVQAEDEADYYCGGYDQSSYTNPFGGGTQLTVL (SEQ ID NO:63);

(b) the VL domain comprises the amino acid sequence of SYELTQPPSVSVSPGQTARITCSGGSYSSYYYAWYQQKPGQAPVTLIYSDDKRPSNIPER FSGSSSGTTVTLTISGVQAEDEADYYCGGYDQSSYTNPFGGGTKLTVL (SEQ ID NO:64); or

(c) the VL domain comprises the amino acid sequence of SYELTQPPSVSVSPGQTARITCSGGSYSSYYYAWYQQKPGQAPVTLIYSDDKRPSNIPER FSGSSSGTTVTLTISGVQAEDEADYYCGGYDQSSYTNPFGGGTELTVL (SEQ ID NO:65).

5. The conjugate of any one of claims 1-4, wherein the antibody or antigen-binding fragment is a monoclonal antibody, a Fab, F(ab')2, Fab'-SH, Fv, or scFv antibody or antibody fragment.

6. The conjugate of any one of claims 1-5, wherein the antibody is a humanized, human, or chimeric antibody or fragment thereof.

7. The conjugate of any one of claims 1-6, wherein the antibody comprises an antibody heavy chain comprising the VH domain and an Fc region.

8. The conjugate of claim 7, wherein the antibody heavy chain comprises a human IgG1, human IgG2, or human IgG4 Fc region.

9. The conjugate of claim 7 or claim 8, wherein the antibody heavy chain comprises:

(a) a human IgG1 Fc region comprising L234A, L235A, and/or G237A substitutions, amino acid position numbering according to EU index;

(b) a wild-type human IgG1 Fc region;

(c) a human IgG1 Fc region comprising an N297A substitution, amino acid position numbering according to EU index;

(d) a human IgG1 Fc region comprising a D265A substitution, amino acid position numbering according to EU index;

(e) a wild-type human IgG2 Fc region;

(f) a human IgG2 Fc region comprising an N297A substitution, amino acid position numbering according to EU index; or

(g) a human IgG4 Fc region comprising an S228P substitution, amino acid position numbering according to EU index.

10. The conjugate of any one of claims 1-9, wherein the antibody comprises an antibody heavy chain comprising the amino acid sequence selected from the group consisting of:
EVQLVESGGGVVQPGGSLRLSCAASGFTFSSNAMSWVRQAPGKGLEWVAGISAGGSDT
YYPASVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARETWNHLFDYWGQGTLVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEA
AGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:88);

EVQLVESGGGVVQPGGSLRLSCAASGFTFSSNAMSWVRQAPGKGLEWVAGISAGGSDT
YYPASVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARETWNHLFDYWGQGTLVT
VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDK
SRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG (SEQ ID NO:87); and

EVQLVESGGGVVQPGGSLRLSCAASGFTFSSNAMSWVRQAPGKGLEWVAGISAGGSDT
YYPASVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARETWNHLFDYWGQGTLVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP
PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:89).

11. The conjugate of any one of claims 1-10, wherein the antibody comprises an antibody light chain comprising the VL domain and a light chain constant (CL) domain, and wherein the CL domain comprises the amino acid sequence

(a)
GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPS
KQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO:69);

(b)
GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPS
KQSSDKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO:70);
or

(c)
GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPS
KQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO:71).

12. The conjugate of any one of claims 1-11, wherein the antibody comprises an antibody light chain comprising an amino acid sequence selected from the group consisting of SEQ ID Nos:72-80.

13. The conjugate of any one of claims 1-3, wherein the antibody comprises:

(a) an antibody heavy chain, with C-terminal Q-tag peptide, comprising the amino acid sequence of SEQ ID NO:68 and an antibody light chain comprising the amino acid sequence of SEQ ID NO:79;

(b) an antibody heavy chain, with C-terminal Q-tag peptide, comprising the amino acid sequence of SEQ ID NO:67 and an antibody light chain comprising the amino acid sequence of SEQ ID NO:79;

(c) an antibody heavy chain, with C-terminal Q-tag peptide, comprising the amino acid sequence of SEQ ID NO:66 and an antibody light chain comprising the amino acid sequence of SEQ ID NO:79;

(d) an antibody heavy chain, with C-terminal Q-tag peptide, comprising the amino acid sequence of SEQ ID NO:68 and an antibody light chain comprising the amino acid sequence of SEQ ID NO:75;

(e) an antibody heavy chain, with C-terminal Q-tag peptide, comprising the amino acid sequence of SEQ ID NO:67 and an antibody light chain comprising the amino acid sequence of SEQ ID NO:75;

(f) an antibody heavy chain, with C-terminal Q-tag peptide, comprising the amino acid sequence of SEQ ID NO:66 and an antibody light chain comprising the amino acid sequence of SEQ ID NO:75;

(g) an antibody heavy chain, with C-terminal Q-tag peptide, comprising the amino acid sequence of SEQ ID NO:68 and an antibody light chain comprising the amino acid sequence of SEQ ID NO:73;

(h) an antibody heavy chain, with C-terminal Q-tag peptide, comprising the amino acid sequence of SEQ ID NO:67 and an antibody light chain comprising the amino acid sequence of SEQ ID NO:73; or

(i) an antibody heavy chain, with C-terminal Q-tag peptide, comprising the amino acid sequence of SEQ ID NO:66 and an antibody light chain comprising the amino acid sequence of SEQ ID NO:73.

14. The conjugate of any one of claims 1-12, wherein each of the one or more Q-tag peptides (Q) comprises a peptide sequence having between 5 and 15 amino acid residues.

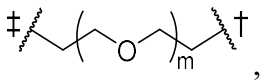
15. The conjugate of claim 14, wherein each of the one or more Q-tag peptides comprises the peptide sequence RPQGF (SEQ ID NO:47), RPQGFPP (SEQ ID NO:48), or RPQGFGPP (SEQ ID NO:49).

16. The conjugate of any one of claims 1-12, 14 and 15, wherein the Q-tag is fused to the C-terminus of one or both of the heavy chains.

17. The conjugate of any one of claims 1-12, 14 and 15, wherein the Q-tag is within the Fc domain.

18. The conjugate of any one of claims 1-17, wherein the conjugate has a DAR of 1 or 2.

19. The conjugate of any one of claims 1-18, wherein the linker L is



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wherein m is an integer ranging from about 0 to about 50, and wherein ~~~ † indicates the point of attachment to T^3, and ~~~ ‡ indicates the point of attachment to the rest of the conjugate.

20. The conjugate of claim 19, wherein m is an integer from 20 to 25.

21. The conjugate of claim 19, wherein m is 24.

22. The conjugate of any one of claims 1, and 18-21, wherein the antibody comprises two antibody light chains, two antibody heavy chains, and two Q-tag peptides; wherein each of the Q-tag peptides is linked to the C-terminus of one of the antibody heavy chains; and wherein one of the Q-tag peptides is linked to an immunomodulating oligonucleotide (P) via an amide bond with the glutamine residue of the Q-tag peptide and linker (L) and wherein:

(a) each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:75; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:68; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:35;

(b) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:75; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:67; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:35;

(c) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:75; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q)

and comprises the amino acid sequence, with Q, of SEQ ID NO:66; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:35;

(d) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:73; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:68; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:35;

(e) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:73; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:67; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:35;

(f) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:73; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:66; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:35;

(g) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:75; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:68; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:34;

(h) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:75; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:67; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:34;

(i) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:75; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:66; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:34;

(j) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:73; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:68; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:34;

(k) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:73; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:67; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:34;

(l) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:73; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:66; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:34;

(m) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:75; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:68; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:163;

(n) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:75; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:67; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:163;

(o) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:75; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:66; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:163;

(p) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:73; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:68; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:163;

(q) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:73; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:67; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:163; or

(r) wherein each of the antibody light chains comprises the amino acid sequence of SEQ ID NO:73; wherein each of the antibody heavy chains is linked to a C-terminal Q-tag peptide (Q) and comprises the amino acid sequence, with Q, of SEQ ID NO:66; and wherein the immunomodulating oligonucleotide and the linker comprise the structure of SEQ ID NO:163.

23. A pharmaceutical composition comprising the conjugate of any one of claims 1-22 and a pharmaceutically acceptable carrier.

24. Use of the conjugate according to any one of claims 1-22 or the pharmaceutical composition of claim 23, in the manufacture of a medicament for treating cancer in an individual.

25. The use of claim 24, wherein the cancer is lung cancer, intrahepatic cholangiocarcinoma, squamous cell cancer, brain tumors, glioblastoma, head and neck cancer, hepatocellular cancer, colorectal cancer, skin cancer, lung cancer, endometrial cancer, liver cancer, bladder cancer, gastric or stomach cancer, pancreatic cancer, cervical cancer, ovarian cancer, cancer of the urinary tract, urothelial cancer, breast cancer, peritoneal cancer, uterine cancer, salivary gland cancer, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, anal carcinoma, penile carcinoma, testis or testicular cancer, melanoma, multiple myeloma and B-cell lymphoma, non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), Merkel cell carcinoma, hairy cell leukemia, or chronic myeloblastic leukemia (CML), including metastases thereof.

26. The use of claim 24 or claim 25, wherein the cancer is predicted to be non-responsive to an inhibitor of PD-L1 or PD-1 or the individual does not achieve a significant therapeutic response to an inhibitor of PD-L1 or PD-1.

27. The use of any one of claims 24-26, wherein an additional therapeutic agent is to be administered to the individual.

28. The use of claim 27, wherein the additional therapeutic agent comprises an immunotherapy, chemotherapy, radiation therapy, cell-based therapy, anti-cancer vaccine, or anti-cancer agent.

29. The use of any one of claims 24-27, wherein an inhibitor of PD-L1 or PD-1 is to be further administered.

30. A kit or article of manufacture comprising the conjugate of any of claims 1-22.