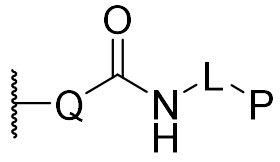
[0008] CpG ODNs may include, for example, oligodeoxynucleotides comprising poly-G tails with phosphorothioate backbones at 3'- and 5'-termini and a central palindromic sequence including a phosphate backbone and a CpG within its central palindrome sequence, or oligodeoxynucleotides having a fully phosphorothioate backbone, and a sequence at the 5' end for TLR9 activation, or oligodeoxynucleotides having a fully phosphorothioate backbone with a 3'-end sequence enabling formation of a duplex. However, CpG ODNs are often susceptible to degradation in serum and thus pharmacokinetics of CpG ODNs may be one of the limiting factors in their development as therapeutics. Also CpG ODNs often exhibit uneven tissue distribution in vivo, with primary sites of accumulation being in liver, kidney, and spleen. Such distribution can elicit off-target activity and local toxicity associated with PAMPs. Therefore, it will be advantageous to design CpG with improved stability properties, potency, and delivery systems.

[0009] There is a need for anti-nectin-4 antibodies conjugated to immunomodulating oligonucleotides to treat diseases, disorders, and conditions, such as cancer.

SUMMARY

[0010] In one aspect, provided herein is a conjugate comprising (i) an anti-nectin-4 antibody or antigen binding fragment thereof 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 each P is independently an immunomodulating oligonucleotide comprising the structure

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;

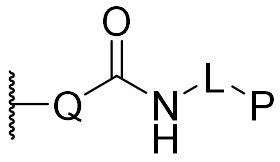
$R^{3'}$ is methoxy;

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

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

n is an integer from 0 to 2.

[0011] In one example, provided herein is a conjugate comprising (i) an anti-nectin-4 antibody or antigen binding fragment thereof and (ii) and one or more immunomodulating oligonucleotides (P), wherein the antibody or antigen-binding fragment is linked to one or more Q-tag peptides (Q), 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)

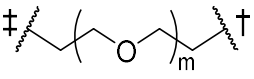


(A),

wherein:

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

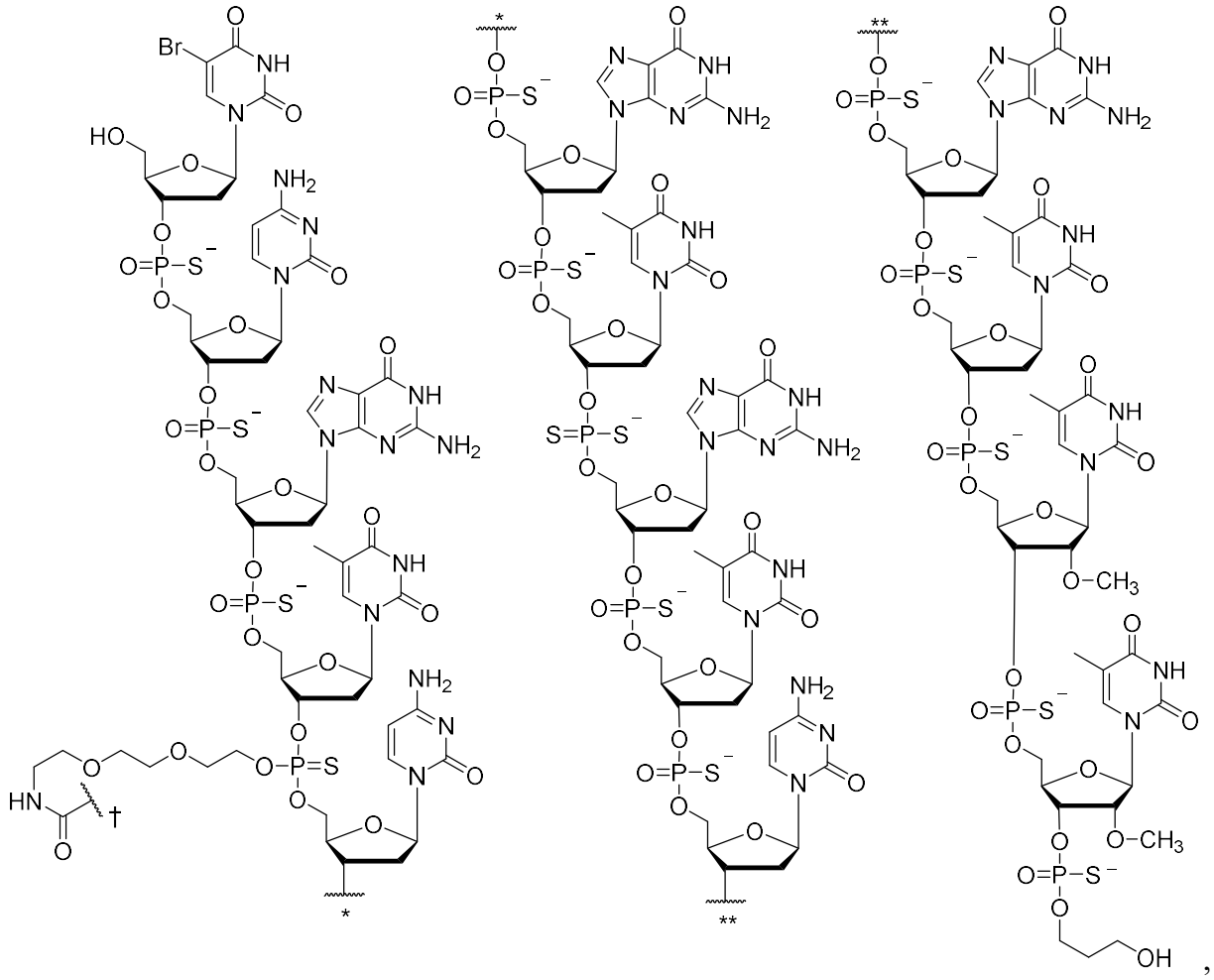
each Q independently comprises a Q-tag peptide sequence RPQGF (SEQ ID NO:47);

each L is independently a bond or a linker moiety 

,

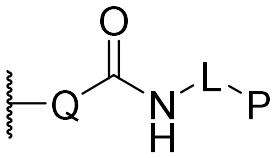
wherein m is an integer ranging from about 0 to about 50, and wherein 〰 † indicates the point of attachment to P, and 〰 ‡ indicates the point of attachment to the rest of the conjugate connected to Q via an amide bond with the glutamine residue; and

each P is independently an immunomodulating oligonucleotide having the structure



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

[0012] In one example, provided herein is a conjugate comprising (i) an anti-nectin-4 antibody or antigen binding fragment thereof 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), 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)

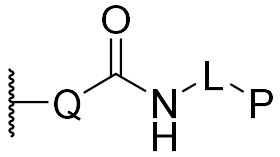

(A),

wherein:

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

[0013] In one example, provided herein is a conjugate comprising (i) an anti-nectin-4 antibody or antigen binding fragment thereof 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), 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).

[0014] In one example, provided herein is a conjugate comprising an anti-nectin-4 antibody or antigen binding fragment thereof, wherein the antibody comprises two antibody light chains, two antibody heavy chains, and two Q-tag peptides each comprising a peptide sequence RPQGF (SEQ ID NO:47); wherein each of the Q-tag peptides is linked to the C-terminus of one of the antibody heavy chains; and wherein at least 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) as shown in **FIG. 9A** or **FIG. 9B**.

[0015] In one example, provided herein is a conjugate comprising an anti-nectin-4 antibody or antigen binding fragment thereof (Ab), at least one Q-tag peptide sequence comprising a glutamine residue, and at least one immunomodulatory oligonucleotide (P), wherein the Q-tag peptide sequence is naturally occurring or synthetic, and wherein each immunomodulatory oligonucleotide is linked to a Q-tag via an amide bond with the glutamine residue and linker (L), wherein at least one Q-tag peptide sequence is selected from the group consisting of SEQ ID NOs:39-55.

[0016] In some examples, the antibody of the conjugate comprises a light chain variable region (VL) domain and a heavy chain variable region (VH) domain, wherein:

(cc) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:930 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:931;

(dd) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO932: and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:933;

(ee) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:934 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:935;

(ff) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:936 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:937;

(gg) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:938 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:939;

(hh) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:940 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:941;

(ii) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:942 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:943; or

(jj) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:944 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:945.

[0017] In some examples, the antibody of the conjugate comprises a heavy chain variable region (VH) domain and a light chain variable region (VL) domain, wherein:

(a) the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 and the VL domain comprises CDR-L1, CDR-L2, and CDR-L3, wherein CDR-H1 comprises SEQ ID NO:275, CDR-H2 comprises SEQ ID NO:276, CDR-H3 comprises SEQ ID NO:277, CDR-L1 comprises SEQ ID NO:272, CDR-L2 comprises SEQ ID NO:273, and CDR-L3 comprises SEQ ID NO:274;

(xx) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3, wherein CDR-L1 comprises SEQ ID NO:796, CDR-L2 comprises SEQ ID NO:797, and CDR-L3 comprises SEQ ID NO:798, wherein CDR-H1 comprises SEQ ID NO:799, CDR-H2 comprises SEQ ID NO:800, and CDR-H3 comprises SEQ ID NO:801;

(yy) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3, wherein CDR-L1 comprises SEQ ID NO:814, CDR-L2 comprises SEQ ID NO:815, and CDR-L3 comprises SEQ ID NO:816, wherein CDR-H1 comprises SEQ ID NO:817, CDR-H2 comprises SEQ ID NO:818, and CDR-H3 comprises SEQ ID NO:819; or

(zz) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3, wherein CDR-L1 comprises SEQ ID NO:832, CDR-L2 comprises SEQ ID NO:833, and CDR-L3 comprises SEQ ID NO:834, wherein CDR-H1 comprises SEQ ID NO:835, CDR-H2 comprises SEQ ID NO:836, and CDR-H3 comprises SEQ ID NO:837.

[0018] In some examples, the antibody of the conjugate comprises a light chain variable region (VL) domain and a heavy chain variable region (VH) domain, wherein:

(a) the VH domain comprises the sequence of amino acids selected from the group consisting of SEQ ID NOs:249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 901, 903, 905, 907, 909, 911, 913, 915, 917, 919, 921, 923, 925, 927, 929, 931, 933, 935, 937, 939, 941, 943, and 945 and/or the VL domain comprises the sequence of amino acids selected from the group consisting of SEQ ID NOs: 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 900, 902, 904, 906, 908, 910, 912, 914, 916, 918, 920, 922, 924, 926, 928, 930, 932, 934, 936, 938, 940, 942, and 944;

(b) the VL domain comprises the sequence of SEQ ID NO:248 and/or the VH domain comprises the sequence of SEQ ID NO:249;

(c) the VL domain comprises the sequence of SEQ ID NO:250 and/or the VH domain comprises the sequence of SEQ ID NO:251;

(d) the VL domain comprises the sequence of SEQ ID NO:252 and/or the VH domain comprises the sequence of SEQ ID NO:253;

(ii) the VL domain comprises the sequence of SEQ ID NO:942 and/or the VH domain comprises the sequence of SEQ ID NO:943; or

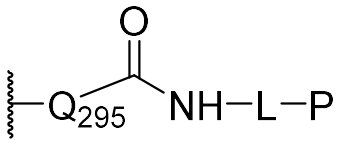
(jj) the VL domain comprises the sequence of SEQ ID NO:944 and/or the VH domain comprises the sequence of SEQ ID NO:945.

[0019] In some examples, the antibody of the conjugate is a monoclonal antibody. In some examples, the antibody of the conjugate is a Fab, F(ab')2, Fab'-SH, Fv, scFv, single domain, single heavy chain, or single light chain antibody or antibody fragment. In some examples, the antibody of the conjugate is a humanized, human, or chimeric antibody or fragment thereof.

[0020] In some examples, the antibody of the conjugate comprises an Fc region. In some examples, the Fc region is a human Fc region selected from the group consisting of an IgG1 Fc region, an IgG2 Fc region, and an IgG4 Fc region. In some examples, the Fc region is a human Fc region comprising one or more amino acid substitutions that reduce binding to C1q. In some examples, the Fc region is a human Fc region comprising one or more amino acid substitutions that increase binding to C1q. In some examples, the Fc region is a human Fc region exhibiting wild-type complement activation. In some examples, the Fc region is a human Fc region comprising one or more amino acid substitutions that increase complement activation. In some examples, the Fc region is a human Fc region comprising one or more amino acid substitutions that reduce effector function, as compared with a human Fc region that lacks the amino acid substitution(s). In some examples, the Fc region is: (a) a human IgG1 Fc region comprising L234A, L235A, and/or G237A substitutions, amino acid position numbering according to EU index; (b) a human IgG2 Fc region comprising A330S and/or P331S substitutions, amino acid position numbering according to EU index; or (c) a human IgG4 Fc region comprising S228P and/or L235E substitutions, amino acid position numbering according to EU index. In some examples, the Fc region is a wild-type human IgG1 Fc region. In some examples, the Fc region is a human IgG1 Fc region. In some examples, the Fc region has been engineered to improve effector function, optionally wherein the improved effector function is antibody-dependent cell-mediated cytotoxicity (ADCC) activity, antibody-dependent cellular phagocytosis (ADCP) activity, or complement-dependent cytotoxicity (CDC) activity. In some examples, the Fc region has been engineered to exhibit at least two features selected from the group consisting of improved ADCC activity, improved ADCP activity, and improved CDC activity. In some examples, the Fc region comprises the substitution G236A, with amino acid position according

to EU index. In some examples, the Fc region comprises the substitution G236A, with amino acid position according to EU index, and the Fc region is non-fucosylated. In some examples, the Fc region has been engineered to improve ADCC activity. In some examples, the Fc region has been engineered to improve ADCP activity. In some examples, the Fc region has been engineered to improve CDC activity. In some examples, the antibody of the conjugate comprises at least one amino acid substitution in the Fc region that improves ADCC activity. In some examples, the antibody of the conjugate comprises at least one amino acid substitution in the Fc region that improves ADCP activity. In some examples, the antibody of the conjugate comprises at least one amino acid substitution in the Fc region that improves CDC activity. In some examples, at least one or at least two of the heavy chains of the antibody of the conjugate is/are non-fucosylated. In some examples, the antibody of the conjugate is produced in a cell line having an alpha1,6-fucosyltransferase (Fut8) knockout or in a cell line overexpressing β1,4-N-acetylglycosminyltransferase III (GnT-III), wherein optionally the cell line is a CHO cell line. In some examples, the antibody of the conjugate is produced in an expression system in the presence of a 2-fluorofucose compound or a 5-alkynylfucose derivative. In some examples, the cell line overexpresses Golgi μ-mannosidase II (ManII), wherein optionally the cell line is a CHO cell line. In some examples, the Fc region comprises an N297A substitution, amino acid position numbering according to EU index. In some examples, the Fc region comprises a D265A substitution, with amino acid position numbering according to EU index.

[0021] In some examples, the conjugate further comprises an immunomodulating oligonucleotide P attached to the Q295 of the Fc region residue as shown in the following formula



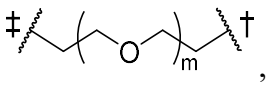
, wherein L is a linker moiety connected to Q295 of the Fc region via an amide bond.

[0022] In some examples, the antibody of the conjugate comprises an antibody heavy chain constant domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:92-107, 111,112, 178, and 494-497. In some examples, the antibody of the conjugate comprises a human lambda light chain. In some examples, the antibody of the conjugate comprises a human kappa light chain. In some examples, the antibody of the conjugate comprises an antibody light chain constant domain comprising an amino acid sequence

selected from the group consisting of SEQ ID Nos:108-110. In some examples, the antibody of the conjugate comprises two antibody heavy chains and two antibody light chains, and wherein one Q-tag is attached to one or both heavy chain(s) of the antibody. In some examples, the Q-tag is fused to the C-terminus of the heavy chain of the antibody(ies). In some examples, the antibody of the conjugate comprises two antibody heavy chains and two antibody light chains, and wherein one Q-tag is attached to one or both light chain(s) of the antibody. In some examples, the Q-tag is within the Fc domain.

[0023] In some examples, the conjugate induces activation of TLR9. In some examples, each Q-tag independently comprises a peptide sequence comprising between 5 and 15 amino acid residues. In some examples, the Q-tag is naturally occurring. In some examples, the peptide sequence of each Q-tag is independently selected from the group consisting of SEQ ID NOs: 39-55. In some examples, the Q-tag comprises the peptide sequence RPQGF (SEQ ID NO:47). In some examples, each Q-tag independently comprises RPQGF (SEQ ID NO:47), RPQGFPP (SEQ ID NO:48), or RPQGFGPP (SEQ ID NO:49). In some examples, each Q-tag independently comprises RPQGFGPP (SEQ ID NO:49). In some examples, 1 or 2 Q-tags is/are linked to the antibody. In some examples, the conjugate has a DAR of 1 or 2.

[0024] In some examples, the linker L comprises a polyethylene glycol moiety. In some examples, the linker L is

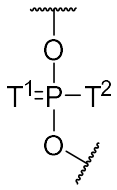


wherein m is an integer ranging from about 0 to about 50, and wherein ~~~ † indicates the point of attachment to T^3, and ~~~ ‡ indicates the point of attachment to the rest of the conjugate

[0025] In some examples, m is about 20 to about 30. In some examples, wherein m is about 24. In some examples, Z is S. In some examples, the oligonucleotide P comprises at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S^-. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 1. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 2. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 3.

In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 5. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 6. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 7. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 8. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 9. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 10. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 11. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 12. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 13. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 14. In some examples, at least one pair of geminal T^1 and T^2 wherein T^1 is S and T^2 is S is located at the 3'-position of nucleoside residue 15. In some examples, the oligonucleotide P comprises at least two pairs of geminal T^1 and T^2 wherein T^1 is S and T^2 is S^-. In some examples, wherein $R^{5'}$ is H. In some examples, $R^{5'}$ is methoxy. In some examples, R^{c1} is H. In some examples, R^{c1} is methoxy. In some examples, R^2 is methyl. In some examples, R^2 is H. In some examples, $U^{5'}$ is bromo. In some examples, $U^{5'}$ is -H. In some examples, m is an integer from 20 to 25. In some examples, m is 24.

[0026] In some examples, each P independently comprises an oligonucleotide selected from Table 2, Table 3, and Table 4. In some examples, each (L) and (P) in the conjugate independently comprises a structure selected from Table 2, Table 5, and Table 6, optionally compound 7.6b or compound 7.7b. In some examples, each (P) and (L) in the conjugate independently comprises an oligonucleotide or a modified oligonucleotide selected from SEQ ID NOS: 1-38 and 129-166. In some examples, each immunomodulating oligonucleotide P is independently

each Y^N is independently an internucleoside linker comprising the structure  ;

wherein each B^N is independently a modified or unmodified nucleobase;

each R^N is independently -H or -O-C_{1-4}-alkyl, wherein the C_{1-4}-alkyl of the -O-C_{1-4}-alkyl is optionally further substituted by -O-C_1-C_4-alkyl;

$B^{5'}$ and $B^{3'}$ are independently a modified or unmodified nucleobase;

$R^{5'}$ and $R^{3'}$ are independently -H or -O-C_1-C_4-alkyl, wherein the C_{1-4}-alkyl of the -O-C_{1-4}-alkyl is optionally further substituted by -O-C_{1-4}-alkyl;

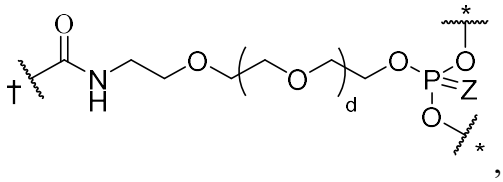
each T_1 is independently O or S;

each T_2 is independently O^- or S^-; and

T_3 is a group comprising an oligoethylene glycol moiety; and

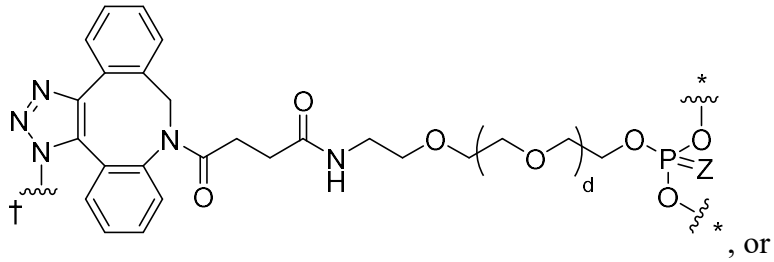
R^1 is C_{1-4}-alkylene-hydroxy.

[0027] In some examples, b is 3. In some examples, (i) P comprises at least one modified nucleoside X^N; (ii) P has at least one modified internucleoside linker Y^N, wherein at least one of T^1 or T^2 is S; or (iii) both (i) and (ii). In some examples, P has at least one phosphorodithioate or phosphorothioate internucleoside linker. In some examples, P comprises 0, 1, 2, or 3 phosphorodithioate internucleoside linkers. In some examples, P comprises a modified nucleoside selected from the group consisting of 2'-O-alkyl nucleoside, 2'-O-alkoxyalkyl nucleoside, 2'-deoxynucleoside and ribonucleoside. In some examples, the modified nucleoside is selected from the group consisting of 5-bromo-2'-O-methyluridine, 5-bromo-2'-deoxyuridine, 2'-O-methyluridine, 2'-deoxyuridine, 2'-O-methylthymidine, 2'-O-methylcytidine, 2'-O-(2-methoxyethyl)thymidine and 8-oxo-7,8-dihydro-2'-deoxyguanosine. In some examples, $X^{5'}$ is a 5-bromo-2'-O-methyluridine, 5-bromo-2'-deoxyuridine, 2'-O-methyluridine or 2'-deoxyuridine. In some examples, $Y^{3'}$ or the Y^N at the 3' position of $X^{5'}$ comprises an unsubstituted or substituted phosphorothioate. In some examples, Y^{PTE} is:

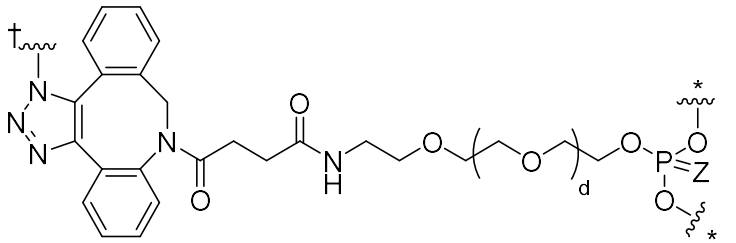

,

wherein Z is O or S; d is an integer from 0 to 95; the two ~~* on the right side of the structure indicate the points of attachment to the adjacent nucleosides X^N in the oligonucleotide P, and the ~~† on the left side of the structure indicates the point of attachment to the linker L.

[0028] In some examples, Y^{PTE} is:



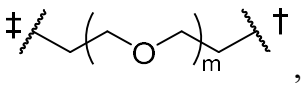
, or



,

wherein Z is O or S; d is an integer from 0 to 95; the two ~~* on the right side of the structure indicate the points of attachment to the adjacent nucleosides X^N in the oligonucleotide P, and the one ~~† on the left side of the structure indicates the point of attachment to the linker L.

[0029] In some examples, Z is S. In some examples, d is an integer from 1 to 25. In some examples, the linker L comprises a polyethylene glycol moiety. In some examples, the linker L is



,

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

[0030] In some examples of the conjugate, P comprises one or more CpG sites. In some examples, P comprises at least 3 CpG sites. In some examples, the antibody of the conjugate 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).

[0031] In some examples of the conjugate:

(a) the antibody comprises a light chain comprising a light chain sequence selected from the group consisting of SEQ ID NOs:236-247 and 1000-1022 and/or a heavy chain comprising a heavy chain sequence and a Q-tag, wherein the heavy chain comprises a sequence selected from the group consisting of SEQ ID NOs:224-235 and 1030-1065;

(b) the antibody comprises a light chain comprising a light chain sequence selected from the group consisting of SEQ ID NOs:236-247 and 1000-1022 and/or a heavy chain comprising a heavy chain sequence selected from the group consisting of SEQ ID NOs:1070-1117;

(c) the antibody comprises a light chain comprising SEQ ID NO:236 and/or a heavy chain comprising SEQ ID NO:224;

(d) the antibody comprises a light chain comprising SEQ ID NO:237 and/or a heavy chain comprising SEQ ID NO:225;

(e) the antibody comprises a light chain comprising SEQ ID NO:238 and/or a heavy chain comprising SEQ ID NO:226;

(f) the antibody comprises a light chain comprising SEQ ID NO:239 and/or a heavy chain comprising SEQ ID NO:227;

(g) the antibody comprises a light chain comprising SEQ ID NO:240 and/or a heavy chain comprising SEQ ID NO:228;

(h) the antibody comprises a light chain comprising SEQ ID NO:241 and/or a heavy chain comprising SEQ ID NO:229;

(i) the antibody comprises a light chain comprising SEQ ID NO:242 and/or a heavy chain comprising SEQ ID NO:230;

(j) the antibody comprises a light chain comprising SEQ ID NO:243 and/or a heavy chain comprising SEQ ID NO:231;

(k) the antibody comprises a light chain comprising SEQ ID NO:244 and/or a heavy chain comprising SEQ ID NO:232;

(l) the antibody comprises a light chain comprising SEQ ID NO:245 and/or a heavy chain comprising SEQ ID NO:233;

(ee) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:934 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:935;

(ff) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:936 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:937;

(gg) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:938 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:939;

(hh) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:940 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:941;

(ii) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:942 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:943; or

(jj) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 sequences from a VL domain of SEQ ID NO:944 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 from a VH domain of SEQ ID NO:945.

[0033] In some examples of the antibody:

(a) the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 and the VL domain comprises CDR-L1, CDR-L2, and CDR-L3, wherein CDR-H1 comprises SEQ ID NO:275, CDR-H2 comprises SEQ ID NO:276, CDR-H3 comprises SEQ ID NO:277, CDR-L1 comprises SEQ ID NO:272, CDR-L2 comprises SEQ ID NO:273, and CDR-L3 comprises SEQ ID NO:274;

(b) the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 and the VL domain comprises CDR-L1, CDR-L2, and CDR-L3, wherein CDR-H1 comprises SEQ ID NO:293, CDR-H2 comprises SEQ ID NO:294, CDR-H3 comprises SEQ ID NO:295, CDR-L1 comprises SEQ ID NO:290, CDR-L2 comprises SEQ ID NO:291, and CDR-L3 comprises SEQ ID NO:292;

(c) the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 and the VL domain comprises CDR-L1, CDR-L2, and CDR-L3, wherein CDR-H1 comprises SEQ ID NO:311,

CDR-H1 comprises SEQ ID NO:817, CDR-H2 comprises SEQ ID NO:818, and CDR-H3 comprises SEQ ID NO:819; or

(zz) the VL domain comprises CDR-L1, CDR-L2, and CDR-L3 and the VH domain comprises CDR-H1, CDR-H2, and CDR-H3, wherein CDR-L1 comprises SEQ ID NO:832, CDR-L2 comprises SEQ ID NO:833, and CDR-L3 comprises SEQ ID NO:834, wherein CDR-H1 comprises SEQ ID NO:835, CDR-H2 comprises SEQ ID NO:836, and CDR-H3 comprises SEQ ID NO:837.

[0034] In some examples of the antibody:

(a) the VH domain comprises the sequence of amino acids selected from the group consisting of SEQ ID NOs:249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 901, 903, 905, 907, 909, 911, 913, 915, 917, 919, 921, 923, 925, 927, 929, 931, 933, 935, 937, 939, 941, 943, and 945 and/or the VL domain comprises the sequence of amino acids selected from the group consisting of SEQ ID NOs: 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 900, 902, 904, 906, 908, 910, 912, 914, 916, 918, 920, 922, 924, 926, 928, 930, 932, 934, 936, 938, 940, 942, and 944;

(b) the VL domain comprises the sequence of SEQ ID NO:248 and/or the VH domain comprises the sequence of SEQ ID NO:249;

(c) the VL domain comprises the sequence of SEQ ID NO:250 and/or the VH domain comprises the sequence of SEQ ID NO:251;

(d) the VL domain comprises the sequence of SEQ ID NO:252 and/or the VH domain comprises the sequence of SEQ ID NO:253;

(e) the VL domain comprises the sequence of SEQ ID NO:254 and/or the VH domain comprises the sequence of SEQ ID NO:255;

(f) the VL domain comprises the sequence of SEQ ID NO:256 and/or the VH domain comprises the sequence of SEQ ID NO:257;

(g) the VL domain comprises the sequence of SEQ ID NO:258 and/or the VH domain comprises the sequence of SEQ ID NO:259;

(h) the VL domain comprises the sequence of SEQ ID NO:260 and/or the VH domain comprises the sequence of SEQ ID NO:261;

(i) the VL domain comprises the sequence of SEQ ID NO:262 and/or the VH domain comprises the sequence of SEQ ID NO:263;

(y) the VL domain comprises the sequence of SEQ ID NO:922 and/or the VH domain comprises the sequence of SEQ ID NO:923;

(z) the VL domain comprises the sequence of SEQ ID NO:924 and/or the VH domain comprises the sequence of SEQ ID NO:925;

(aa) the VL domain comprises the sequence of SEQ ID NO:926 and/or the VH domain comprises the sequence of SEQ ID NO:927;

(bb) the VL domain comprises the sequence of SEQ ID NO:928 and/or the VH domain comprises the sequence of SEQ ID NO:929;

(cc) the VL domain comprises the sequence of SEQ ID NO:930 and/or the VH domain comprises the sequence of SEQ ID NO:931;

(dd) the VL domain comprises the sequence of SEQ ID NO:932 and/or the VH domain comprises the sequence of SEQ ID NO:933;

(ee) the VL domain comprises the sequence of SEQ ID NO:934 and/or the VH domain comprises the sequence of SEQ ID NO:935;

(ff) the VL domain comprises the sequence of SEQ ID NO:936 and/or the VH domain comprises the sequence of SEQ ID NO:937;

(gg) the VL domain comprises the sequence of SEQ ID NO:938 and/or the VH domain comprises the sequence of SEQ ID NO:939;

(hh) the VL domain comprises the sequence of SEQ ID NO:940 and/or the VH domain comprises the sequence of SEQ ID NO:941;

(ii) the VL domain comprises the sequence of SEQ ID NO:942 and/or the VH domain comprises the sequence of SEQ ID NO:943; or

(jj) the VL domain comprises the sequence of SEQ ID NO:944 and/or the VH domain comprises the sequence of SEQ ID NO:945.

[0035] In some examples, the antibody is linked to one or more Q-tag peptides (Q) comprising at least one glutamine residue. In some examples, antibody comprises two antibody heavy chains and two antibody light chains, and wherein one Q-tag is attached to one or both heavy chain(s) of the antibody. In some examples, the Q-tag is fused to the C-terminus of the heavy chain of the antibody. In some examples, each Q-tag independently comprises a peptide sequence comprising between 5 and 15 amino acid residues. In some examples, the Q-tag is naturally occurring. In some examples, the peptide sequence of each Q-tag is

independently selected from the group consisting of SEQ ID NOs:39-55. In some examples, the Q-tag comprises the peptide sequence RPQGF (SEQ ID NO:47). In some examples, each Q-tag independently comprises RPQGF (SEQ ID NO:47), RPQGFPP (SEQ ID NO:48), or RPQGFGPP (SEQ ID NO:49). In some examples, 1 or 2 Q-tags is/are linked to the antibody. In some examples, the antibody further comprises an amino acid sequence selected from the group consisting of SEQ ID Nos:92-107, 111, 112, 178, and 494-497.

[0036] In some examples, the antibody is a Fab, F(ab')2, Fab'-SH, Fv, scFv, single domain, single heavy chain, or single light chain antibody or antibody fragment. In some examples, the antibody comprises an Fc region. In some examples, the Fc region is a human Fc region selected from the group consisting of an IgG1 Fc region, an IgG2 Fc region, and an IgG4 Fc region. In some examples, the Fc region is a human Fc region comprising one or more amino acid substitutions that reduce binding to C1q. In some examples, the Fc region is a human Fc region comprising one or more amino acid substitutions that increase binding to C1q. In some examples, the Fc region is a human Fc region exhibiting wild-type complement activation. In some examples, the Fc region is a human Fc region comprising one or more amino acid substitutions that increase complement activation. In some examples, the Fc region is a human Fc region comprising one or more amino acid substitutions and exhibiting wild-type binding to C1q. In some examples, the Fc region is a human Fc region comprising one or more amino acid substitutions that reduce effector function, as compared with a human Fc region that lacks the amino acid substitution(s). In some examples, the Fc region is: (a) a human IgG1 Fc region comprising L234A, L235A, and/or G237A substitutions, amino acid position numbering according to EU index; (b) a human IgG2 Fc region comprising A330S and/or P331S substitutions, amino acid position numbering according to EU index; or (c) a human IgG4 Fc region comprising S228P and/or L235E substitutions, amino acid position numbering according to EU index. In some examples, the Fc region further comprises an N297A substitution, amino acid position numbering according to EU index. In some examples, the Fc region is a wild-type human IgG1 Fc region. In some examples, the Fc region is a human IgG1 Fc region that has been engineered to improve antibody-dependent cell-mediated cytotoxicity (ADCC) activity. In some examples, at least one or two of the heavy chains of the antibody are non-fucosylated. In some examples, the antibody is produced in a cell line having a alpha1,6-fucosyltransferase (Fut8) knockout. In some examples, the antibody is produced in a cell line overexpressing β1,4-N-

acetylglycosminyltransferase III (GnT-III). In some examples, the cell line additionally overexpresses Golgi μ-mannosidase II (ManII). In some examples, the antibody comprises at least one amino acid substitution in the Fc region that improves ADCC activity. In some examples, the antibody comprises at least one amino acid substitution in the Fc region that improves ADCP activity. In some examples, the antibody comprises at least one amino acid substitution in the Fc region that improves CDC activity. In some examples, the Fc region comprises the substitution G236A, with numbering according to EU index. In some examples, the Fc region comprises the substitution G236A, with numbering according to EU index, and the Fc region is non-fucosylated.

[0037] In some examples of the antibody:

(a) the antibody comprises a light chain comprising a light chain sequence selected from the group consisting of SEQ ID NOs:236-247 and 1000-1022 and/or a heavy chain comprising a heavy chain sequence and a Q-tag, wherein the heavy chain comprises a sequence selected from the group consisting of SEQ ID NOs:224-235 and 1030-1065;

(b) the antibody comprises a light chain comprising a light chain sequence selected from the group consisting of SEQ ID NOs:236-247 and 1000-1022 and/or a heavy chain comprising a heavy chain sequence selected from the group consisting of SEQ ID NOs:1070-1117;

(c) the antibody comprises a light chain comprising SEQ ID NO:236 and/or a heavy chain comprising SEQ ID NO:224;

(d) the antibody comprises a light chain comprising SEQ ID NO:237 and/or a heavy chain comprising SEQ ID NO:225;

(e) the antibody comprises a light chain comprising SEQ ID NO:238 and/or a heavy chain comprising SEQ ID NO:226;

(f) the antibody comprises a light chain comprising SEQ ID NO:239 and/or a heavy chain comprising SEQ ID NO:227;

(g) the antibody comprises a light chain comprising SEQ ID NO:240 and/or a heavy chain comprising SEQ ID NO:228;

(h) the antibody comprises a light chain comprising SEQ ID NO:241 and/or a heavy chain comprising SEQ ID NO:229;

(i) the antibody comprises a light chain comprising SEQ ID NO:242 and/or a heavy chain comprising SEQ ID NO:230;

(gggg) the antibody comprises a light chain comprising SEQ ID NO:1022 and/or a heavy chain comprising SEQ ID NO:1104;

(hhhh) the antibody comprises a light chain comprising SEQ ID NO:236 and/or a heavy chain comprising SEQ ID NO:1105;

(iiii) the antibody comprises a light chain comprising SEQ ID NO:242 and/or a heavy chain comprising SEQ ID NO:1106;

(jjjj) the antibody comprises a light chain comprising SEQ ID NO:243 and/or a heavy chain comprising SEQ ID NO:1107;

(kkkk) the antibody comprises a light chain comprising SEQ ID NO:245 and/or a heavy chain comprising SEQ ID NO:1108;

(llll) the antibody comprises a light chain comprising SEQ ID NO:1007 and/or a heavy chain comprising SEQ ID NO:1109;

(mmmm) the antibody comprises a light chain comprising SEQ ID NO:1008 and/or a heavy chain comprising SEQ ID NO:1110;

(nnnn) the antibody comprises a light chain comprising SEQ ID NO:1012 and/or a heavy chain comprising SEQ ID NO:1111;

(oooo) the antibody comprises a light chain comprising SEQ ID NO:1017 and/or a heavy chain comprising SEQ ID NO:1112;

(pppp) the antibody comprises a light chain comprising SEQ ID NO:1018 and/or a heavy chain comprising SEQ ID NO:1113;

(qqqq) the antibody comprises a light chain comprising SEQ ID NO:1019 and/or a heavy chain comprising SEQ ID NO:1114;

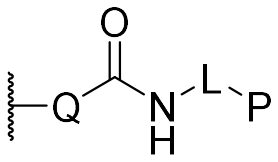
(rrrr) the antibody comprises a light chain comprising SEQ ID NO:1020 and/or a heavy chain comprising SEQ ID NO:1115;

(ssss) the antibody comprises a light chain comprising SEQ ID NO:1021 and/or a heavy chain comprising SEQ ID NO:1116; or

(tttt) the antibody comprises a light chain comprising SEQ ID NO:1022 and/or a heavy chain comprising SEQ ID NO:1117.

[0038] In some examples, the antibody is a bispecific or multispecific antibody that comprises at least a second VL domain and a second VH domain, wherein the second VL domain and second VH domain specifically bind a different target than human nectin-4.

[0039] In one example, provided herein is a method for preparing a conjugate that comprises (i) an antibody or antigen-binding fragment thereof (Ab) that specifically binds human nectin-4 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 the amino acid sequence RPQGF (SEQ ID NO:47), 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:

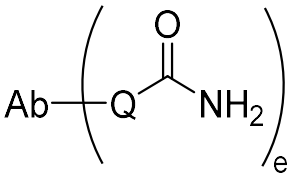
〰 indicates the point of attachment of each Q to the antibody or antigen-binding fragment thereof (Ab);

each Q independently comprises a Q-tag peptide sequence RPQGF (SEQ ID NO:47);

each L is independently a bond or a linker moiety connected to Q via an amide bond with the glutamine residue; and

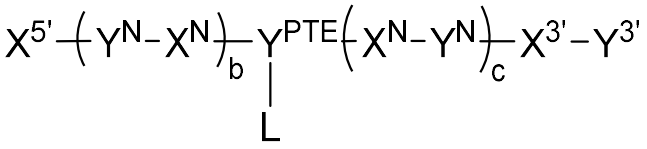
each P is independently an immunomodulating oligonucleotide;

comprising contacting a compound of formula (B)


(B),

wherein Ab and Q are as defined for formula (A) above, and e is an integer from 1 to 20, with one or more immunomodulating oligonucleotides P, wherein each P independently:

(i) has the following formula:


,

wherein

$X^{5'}$ is a 5' terminal nucleoside;

$X^{3'}$ is a 3' terminal nucleoside;

Y^{PTE} is an internucleoside phosphotriester;

$Y^{3'}$ is a terminal phosphotriester;

each X^N is independently a nucleoside;

each Y^N is independently an internucleoside linker;

b and c are each independently an integer from 1 to 25; with the proviso that the sum of b and c is at least 5; and

L is a linker moiety comprising a terminal amine; or

(ii) is an immunomodulating oligonucleotide of formula (C) or (D);

in the presence of a transglutaminase. In some examples, each immunomodulating oligonucleotide is independently an oligonucleotide of formula (C) or formula (D) is selected from the group consisting of the oligonucleotides of Table 4 and Table 6. In some examples, the antibody is according to any one of the antibodies described above. In some examples, the method further comprises separating the conjugate having a DAR of 1 from free oligonucleotide, unconjugated antibody, and conjugates having a DAR of 2.

[0040] In one example, provided herein is a conjugate comprising any one of the antibodies described above conjugated to an agent. In some examples, the agent is a label. In some examples, the agent is a cytotoxic agent. In some examples, the agent is a moiety that modulates the immune system. In some examples, the moiety is selected from the group consisting of an IDO/TDO inhibitor, AhR inhibitor, arginase inhibitor, A2aR inhibitor, TLR agonist, STING agonist, and Rig-1 agonist. In some examples, the moiety comprises a cytokine. In some examples, the cytokine is selected from the group consisting of IL2, IL7, IL10, IL15, or an IFN. In some examples, the moiety modulates the activity of a cytokine. In some examples, the moiety modulates the activity of IL2, IL7, IL10, IL15, or an interferon. In some examples, the moiety comprises a cancer vaccine.

[0040a] In one aspect, the present disclosure refers to a conjugate comprising the antibody disclosed herein conjugated to an agent, wherein the agent is a label, a cytotoxic agent, or a moiety that modulates the immune system.

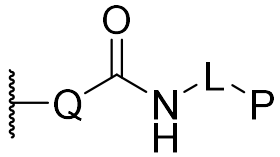
[0041] In some examples of the antibodies described above or the conjugates described above, the antibody or the antibody of the conjugate is linked to a modified oligonucleotide structure according to any one of the modified oligonucleotide structures of Tables 3-6.

[0042] In one example, provided herein is a pharmaceutical composition comprising any one of the antibodies described above or any one of the conjugates described above, and a pharmaceutically acceptable carrier.

[0042a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising the conjugate disclosed herein or the antibody disclosed herein, and a pharmaceutically acceptable carrier.

[0042b] In one aspect, the present disclosure refers to a pharmaceutical composition comprising the conjugate disclosed herein and a pharmaceutically acceptable carrier.

[0043] In one example, provided herein is a conjugate comprising (i) an anti-nectin-4 antibody or antigen binding fragment thereof and (ii) and one or more immunomodulating oligonucleotides (P), wherein the antibody or antigen-binding fragment is linked to one or more Q-tag peptides (Q), 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)

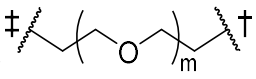


(A),

wherein:

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

each Q independently comprises a Q-tag peptide sequence RPQGFGPP (SEQ ID NO:49);

each L is independently a bond or a linker moiety 

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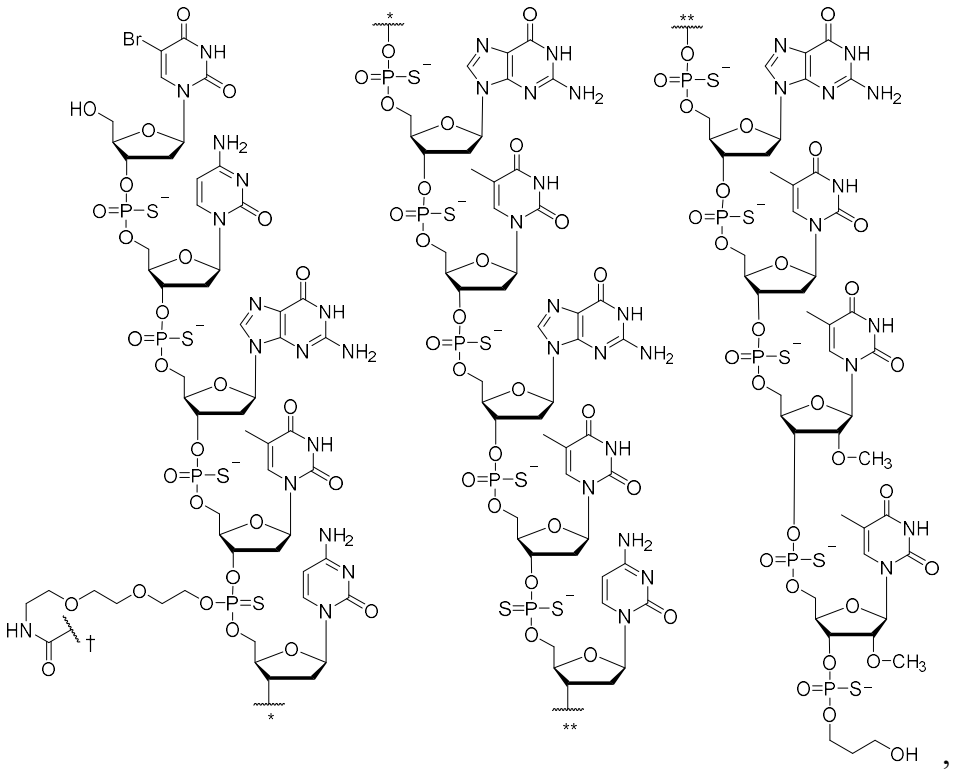
wherein m is an integer ranging from about 0 to about 50, and wherein 〰 † indicates the point of attachment to P, and 〰 ‡ indicates the point of attachment to the rest of the conjugate connected to Q via an amide bond with the glutamine residue; and

each P is independently an immunomodulating oligonucleotide having the structure



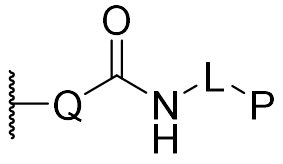
wherein ~~~ * and ~~~ ** indicate the points of attachment within the oligonucleotide, and wherein ~~~ † indicates the point of attachment to the linker L;

wherein the antibody comprises a heavy chain variable region (VH) domain and a light chain variable region (VL) domain, wherein the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 and the VL domain comprises CDR-L1, CDR-L2, and CDR-L3, wherein CDR-H1 comprises the sequence of SEQ ID NO:275, CDR-H2 comprises the sequence of SEQ ID NO:276, CDR-H3 comprises the sequence of SEQ ID NO:277, CDR-L1 comprises the sequence of SEQ ID NO:272, CDR-L2 comprises the sequence of SEQ ID NO:273, and CDR-L3 comprises the sequence of SEQ ID NO:274.

[0044] In one example, provided herein is a conjugate comprising (i) an anti-nectin-4 antibody or antigen binding fragment thereof and (ii) and one or more immunomodulating oligonucleotides (P), wherein the antibody or antigen-binding fragment is linked to one or more Q-tag peptides (Q), 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)

wherein the antibody comprises a heavy chain variable region (VH) domain and a light chain variable region (VL) domain, wherein the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 and the VL domain comprises CDR-L1, CDR-L2, and CDR-L3, wherein CDR-H1 comprises the sequence of SEQ ID NO:401, CDR-H2 comprises the sequence of SEQ ID NO:402, CDR-H3 comprises the sequence of SEQ ID NO:403, CDR-L1 comprises the sequence of SEQ ID NO:398, CDR-L2 comprises the sequence of SEQ ID NO:399, and CDR-L3 comprises the sequence of SEQ ID NO:400.

[0045] In one example, provided herein is a conjugate comprising (i) an anti-nectin-4 antibody or antigen binding fragment thereof and (ii) and one or more immunomodulating oligonucleotides (P), wherein the antibody or antigen-binding fragment is linked to one or more Q-tag peptides (Q), 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)

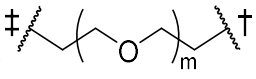


(A),

wherein:

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

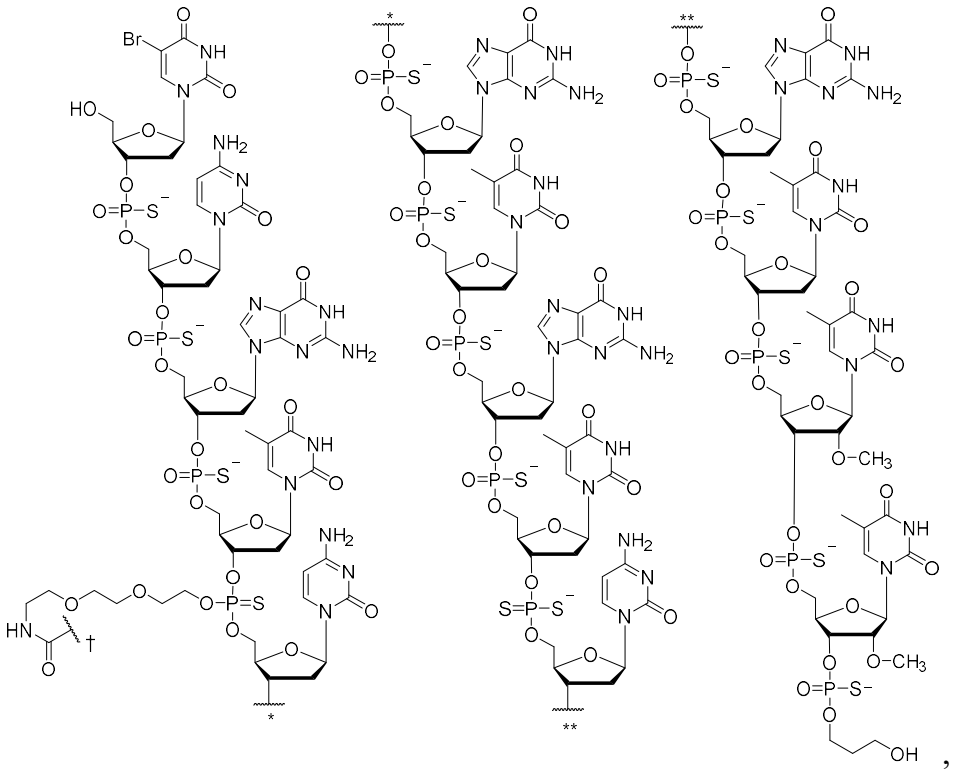
each Q independently comprises a Q-tag peptide sequence RPQGFGPP (SEQ ID NO:49);

each L is independently a bond or a linker moiety 

,

wherein m is an integer ranging from about 0 to about 50, and wherein 〰 † indicates the point of attachment to P, and 〰 ‡ indicates the point of attachment to the rest of the conjugate connected to Q via an amide bond with the glutamine residue; and

each P is independently an immunomodulating oligonucleotide having the structure



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

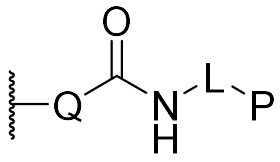
wherein the antibody comprises a heavy chain variable region (VH) domain and a light chain variable region (VL) domain, wherein the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 and the VL domain comprises CDR-L1, CDR-L2, and CDR-L3, wherein CDR-H1 comprises the sequence of SEQ ID NO:679, CDR-H2 comprises the sequence of SEQ ID NO:680, CDR-H3 comprises the sequence of SEQ ID NO:681, CDR-L1 comprises the sequence of SEQ ID NO:676, CDR-L2 comprises the sequence of SEQ ID NO:677, and CDR-L3 comprises the sequence of SEQ ID NO:678.

[0046] In one example, provided herein is a conjugate comprising (i) an anti-nectin-4 antibody or antigen binding fragment thereof and (ii) and one or more immunomodulating oligonucleotides (P), wherein the antibody or antigen-binding fragment is linked to one or more Q-tag peptides (Q) , 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)

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

wherein the antibody comprises a heavy chain variable region (VH) domain and a light chain variable region (VL) domain, wherein the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 and the VL domain comprises CDR-L1, CDR-L2, and CDR-L3, wherein CDR-H1 comprises the sequence of SEQ ID NO:275, CDR-H2 comprises the sequence of SEQ ID NO:276, CDR-H3 comprises the sequence of SEQ ID NO:277, CDR-L1 comprises the sequence of SEQ ID NO:272, CDR-L2 comprises the sequence of SEQ ID NO:273, and CDR-L3 comprises the sequence of SEQ ID NO:274.

[0047] In one example, provided herein is a conjugate comprising (i) an anti-nectin-4 antibody or antigen binding fragment thereof and (ii) and one or more immunomodulating oligonucleotides (P), wherein the antibody or antigen-binding fragment is linked to one or more Q-tag peptides (Q), 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)

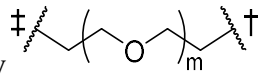


(A),

wherein:

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

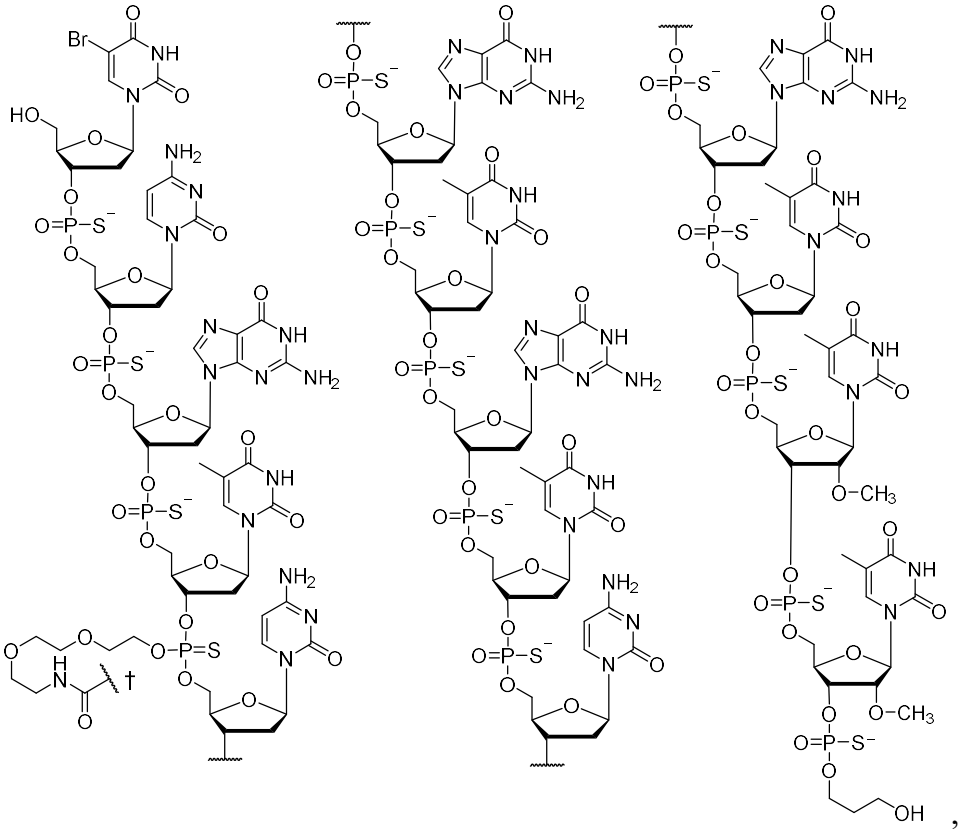
each Q independently comprises a Q-tag peptide sequence RPQGFGPP (SEQ ID NO:49);

each L is independently a bond or a linker moiety 

,

wherein m is an integer ranging from about 0 to about 50, and wherein ~~† indicates the point of attachment to P, and ~~‡ indicates the point of attachment to the rest of the conjugate connected to Q via an amide bond with the glutamine residue; and

each P is independently an immunomodulating oligonucleotide having the structure



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

wherein the antibody comprises a heavy chain variable region (VH) domain and a light chain variable region (VL) domain, wherein the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 and the VL domain comprises CDR-L1, CDR-L2, and CDR-L3, wherein CDR-H1 comprises the sequence of SEQ ID NO:401, CDR-H2 comprises the sequence of SEQ ID NO:402, CDR-H3 comprises the sequence of SEQ ID NO:403, CDR-L1 comprises the sequence of SEQ ID NO:398, CDR-L2 comprises the sequence of SEQ ID NO:399, and CDR-L3 comprises the sequence of SEQ ID NO:400.

[0048] In one example, provided herein is a conjugate comprising (i) an anti-nectin-4 antibody or antigen binding fragment thereof and (ii) and one or more immunomodulating oligonucleotides (P), wherein the antibody or antigen-binding fragment is linked to one or more Q-tag peptides (Q), 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)

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

wherein the antibody comprises a heavy chain variable region (VH) domain and a light chain variable region (VL) domain, wherein the VH domain comprises CDR-H1, CDR-H2, and CDR-H3 and the VL domain comprises CDR-L1, CDR-L2, and CDR-L3, wherein CDR-H1 comprises the sequence of SEQ ID NO:679, CDR-H2 comprises the sequence of SEQ ID NO:680, CDR-H3 comprises the sequence of SEQ ID NO:681, CDR-L1 comprises the sequence of SEQ ID NO:676, CDR-L2 comprises the sequence of SEQ ID NO:677, and CDR-L3 comprises the sequence of SEQ ID NO:678.

[0049] In some examples of the conjugate, the antibody of the conjugate comprises (a) a heavy chain variable region (VH) domain comprising SEQ ID NO: 935 and a light chain variable region (VL) domain comprising SEQ ID NO: 934; (b) a heavy chain comprising a heavy chain sequence and a Q-tag, wherein the heavy chain comprises SEQ ID NO: 1047, and a light chain comprising SEQ ID NO: 1017; (c) a heavy chain comprising a heavy chain sequence and a Q-tag, wherein the heavy chain comprises SEQ ID NO: 1060 and a light chain comprising SEQ ID NO: 1017; (d) a heavy chain comprising SEQ ID NO:1099 and a light chain comprising SEQ ID NO:1017; or (e) a heavy chain comprising SEQ ID NO:1112 and a light chain comprising SEQ ID NO:1017. In some examples of the conjugate, the antibody of the conjugate comprises (a) a heavy chain variable region (VH) domain comprising SEQ ID NO: 937 and a light chain variable region (VL) domain comprising SEQ ID NO: 936; (b) a heavy chain comprising a heavy chain sequence and a Q-tag, wherein the heavy chain comprises SEQ ID NO: 1048, and a light chain comprising SEQ ID NO:1018; (c) a heavy chain comprising a heavy chain sequence and a Q-tag, wherein the heavy chain comprises SEQ ID NO: 1061 and a light chain comprising SEQ ID NO:1018; (d) a heavy chain comprising SEQ ID NO:1100 and a light chain comprising SEQ ID NO:1018; or (e) a heavy chain comprising SEQ ID NO:1113 and a light chain comprising SEQ ID NO:1018. In some examples of the conjugate, the antibody of the conjugate comprises (a) a heavy chain variable region (VH) domain comprising SEQ ID NO: 939 and a light chain variable region (VL) domain comprising SEQ ID NO: 938; (b) a heavy chain comprising a heavy chain sequence and a Q-tag, wherein the heavy chain comprises SEQ ID NO: 1049, and a light chain comprising SEQ ID NO: 1019; (c) a heavy chain comprising a heavy chain sequence and a Q-tag, wherein the heavy chain comprises SEQ ID NO: 1062 and a light chain comprising SEQ ID NO:

1019; (d) a heavy chain comprising SEQ ID NO:1101 and a light chain comprising SEQ ID NO:1019; or (e) a heavy chain comprising SEQ ID NO:1114 and a light chain comprising SEQ ID NO:1019.

[0050] In some examples of the conjugate, m is from about 20 to about 30. In some examples of the conjugate, m is about 24 or m is 24. In some examples of the conjugate, L comprises a polyethylene glycol moiety. In some examples of the conjugate, the polyethylene glycol moiety contains about 24 ethylene glycol units or contains 24 ethylene glycol units. In some examples of the conjugate, each (P) and (L) in the conjugate independently comprise a modified oligonucleotide of SEQ ID NO:35. In some examples of the conjugate, each (P) and (L) in the conjugate independently comprise a modified oligonucleotide of SEQ ID NO:9. In some examples of the conjugate, the antibody of the conjugate comprises an Fc region. In some examples of the conjugate, the Fc region is a human IgG1 Fc region. In some examples of the conjugate, the Fc region is non-fucosylated. In some examples of the conjugate, the Fc region comprises the substitution G236A, with numbering according to EU index. In some examples of the conjugate, the Fc region comprises the substitution G236A, with numbering according to EU index, and the Fc region is non-fucosylated. In some examples of the conjugate, the conjugate has a DAR of 1 or 2.

[0051] In one example, provided herein is a pharmaceutical composition comprising any one of the conjugates described above and a pharmaceutically acceptable carrier.

[0052] In one example, provided herein is a method for treating cancer, comprising administering to an individual an effective amount of any one of the conjugates described above, any one of the antibodies described above, or any one of the pharmaceutical compositions described above. In some examples, the cancer tumor cells overexpress nectin-4 compared to the normal cells the cancer is derived from. In some examples, the cancer tumor cells express normal or moderate levels of nectin-4 compared to normal cells the cancer is derived from. In some examples, the cancer tumor cells express low levels of nectin-4 compared to the normal cells the cancer is derived from. In some examples, the method further comprises administering at least one additional cancer therapeutic. In some examples, at least one additional cancer therapeutic comprises a chemotherapeutic, an immunotherapeutic, a small molecule inhibitor (SMQ), a therapeutic antibody, or a cancer vaccine. In some examples, the

cancer is a solid cancer. In some examples, the cancer is a liquid tumor. In some examples, the cancer is esophageal cancer, stomach cancer, breast cancer, ovarian cancer, lung cancer, pancreatic adenocarcinoma, colon carcinoma, bladder cancer, cervical cancer, thyroid cancer, uterine cancer, rectal cancer, or gallbladder cancer. In some examples, administration of the conjugate or the pharmaceutical composition activates T cells, dendritic cells, monocytes, and/or NK cells.

[0052a] In one aspect, the present disclosure refers to use of the conjugate disclosed herein, the antibody disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating cancer in an individual.

[0053] In one example, provided herein is a method of activating immune cells in an individual, the method comprising administering to the individual an effective amount of any one of the conjugates described above or any one of the pharmaceutical compositions described above comprising a conjugate, wherein administration of the conjugate or the pharmaceutical composition activates T cells, dendritic cells, monocytes, and/or NK cells. In some examples, the individual has a cancer. In some examples, the method further comprises administering at least one additional cancer therapeutic. In some examples, the at least one additional cancer therapeutic comprises a chemotherapeutic, an immunotherapeutic, a small molecule inhibitor (SMQ), a therapeutic antibody, or a cancer vaccine. In some examples, the cancer is a solid cancer. In some examples, the cancer is a liquid tumor. In some examples, the cancer is esophageal cancer, stomach cancer, breast cancer, ovarian cancer, lung cancer, pancreatic adenocarcinoma, colon carcinoma, bladder cancer, cervical cancer, thyroid cancer, uterine cancer, rectal cancer, or gallbladder cancer. In some examples, the cancer is refractory to immune checkpoint inhibitor therapy. In some examples, the immune checkpoint inhibitor therapy comprises a PD-1 inhibitor or a PD-L1 inhibitor.

[0054] In one example, provided herein is a method of treating a tumor or tumor cells, comprising administering an effective amount of any one of the conjugates described above, any one of the antibodies described above, or any one of the pharmaceutical compositions described above. In some examples, treating the tumor or tumor cells comprises killing the tumor or tumor cells, inducing cytotoxicity of the tumor or tumor cells, reducing or inhibiting viability of the tumor or tumor cells, inhibiting growth of the tumor or tumor cells, inhibiting establishment of the tumor or tumor cells, inhibiting or reducing metastasis of the tumor or tumor cells, reducing the size of the tumor, or activiating an immune response against the tumor or tumor cells.

[0055] In one example, provided herein is a nucleic acid encoding the antibody of any one of the conjugate described above or any one of the antibodies described above.

[0055a] In one aspect, the present disclosure refers to a nucleic acid encoding the antibody of the conjugate disclosed herein, or the antibody disclosed herein.

[0056] In one example, provided herein is a vector comprising the nucleic acid described above. In some examples, the vector is an expression vector.

[0057] In one example, provided herein is a host cell comprising any one of the vectors described above. In some examples, the host cell is a mammalian cell, a yeast cell, or a bacterial cell. In some examples, the host cell is a CHO cell.

[0058] In one example, provided herein is a method of producing any one of the antibodies described above, the method comprising culturing any one of the host cells described above under conditions to express the antibody in the host cell. In some examples, the method further comprises isolating and/or purifying the antibody from the host cell.

BRIEF DESCRIPTION OF THE FIGURES

[0059] The present application can be understood by reference to the following description taken in conjunction with the accompanying figures.

[0060] **FIGS. 1A-1B** depict the activity of immunomodulating oligonucleotides alone in human PBMCs based upon observed increased expression of (a) HLADR (**FIG. 1A**) and (b) CD40 (**FIG. 1B**).

[0061] **FIGS. 2A-2C** show the effect of immunomodulating oligonucleotides and their antibody conjugates on increasing B cells numbers and activation. **FIG. 2A** depicts the observed effect on B cell numbers by the various immunomodulating polypeptides alone. **FIGS. 2B-2C** depict the observed activation of B cells (via detection of CD40 expression) produced by the immunomodulating oligonucleotides alone.

[0062] **FIG. 3** shows the percentage yields of transglutaminase-mediated conjugations and deconjugations with a polyethylene glycol linker (-NH-C(=O)-PEG_{23}-NH_2) and various Q-tags. Shown are SEQ ID Nos:39-47 and 50-52.

[0063] **FIGS. 4A** and **4B** show the percentage change of conjugation and decongjuation over time in transglutaminase conjugation of two Q-tag peptides (LSLSPGLLQGG, SEQ ID NO:39; and RPQGF, SEQ ID NO:47).

[0064] **FIG. 5** shows activity of indicated free CpG oligonucleotides on human PBMCs, as assayed by CD40 expression on $CD19^+$ B cells.

[0065] **FIG. 6** shows activity of indicated free CpG oligonucleotides on human PBMCs, as assayed by Ramos NFkb Reporter Assay.