RECOMBINANT SIALIDASES WITH REDUCED PROTEASE SENSITIVITY, SIALIDASE FUSION PROTEINS, AND METHODS OF USING THE SAME

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S. Provisional Patent Application serial number 63/047,989, filed July 3, 2020, and U.S. Provisional Patent Application serial number 63/134,411, filed January 6, 2021, the entire disclosure of each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The invention relates generally to recombinant sialidases (for example, recombinant sialidases having reduced protease sensitivity) and recombinant fusion proteins, and their use in the treatment of cancer.

BACKGROUND

[0003] A growing body of evidence supports roles for glycans, and in particular, sialoglycans, at various pathophysiological steps of tumor progression. Glycans regulate tumor proliferation, invasion, hematogenous metastasis and angiogenesis (Fuster *et al.* (2005) NAT. REV. CANCER 5(7): 526-42). The sialylation of cell surface glycoconjugates is frequently altered in cancers, resulting in the expression of sialylated tumor-associated carbohydrate antigens. The expression of sialylated glycans by tumor cells is often associated with increased aggressiveness and metastatic potential of a tumor (Julien S., Delannoy P. (2015) Sialic Acid and Cancer. In: Taniguchi N., Endo T., Hart G., Seeberger P., Wong CH. (eds) GLYCOSCIENCE: BIOLOGY AND MEDICINE, Springer, Tokyo. https://doi.org/10.1007/978-4-431-54841-6_193).

[0004] It has recently become apparent that Siglecs (sialic acid-binding immunoglobulin-like lectins), a family of sialic acid binding lectins, play a role in cancer immune suppression by binding to hypersialylated cancer cells and mediating the suppression of signals from activating NK cell receptors, thereby inhibiting NK cell-mediated killing of tumor cells (Jandus *et al.* (2014) J. CLIN. INVEST. 124: 1810-1820; Läubli *et al.* (2014) PROC. NATL. ACAD. SCI. USA 111: 14211-14216; Hudak *et al.* (2014) NAT. CHEM. BIOL. 10: 69-75). Likewise, enzymatic removal of sialic acids by treatment with sialidase can enhance NK cell-mediated killing of tumor cells (Jandus, *supra*; Hudak, *supra;* Xiao *et al.* (2016) PROC. NATL. ACAD. SCI. USA 113(37): 10304-9).

[0005] Cancer immunotherapy with immune checkpoint inhibitors, including antibodies blocking the PD-1/PD-L1 pathway, has improved the outcome of many cancer patients. However, despite advances that have been made to date, many patients do not respond to currently available immune checkpoint inhibitors. Accordingly, there is still a need for effective interventions that overcome the immune suppressive tumor microenvironment and for treating cancers associated with hypersialylated cancer cells.

SUMMARY

[0006] The disclosure is based, in part, upon the discovery that it is possible to produce recombinant mutant forms of sialidase enzymes, including, for example, sialidase enzymes that are less sensitive to protease degradation than a corresponding sialidase enzyme without the mutation or mutations that render the sialidase less sensitive to protease degradation. The sialidase enzymes can be used in fusion proteins and/or antibody conjugates containing such sialidase enzymes that have suitable substrate specificities and activities to be useful in removing sialic acid and/or sialic acid containing molecules from the surface of cells of interest (*e.g.*, cancer cells) and/or removing sialic acid and/or sialic acid containing molecules from the tumor microenvironment, and/or reducing the concentration of sialic acid and/or sialic acid containing molecules in the tumor microenvironment.

[0006a] In one aspect, the present disclosure refers to a recombinant mutant human Neu2 sialidase, wherein the sialidase comprises (i) a substitution of an alanine residue at a position corresponding to position 42 of wild-type human Neu2 (SEQ ID NO: 1) with an arginine residue (A42R), and (ii) an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 198.

[0007] Accordingly, in one example, the disclosure relates to a recombinant mutant sialidase enzyme, *e.g.*, a human mutant sialidase enzyme, wherein the sialidase comprises a mutation that increases resistance (decreases sensitivity) to cleavage by a protease. In certain examples, incubation of the recombinant mutant sialidase (*e.g.*, human sialidase) with the protease results in less than 50% (*e.g.*, less than 40%, less than 30%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5%) of the proteolytic cleavage of a corresponding wild-type sialidase (or modified wild-type sialidase lacking the mutations described herein) when incubated with the protease under the same conditions. In certain examples, the protease is trypsin.

[0008] In certain examples, the sialidase is a human sialidase that comprises a substitution of an alanine residue at a position corresponding to position 213 of wild-type human Neu2 (A213); a substitution of a leucine residue at a position corresponding to position 240 of wild-type human Neu2 (L240); a substitution of an arginine residue at a position corresponding to position 241 of wild-type human Neu2 (R241); a substitution of an alanine residue at a position corresponding to position 242 of wild-type human Neu2 (A242);

a substitution of an arginine residue at a position corresponding to position 243 of wild-type human Neu2 (R243); a substitution of a valine residue at a position corresponding to position 244 of wild-type human Neu2 (V244); a substitution of a serine residue at a position corresponding to position 258 of wild-type human Neu2 (S258); a substitution of a leucine residue at a position corresponding to position 260 of wild-type human Neu2 (L260); a substitution of a valine residue at a position corresponding to position 265 of wild-type human Neu2 (V265); or a combination of any of the foregoing substitutions.

[0009] In certain examples, in the sialidase, the alanine residue at a position corresponding to position 213 of wild-type human Neu2 is substituted by cysteine (A213C), asparagine (A213N), serine (A213S), or threonine (A213T); the leucine residue at a position corresponding to position 240 of wild-type human Neu2 (L240) is substituted by aspartic acid (L240D), asparagine (L240N), or tyrosine (L240Y); the arginine residue at a position corresponding to position 241 of wild-type human Neu2 (R241) is substituted by alanine (R241A), aspartic acid (R241D), leucine (R241L), glutamine (R241Q). or tyrosine (R241Y); the alanine residue at a position corresponding to position 242 of wild-type human Neu2 (A242) is substituted by cysteine (A242C), phenylalanine (A242F), glycine (A242G), histidine (A242H), isoleucine (A242I), lysine (A242K), leucine (A242L), methionine (A242M), asparagine (A242N), glutamine (A242Q), arginine (A242R), serine (A242S), valine (A242V), tryptophan (A242W), or tyrosine (A242Y); the arginine residue at a position corresponding to position 243 of wild-type human Neu2 (R243) is substituted by glutamic acid (R243E), histidine (R243H), asparagine (R243N), glutamine (A243Q), or lysine (A243K); the valine residue at a position corresponding to position 244 of wild-type human Neu2 (V244) is substituted by isoleucine (V244I), lysine (V244K), or proline (V244P); the serine residue at a position corresponding to position 258 of wild-type human Neu2 (S258) is substituted by cysteine (S258C); the leucine residue at a position corresponding to position 260 of wild-type human Neu2 (L260) is substituted by aspartic acid (L260D), phenylalanine (L260F), glutamine (L260Q), or threonine (L260T); the valine residue at a position corresponding to position 265 of wild-type human Neu2 (V265) is substituted by phenylalanine (V265F); or the sialidase comprises a combination of any of the foregoing substitutions.

[0010] In certain examples, the sialidase comprises a combination of substitutions as set forth in **TABLE 2**, hereinbelow.

[0011] In another example, the disclosure provides a recombinant mutant human sialidase enzyme, wherein the sialidase comprises: (a) a substitution of a proline residue at a position corresponding to position 5 of wild-type human Neu2 (P5); (b) a substitution of a lysine residue at a position corresponding to position 9 of wild-type human Neu2 (K9); (c) a substitution of an alanine residue at a position corresponding to position 42 of wild-type human Neu2 (A42); (d) a substitution of a lysine residue at a position corresponding to position 44 of wild-type human Neu2 (K44); (e) a substitution of a lysine residue at a position corresponding to position 45 of wild-type human Neu2 (K45); (f) a substitution of a leucine residue at a position corresponding to position 54 of wild-type human Neu2 (L54); (g) a substitution of a proline residue at a position corresponding to position 62 of wild-type human Neu2 (P62); (h) a substitution of a glutamine residue at a position corresponding to position 69 of wild-type human Neu2 (Q69); (i) a substitution of an arginine residue at a position corresponding to position 78 of wild-type human Neu2 (R78); (j) a substitution of an aspartic acid residue at a position corresponding to position 80 of wild-type human Neu2 (D80); (k) a substitution of an alanine residue at a position corresponding to position 93 of wild-type human Neu2 (A93); (l) a substitution of a glycine residue at a position corresponding to position 107 of wild-type human Neu2 (G107); (m) a substitution of a glutamine residue at a position corresponding to position 108 of wild-type human Neu2 (Q108); (n) a substitution of a glutamine residue at a position corresponding to position 112 of wild-type human Neu2 (Q112); (o) a substitution of a cysteine residue at a position corresponding to position 125 of wild-type human Neu2 (C125); (p) a substitution of a glutamine residue at a position corresponding to position 126 of wild-type human Neu2 (Q126); (q) a substitution of an alanine residue at a position corresponding to position 150 of wild-type human Neu2 (A150); (r) a substitution of a cysteine residue at a position corresponding to position 164 of wild-type human Neu2 (C164); (s) a substitution of an arginine residue at a position corresponding to position 170 of wild-type human Neu2 (R170); (t) a substitution of an alanine residue at a position corresponding to position 171 of wild-type human Neu2 (A171); (u) a substitution of a glutamine residue at a position corresponding to position 188 of wild-type human Neu2 (Q188); (v) a substitution of an arginine residue at a position corresponding to position 189 of wild-type human Neu2 (R189); (w) a substitution of an alanine residue at a position corresponding to position 213 of wild-type human Neu2 (A213); (x) a substitution of a leucine residue at a position corresponding to position 217 of wild-type human Neu2 (L217); (y) a substitution of a glutamic acid residue at a position corresponding to position 225 of wild-type human Neu2

(E225); (z) a substitution of a histidine residue at a position corresponding to position 239 of wild-type human Neu2 (H239); (aa) a substitution of a leucine residue at a position corresponding to position 240 of wild-type human Neu2 (L240); (bb) a substitution of an arginine residue at a position corresponding to position 241 of wild-type human Neu2 (R241); (cc) a substitution of an alanine residue at a position corresponding to position 242 of wild-type human Neu2 (A242); (dd) a substitution of a valine residue at a position corresponding to position 244 of wild-type human Neu2 (V244); (ee) a substitution of a threonine residue at a position corresponding to position 249 of wild-type human Neu2 (T249); (ff) a substitution of an aspartic acid residue at a position corresponding to position 251 of wild-type human Neu2 (D251); (gg) a substitution of a glutamic acid residue at a position corresponding to position 257 of wild-type human Neu2 (E257); (hh) a substitution of a serine residue at a position corresponding to position 258 of wild-type human Neu2 (S258); (ii) a substitution of a leucine residue at a position corresponding to position 260 of wild-type human Neu2 (L260); (jj) a substitution of a valine residue at a position corresponding to position 265 of wild-type human Neu2 (V265); (kk) a substitution of a glutamine residue at a position corresponding to position 270 of wild-type human Neu2 (Q270); (ll) a substitution of a tryptophan residue at a position corresponding to position 292 of wild-type human Neu2 (W292); (mm) a substitution of a serine residue at a position corresponding to position 301 of wild-type human Neu2 (S301); (nn) a substitution of a tryptophan residue at a position corresponding to position 302 of wild-type human Neu2 (W302); (oo) a substitution of a valine residue at a position corresponding to position 363 of wild-type human Neu2 (V363); or (pp) a substitution of a leucine residue at a position corresponding to position 365 of wild-type human Neu2 (L365); or a combination of any of the foregoing substitutions. For example, the sialidase may comprise a substitution of K9, A42, P62, A93, Q216, A242, Q270, S301, W302, V363, or L365, or a combination of any of the foregoing substitutions.

[0012] In certain examples, in the sialidase: (a) the proline residue at a position corresponding to position 5 of wild-type human Neu2 is substituted by histidine (P5H); (b) the lysine residue at a position corresponding to position 9 of wild-type human Neu2 is substituted by aspartic acid (K9D); (c) the alanine residue at a position corresponding to position 42 of wild-type human Neu2 is substituted by arginine (A42R) or aspartic acid (A42D); (d) the lysine residue at a position corresponding to position 44 of wild-type human Neu2 is substituted by arginine (K44R) or glutamic acid (K44E); (e) the lysine residue at a

position corresponding to position 45 of wild-type human Neu2 is substituted by alanine (K45A), arginine (K45R), or glutamic acid (K45E); (f) the leucine residue at a position corresponding to position 54 of wild-type human Neu2 is substituted by methionine (L54M); (g) the proline residue at a position corresponding to position 62 of wild-type human Neu2 is substituted by asparagine (P62N), aspartic acid (P62D), histidine (P62H), glutamic acid (P62E), glycine (P62G), serine (P62S), or threonine (P62T); (h) the glutamine residue at a position corresponding to position 69 of wild-type human Neu2 is substituted by histidine (Q69H); (i) the arginine residue at a position corresponding to position 78 of wild-type human Neu2 is substituted by lysine (R78K); (j) the aspartic acid residue at a position corresponding to position 80 of wild-type human Neu2 is substituted by proline (D80P); (k) the alanine residue at a position corresponding to position 93 of wild-type human Neu2 is substituted by glutamic acid (A93E) or lysine (A93K); (l) the glycine residue at a position corresponding to position 107 of wild-type human Neu2 is substituted by aspartic acid (G107D); (m) the glutamine residue at a position corresponding to position 108 of wild-type human Neu2 is substituted by histidine (Q108H); (n) the glutamine residue at a position corresponding to position 112 of wild-type human Neu2 is substituted by arginine (Q112R) or lysine (Q112K); (o) the cysteine residue at a position corresponding to position 125 of wild-type human Neu2 is substituted by leucine (C125L); (p) the glutamine residue at a position corresponding to position 126 of wild-type human Neu2 is substituted by leucine (Q126L), glutamic acid (Q126E), phenylalanine (Q126F), histidine (Q126H), isoleucine (Q126I), or tyrosine (Q126Y); (q) the alanine residue at a position corresponding to position 150 of wild-type human Neu2 is substituted by valine (A150V); (r) the cysteine residue at a position corresponding to position 164 of wild-type human Neu2 is substituted by glycine (C164G); (s) the arginine residue at a position corresponding to position 170 of wild-type human Neu2 is substituted by proline (R170P); (t) the alanine residue at a position corresponding to position 171 of wild-type human Neu2 is substituted by glycine (A171G); (u) the glutamine residue at a position corresponding to position 188 of wild-type human Neu2 is substituted by proline (Q188P); (v) the arginine residue at a position corresponding to position 189 of wild-type human Neu2 is substituted by proline (R189P); (w) the alanine residue at a position corresponding to position 213 of wild-type human Neu2 is substituted by cysteine (A213C), asparagine (A213N), serine (A213S), or threonine (A213T); (x) the leucine residue at a position corresponding to position 217 of wild-type human Neu2 is substituted by alanine (L217A) or valine (L217V); (y) the threonine residue at a position corresponding to position 249 of wild-type human Neu2 is substituted by alanine (T249A);

(z) the aspartic acid residue at a position corresponding to position 251 of wild-type human Neu2 is substituted by glycine (D251G); (aa) the glutamic acid residue at a position corresponding to position 225 of wild-type human Neu2 is substituted by proline (E225P); (bb) the histidine residue at a position corresponding to position 239 of wild-type human Neu2 is substituted by proline (H239P); (cc) the leucine residue at a position corresponding to position 240 of wild-type human Neu2 is substituted by aspartic acid (L240D), asparagine (L240N), or tyrosine (L240Y); (dd) the arginine residue at a position corresponding to position 241 of wild-type human Neu2 is substituted by alanine (R241A), aspartic acid (R241D), leucine (R241L), glutamine (R241Q). or tyrosine (R241Y); (ee) the alanine residue at a position corresponding to position 242 of wild-type human Neu2 is substituted by cysteine (A242C), phenylalanine (A242F), glycine (A242G), histidine (A242H), isoleucine (A242I), lysine (A242K), leucine (A242L), methionine (A242M), asparagine (A242N), glutamine (A242Q), arginine (A242R), serine (A242S), valine (A242V), tryptophan (A242W), or tyrosine (A242Y); (ff) the valine residue at a position corresponding to position 244 of wild-type human Neu2 is substituted by isoleucine (V244I), lysine (V244K), or proline (V244P); (gg) the glutamic acid residue at a position corresponding to position 257 of wild-type human Neu2 is substituted by proline (E257P); (hh) the serine residue at a position corresponding to position 258 is substituted by cysteine (S258C); (ii) the leucine residue at a position corresponding to position 260 of wild-type human Neu2 is substituted by aspartic acid (L260D), phenylalanine (L260F), glutamine (L260Q), or threonine (L260T); (jj) the valine residue at a position corresponding to position 265 of wild-type human Neu2 is substituted by phenylalanine (V265F); (kk) the glutamine residue at a position corresponding to position 270 of wild-type human Neu2 is substituted by alanine (Q270A), histidine (Q270H), phenylalanine (Q270F), proline (Q270P), serine (Q270S), or threonine (Q270T); (ll) the tryptophan residue at a position corresponding to position 292 of wild-type human Neu2 is substituted by arginine (W292R); (mm) the serine residue at a position corresponding to position 301 of wild-type human Neu2 is substituted by alanine (S301A), aspartic acid (S301D), glutamic acid (S301E), phenylalanine (S301F), histidine (S301H), lysine (S301K), leucine (S301L), methionine (S301M), asparagine (S301N), proline (S301P), glutamine (S301Q), arginine (S301R), threonine (S301T), valine (S301V), tryptophan (S301W), or tyrosine (S301Y)); (nn) the tryptophan residue at a position corresponding to position 302 of wild-type human Neu2 is substituted by alanine (W302A), aspartic acid (W302D), phenylalanine (W302F), glycine (W302G), histidine (W302H), isoleucine (W302I), lysine (W302K), leucine (W302L), methionine (W302M), asparagine (W302N), proline (W302P),

glutamine (W302Q), arginine (W302R), serine (W302S), threonine (W302T), valine (W302V), or tyrosine (W302Y); (oo) the valine residue at a position corresponding to position 363 of wild-type human Neu2 is substituted by arginine (V363R); or (pp) the leucine residue at a position corresponding to position 365 of wild-type human Neu2 is substituted by glutamine (L365Q), histidine (L365H), isoleucine (L365I), lysine (L365K) or serine (L365S); or the sialidase comprises a combination of any of the foregoing substitutions. For example, the sialidase may comprise a substitution selected from K9D, A42R, P62G, P62N, P62S, P62T, A93E, Q126Y, A242F, A242W, A242Y, Q270A, Q270T, S301A, S301R, W302K, W302R, V363R, and L365I, or a combination of any of the foregoing substitutions.

[0013] In certain examples of any of the foregoing sialidases, the sialidase further comprises: (a) a substitution or deletion of a methionine residue at a position corresponding to position 1 of wild-type human Neu2 (M1); (b) a substitution of a valine residue at a position corresponding to position 6 of wild-type human Neu2 (V6); (c) a substitution of an isoleucine residue at a position corresponding to position 187 of wild-type human Neu2 (I187); or (d) a substitution of a cysteine residue at a position corresponding to position 332 of wild-type human Neu2 (C332); or a combination of any of the foregoing substitutions.

[0014] In certain examples, in the sialidase: (a) the methionine residue at a position corresponding to position 1 of wild-type human Neu2 is deleted (ΔM1), is substituted by alanine (M1A), or is substituted by aspartic acid (M1D); (b) the valine residue at a position corresponding to position 6 of wild-type human Neu2 is substituted by tyrosine (V6Y); (c) the isoleucine residue at a position corresponding to position 187 of wild-type human Neu2 is substituted by lysine (I187K); or (d) the cysteine residue at a position corresponding to position 332 of wild-type human Neu2 is substituted by alanine (C332A); or the sialidase comprises a combination of any of the foregoing substitutions.

[0015] In certain examples of any of the foregoing sialidases, the sialidase comprises: (a) the M1D, V6Y, P62G, A93E, I187K, and C332A substitutions; (b) the M1D, V6Y, K9D, A93E, I187K, C332A, V363R, and L365I substitutions; (c) the M1D, V6Y, P62N, I187K, and C332A substitutions; (d) the M1D, V6Y, I187K, Q270A, S301R, W302K, and C332A substitutions; (e) the M1D, V6Y, P62S, I187K, Q270A, S301R, W302K, and C332A substitutions; (f) the M1D, V6Y, P62T, I187K, Q270A, S301R, W302K, and C332A substitutions; (g) the M1D, V6Y, P62N, I187K, Q270A, S301R, W302K, and C332A substitutions; (h) the M1D, V6Y, P62G, A93E, I187K, S301A, W302R, and C332A substitutions; (i) the M1D, V6Y, P62G, A93E, Q126Y, I187K, Q270T, and C332A

substitutions; (j) the M1D, V6Y, P62G, A93E, Q126Y, I187K, and C332A substitutions; (k) the M1D, V6Y, P62G, A93E, Q126Y, I187K, A242F, Q270T, and C332A substitutions; or (l) the M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, A242F, Q270T, and C332A substitutions.

[0016] In certain examples of any of the foregoing sialidases, the sialidase has a different substrate specificity than the corresponding wild-type sialidase. For example, in certain examples the sialidase can cleave α2,3, α2,6, and/or α2,8 linkages. In certain examples the sialidase can cleave α2,3 and α2,8 linkages.

[0017] In certain examples of any of the foregoing sialidases, the sialidase comprises any one of SEQ ID NOs: 48-54, 149, 154, 159, 191, or 198, or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 48-54, 149, 154, 159, 191, or 198.

[0018] In addition, the disclosure provides a recombinant mutant human sialidase comprising a mutation or combination of mutations set forth in any one of **TABLES 1, 2, 7-9, 11-13, 15-30**, **34**, or **35**, hereinbelow. In certain examples, the sialidase further comprises a mutation or combination of mutations set forth in any one of **TABLES 3-6**, hereinbelow.

[0019] In another aspect, the present disclosure provides a fusion protein comprising: (a) the recombinant enzyme as described herein; and (b) an immunoglobulin Fc domain and/or an immunoglobulin antigen-binding domain; wherein the enzyme and the immunoglobulin Fc domain and/or the immunoglobulin antigen-binding domain are linked by a peptide bond or an amino acid linker. In addition, the disclosure provides a fusion protein comprising (or consisting essentially of): (a) a recombinant mutant human sialidase disclosed herein; and (b) an immunoglobulin Fc domain and/or an immunoglobulin antigen-binding domain; wherein the sialidase and the Fc domain and/or the antigen-binding domain are linked by a peptide bond or an amino acid linker. In certain examples, the fusion protein further comprises a linker, for example, an amino acid linker, connecting the sialidase enzyme and the Fc domain and/or the antigen-binding domain. In certain examples, the immunoglobulin antigen-binding domain is associated (for example, covalently or non-covalently associated) with a second immunoglobulin antigen-binding domain to produce an antigen-binding site.

[0020] In certain examples, the immunoglobulin Fc domain is derived from a human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM Fc domain, *e.g.,* the immunoglobulin Fc

domain is derived from a human IgG1, IgG2, IgG3, or IgG4 Fc domain, *e.g.,* the immunoglobulin Fc domain is derived from a human IgG1 Fc domain.

[0021] In certain examples, the immunoglobulin antigen-binding domain is derived from an antibody selected from trastuzumab, daratumumab, girentuximab, ofatumumab, avelumab and rituximab.

[0022] In certain examples, the fusion protein comprises any one of SEQ ID NOs: 203-210, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, or 242, or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 203-210, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, or 242.

[0023] In addition, in another aspect the disclosure provides an antibody conjugate comprising any of the foregoing fusion proteins. In certain examples, the antibody conjugate comprises a single sialidase. In other examples, the antibody conjugate comprises two sialidases, which can be the same or different. In certain examples the antibody conjugate comprises two identical sialidases. In certain examples, the antibody conjugate comprises a single antigen-binding site. In other examples, the antibody conjugate comprises two antigen-binding sites, which can be the same or different. In certain examples, the antibody conjugate comprises two identical antigen-binding sites.

[0024] In certain examples, the antibody conjugate has a molecular weight from about 135 kDa to about 165 kDa, or the antibody conjugate has a molecular weight from about 215 kDa to about 245 kDa.

[0025] In certain examples, the antibody conjugate comprises: (a) a first polypeptide comprising an immunoglobulin light chain; (b) a second polypeptide comprising an immunoglobulin heavy chain; and (c) a third polypeptide comprising an immunoglobulin Fc domain and a sialidase; wherein the first and second polypeptides are covalently linked together and the second and third polypeptides are covalently linked together, and wherein the first polypeptide and the second polypeptide together define an antigen-binding site. The third polypeptide may, for example, comprise the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation.

[0026] In certain examples, the antibody conjugate comprises: (a) a first polypeptide comprising a first immunoglobulin light chain; (b) a second polypeptide comprising a first immunoglobulin heavy chain and a first sialidase; (c) a third polypeptide comprising a second immunoglobulin heavy chain and a second sialidase; and (d) a fourth polypeptide comprising a second immunoglobulin light chain; wherein the first and second polypeptides are covalently linked together, the third and fourth polypeptides are covalently linked together, and the second and third polypeptides are covalently linked together, and wherein the first polypeptide and the second polypeptide together define a first antigen-binding site, and the

third polypeptide and the fourth polypeptide together define a second antigen-binding site. The second and third polypeptides may, for example, comprise the first and second immunoglobulin heavy chain and the first and second sialidase, respectively, in an N- to C-terminal orientation.

[0027] In certain examples, the antibody conjugate comprises: (a) a first polypeptide comprising a first sialidase, a first immunoglobulin Fc domain, and a first single chain variable fragment (scFv); and (b) a second polypeptide comprising a second sialidase, a second immunoglobulin Fc domain, and an optional second single chain variable fragment (scFv); wherein the first and second polypeptides are covalently linked together, and wherein the first scFv defines a first antigen-binding site, and the second scFv, when present, defines a second antigen-binding site. The first polypeptide may, for example comprise the first sialidase, the first immunoglobulin Fc domain, and the first scFv in an N- to C-terminal orientation. The second polypeptide may, for example, comprise the second sialidase, the second immunoglobulin Fc domain, and the optional second scFv in an N- to C-terminal orientation.

[0028] In certain examples, the antibody conjugate comprises: (a) a first polypeptide comprising an immunoglobulin light chain; (b) a second polypeptide comprising an immunoglobulin heavy chain and a single chain variable fragment (scFv); and (c) a third polypeptide comprising an immunoglobulin Fc domain and a sialidase, wherein the first and second polypeptides are covalently linked together and the second and third polypeptides are covalently linked together, and wherein the immunoglobulin light chain and immunoglobulin heavy chain together define a first antigen-binding site and the scFv defines a second antigen-binding site. The second polypeptide may, for example comprise the immunoglobulin heavy chain and the scFv in an N- to C-terminal orientation. The third polypeptide may, for example, comprise the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation.

[0029] In another aspect, the present disclcosure provides an isolated nucleic acid comprising a nucleotide sequence encoding the recombinant enzyme as described herein, the fusion protein as described herein, or at least a portion of the antibody conjugate as described herein. In another example, the disclosure provides an isolated nucleic acid comprising a nucleotide sequence encoding any of the foregoing recombinant mutant human sialidases, any of the foregoing fusion proteins, or at least a portion of any of the foregoing antibody conjugates. In another aspect, the disclosure provides an expression vector comprising any of the

foregoing nucleic acids. In another aspect, the disclosure provides a host cell comprising any of the foregoing expression vectors.

[0030] In a further aspect, the present disclosure provides a pharmaceutical composition comprising the recombinant enzyme as described herein, the fusion protein as described herein, or the antibody conjugate of as described herein. In another example, the disclosure provides a pharmaceutical composition comprising any of the foregoing recombinant mutant human sialidases, any of the foregoing fusion proteins, or any of the foregoing antibody conjugates.

[0031] In a further aspect, the present disclosure provides a use of the recombinant enzyme as described herein, the fusion protein as described herein, or at least a portion of the antibody conjugate as described herein, or the pharmaceutical composition as described herein in the preparation of a medicament for the treatment of cancer in a subject. In another example, the disclosure provides a method of treating cancer in a subject in need thereof. The method comprises administering to the subject an effective amount of any of the foregoing sialidases, any of the foregoing fusion proteins, any of the foregoing antibody conjugates, or any of the foregoing pharmaceutical compositions. In certain examples, the cancer is an epithelial cancer. In certain examples, the cancer is a solid tumor, soft tissue tumor, hematopoietic tumor or metastatic lesion. In certain examples, the solid tumor is a sarcoma, adenocarcinoma, or carcinoma. In certain examples, the solid tumor is a head and neck (*e.g.,* pharynx), thyroid, lung (*e.g.,* small cell or non-small cell lung carcinoma (NSCLC)), breast, lymphoid, gastrointestinal (*e.g.*, oral, esophageal, stomach, liver, pancreas, small intestine, colon and rectum, anal canal), genital or genitourinary tract (*e.g.*, renal, urothelial, bladder, ovarian, uterine, cervical, endometrial, prostate, testicular), CNS (*e.g.,* neural or glial cell, *e.g.*, neuroblastoma or glioma), or skin (*e.g.,* melanoma) tumor. In certain examples, the hematopoietic tumor is a leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), *e.g.*, transformed CLL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, hairy cell leukemia, myelodyplastic syndrome (MDS), lymphoma, Hodgkin's disease, malignant lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, or Richter's Syndrome (Richter's Transformation). In certain examples, the cancer is selected from an endometrial cancer, ovarian cancer, cervical cancer, vulvar cancer, uterine cancer, fallopian tube cancer, breast cancer, prostate cancer, lung cancer, pancreatic cancer, urinary cancer, bladder cancer, head and neck cancer, oral cancer and liver cancer.

[0032] In another example, the disclosure provides a method of increasing expression of HLA-DR, CD86, CD83, IFNγ, IL-1b, IL-6, TNFα, IL-17A, IL-2, or IL-6 in a cell, tissue, or subject. The method comprises contacting the cell, tissue, or subject with an effective amount of any of the foregoing sialidases, any of the foregoing fusion proteins, any of the foregoing antibody conjugates, or any of the foregoing pharmaceutical compositions. In certain examples, the cell is selected from a dendritic cell and a peripheral blood mononuclear cell (PBMC).

[0033] These and other examples and features of the disclosure are described in the following detailed description and claims.

DESCRIPTION OF THE DRAWINGS

[0034] The invention can be more completely understood with reference to the following drawings.

[0035] FIGURE 1 depicts an SDS-PAGE gel showing recombinant human Neu1, Neu2, Neu3, and *Salmonella typhimurium* (St-sialidase) under non-reducing and reducing conditions. Monomer and dimer species are indicated.

[0036] FIGURE 2 is a bar graph showing the enzymatic activity of recombinant human Neu1, Neu2, and Neu3.

[0037] FIGURE 3 is a line graph showing enzymatic activity as a function of substrate concentration for recombinant human Neu2 and Neu3 at the indicated pH.

[0038] FIGURE 4 depicts a schematic representation of an exemplary sialic acid biotinylated probe that can be used in phage display or yeast display screening for Neu2 variants.

[0039] FIGURE 5 depicts an exemplary protocol that facilitates phage display screening of Neu2 variants.

[0040] FIGURE 6 depicts an exemplary protocol that facilitates yeast display screening of Neu2 variants.

[0041] FIGURE 7A depicts an SDS-PAGE gel showing recombinant Neu2-Fc (wildtype) and Neu2-M106-Fc under non-reducing and reducing conditions. **FIGURE 7B** is an SEC-HPLC trace of Neu2-Fc (wildtype) and Neu2-M106-Fc. The monomer species has a retention time of 21 minutes.

[0042] FIGURE 8 is a line graph depicting the enzymatic activity of Neu2 variant M106.

[0043] FIGURES 9A-9I depict schematic representations of certain antibody conjugate constructs containing a sialidase enzyme, *e.g.*, a human sialidase enzyme, and an antigen binding site. For each antibody conjugate construct that contains more than one (*e.g.,* two) sialidase, each sialidase may be the same or different. For each antibody conjugate construct that contains more than one (*e.g.,* two) antigen binding site, each antigen binding site may be the same or different. For each antibody conjugate construct that contains an Fc domain, it is

understood that the Fc domain can be a wild type Fc domain or can be an engineered Fc domain. For example, the Fc domain may be engineered to contain either a "knob" mutation, *e.g.,* T366Y, or a "hole" mutation, *e.g.,* Y407T, or both, to promote heterodimerization, or the Fc domain may be engineered to contain one or more modifications, *e.g.*, point mutations, to provide any other modified Fc domain functionality.

[0044] FIGURE 10 depicts schematic representations of certain antibody conjugate constructs containing a sialidase enzyme, *e.g.*, a human sialidase enzyme, and an antigen binding site. For each antibody conjugate construct that contains more than one (*e.g.,* two) antigen binding site, each antigen binding site may be the same or different. For each antibody conjugate construct that contains an Fc domain, it is understood that the Fc domain can be a wild type Fc domain or can be an engineered Fc domain. For example, the Fc domain may be engineered to contain either a "knob" mutation, *e.g.,* T366Y, or a "hole" mutation, *e.g.,* Y407T, or both, to promote heterodimerization, or the Fc domain may be engineered to contain one or more modifications, *e.g.*, point mutations, to provide any other modified Fc domain functionality.

[0045] FIGURES 11A-11E are schematic representations of exemplary fusion protein conjugates referred to as a Raptor antibody sialidase conjugate (**FIGURE 11A**), a Janus antibody sialidase conjugate (**FIGURE 11B**), a Lobster antibody sialidase conjugate (**FIGURE 11C**), a Bunk antibody sialidase conjugate (**FIGURE 11D**), and a Lobster-Fab antibody sialidase conjugate (**FIGURE 11E**).

[0046] FIGURE 12 depicts an SDS-PAGE gel showing purified recombinant human Janus Trastuzumab under non-reducing and reducing conditions.

[0047] FIGURE 13 depicts an SEC-HPLC trace of purified Janus Trastuzumab, showing approximately 90% monomer purity.

[0048] FIGURE 14 depicts the enzyme activity of Janus Trastuzumab assayed using 4-MU-Neu5Ac as a substrate.

[0049] FIGURE 15 depicts binding to HER2 antigen as determined by ForteBio Octet for Janus Trastuzumab (top), and trastuzumab (bottom). Equilibrium dissociation constants (KD) are indicated.

[0050] FIGURES 16A-D depict the testing of various configurations of antibody sialidase conjugates in a mouse syngeneic tumor model utilizing EMT6 mouse breast cancer cells engineered to express human HER2. Mice are treated via intraperitoneal injection of 10

mg/kg of each test article on the days marked with black triangles and tumor volume (mm^3) recorded. Each line represents an individual mouse. Mice are treated with either trastuzumab (**FIGURE 16A**), Raptor (**FIGURE 16B**), Janus (**FIGURE 16C**) or Lobster (**FIGURE 16D**).

[0051] FIGURES 17A-D depict the testing of the Janus antibody sialidase conjugate in a mouse syngeneic tumor model utilizing EMT6 mouse breast cancer cells engineered to express human HER2. Mice were treated via intraperitoneal injection of 10 mg/kg of Janus on the days marked with black triangles and tumor volume (mm^3) recorded. Mice were also treated on the same days as Janus with either anti-mouse NK1.1 (10 mg/kg) to deplete natural killer cells (**FIGURE 17A**), liposomal clodronate (0.5 mg/ mouse, three times a week for two weeks) to deplete macrophages (**FIGURE 17B**), or anti-mouse CD8α (10 mg/kg) to deplete CD8+ T cells (**FIGURE 17C**). Each line represents an individual mouse. **FIGURE 17D** depicts the mean tumor volume with error bars of the indicated treatment groups from Example 5.

[0052] FIGURES 18A-B depict the testing of the Janus antibody sialidase conjugate in a mouse syngeneic orthotopic tumor model utilizing a second source of EMT6 mouse breast cancer cells engineered to express human HER2. Mice are treated via intraperitoneal injection of 10 mg/kg of each test article on the days marked with black triangles and tumor volume (mm^3) recorded. Each line represents an individual mouse. Mice are treated (▼) with either vehicle, trastuzumab, Janus or Janus Loss of Function (**FIGURE 18A**). **FIGURE 18B** depicts the rechallenge experiment of either the three mice treated with Janus from **FIGURE 18A** with complete regressions of the original EMT6-HER2 tumors (cured mice) or naïve mice. Cured mice were inoculated with either EMT6-HER2 cells or parental EMT6 cells on the left and right lower flank region. Naïve mice were inoculated with EMT6-HER2 cells.

[0053] FIGURES 19A-B depict the testing of the Janus antibody sialidase conjugate in a mouse syngeneic orthotopic tumor model in combination with anti-mouse PD1. Mice are treated via intraperitoneal injection of 10 mg/kg of either anti-mouse PD1 alone (**FIGURE 19A**) or Janus and anti-mouse PD1 (10 mg/kg of each, **FIGURE 19B**) on the days marked with black triangles (▼) and tumor volume (mm^3) recorded. Each line represents an individual mouse.

[0054] FIGURE 20 depicts the testing of various test articles in a mouse syngeneic tumor model injected with a B16 melanoma cell line expressing human HER2. Mice are treated via

intraperitoneal injection of 10 mg/kg of either Janus, trastuzumab or a combination of anti-mouse PD1 and anti-mouse CTLA4 (10 mg/kg of each) on the days marked with black triangles (▼) and tumor volume (mm^3) recorded. Each line represents an individual mouse.

[0055] FIGURE 21 depicts the testing of Janus Trastuzumab in a mouse syngeneic tumor model utilizing EMT6 mouse breast cancer cells engineered to express human HER2. Each line represents an individual mouse. Tick marks indicate dosing frequency (total of 5 doses, biweekly). Mice are treated with either Janus Trastuzumab or isotype control.

[0056] FIGURE 22A depicts an SDS-PAGE gel showing Neu2-M173-Fc under non-reducing and reducing conditions. **FIGURE 22B** is an SEC-HPLC trace of Neu2-M173-Fc. The monomer species has a retention time of 6.367 minutes. The monomer species has a purity of approximately 90% after purification by Protein A and CHT chromatography.

[0057] FIGURE 23 depicts the enzyme activity of Neu2-M173-Fc, using 4-MU-Neu5Ac as the substrate, and fixing enzyme concentration to 2 µg/well.

[0058] FIGURE 24A depicts an SDS-PAGE gel showing Neu2-M106 under non-reducing (NR) and reducing (R) conditions. **FIGURE 24B** depicts a schematic representation of the Neu2 structure with the position of the R243 cleavage site indicated.

[0059] FIGURE 25 depicts a reducing SDS-PAGE gel showing Neu2-M106 produced by a large or small scale expression with (+) or without (-) trypsin treatment.

[0060] FIGURE 26 depicts an SDS-PAGE gel showing Neu2-M106 following incubation with trypsin and one of the protease inhibitors iron citrate (Fe Cit), aprotinin, AEBSF, leupeptin, or E-64 at the indicated concentrations.

[0061] FIGURE 27A is a table depicting a sequence alignment of different sialidase sequences, showing conservation of the P1 arginine, which is a protease cleavage site. **FIGURE 27B** is a chart showing different mutations and combinations of mutations surrounding the trypsin cleavage site in Neu2.

[0062] FIGURE 28A depicts a reducing SDS-PAGE analysis of Neu2 variants with the indicated mutation at position A242 with or without trypsin treatment. Trypsin digestion was for 5 minutes at 4 °C using a 5,000% dilution of trypsin. The digestion was quenched by addition of SDS, and 2 µg of protein was loaded on the gel. **FIGURE 28B** depicts the enzymatic activity of Neu2 variants with the indicated mutation at position A242. **FIGURE 28C** is an SEC-HPLC trace of Neu2 variants with the indicated mutation at position A242.

Neu2-M106 (the mutational background in which the mutations at position A242 were tested) is shown as a control.

[0063] FIGURE 29 depicts a reducing SDS-PAGE analysis of the indicated Neu2 variants with or without trypsin treatment. Neu2-M106 is shown as a control. For example, Neu2-M255 was shown to have a greater than 10 fold improved trypsin resistance relative to Neu2-M106.

[0064] FIGURE 30A depicts an SDS-PAGE gel showing recombinant Neu2-M259-Fc under non-reducing and reducing conditions. **FIGURE 30B** is an SEC-HPLC trace of Neu2-M259-Fc.

[0065] FIGURE 31A is a line graph showing enzymatic activity of the indicated Neu2-Fc variants as a function of substrate (4-MU-Neu5Ac) concentration. **FIGURE 31B** is a line graph showing enzymatic activity of the indicated Neu2-Fc variants as a function of enzyme concentration.

[0066] FIGURE 32 is a line graph depicting thermal stability of the indicated Neu2-Fc variants.

[0067] FIGURE 33 depicts testing of a Neu2-Fc fusion protein in a mouse syngeneic subcutaneous tumor model. Mean tumor volumes over 21 days for the indicated treatments are indicated in **FIGURE 33A**. Triangles indicate dosing. Individual tumor volumes on day 21 are depicted in **FIGURE 33B**.

[0068] FIGURE 34 is a bar graph depicting enzymatic activity of the indicated Neu2-Fc variants following incubation at 37 °C for the indicated length of time.

[0069] FIGURE 35 is an SEC-HPLC trace of Janus Trastuzumab 2.

[0070] FIGURE 36 depicts binding to HER2 antigen as determined by ForteBio Octet for Janus Trastuzumab 2.

[0071] FIGURE 37 depicts the testing of Janus Trastuzumab 2 in a mouse syngeneic tumor model utilizing EMT6 mouse breast cancer cells engineered to express human HER2, where tumor volume was measured after treatment with an isotype control (**FIGURE 37A**), 1 mg/kg Trastuzumab **(FIGURE 37B)**, 10 mg/kg Trastuzumab (**FIGURE 37C**), 1 mg/kg Janus Trastuzumab 2 (**FIGURE 37D**), or 10 mg/kg Janus Trastuzumab 2 (**FIGURE 37E**), where each line represents an individual mouse, and in **FIGURE 37F**, each line represents the mean

tumor volume for the indicated treatment group. Triangles indicate dosing frequency. In **FIGURES 37A-E**, Complete Responses (CR) and Partial Responses (PR) are indicated.

[0072] Various features and aspects of the invention are discussed in more detail below.

DETAILED DESCRIPTION

[0073] The invention relates to a recombinant sialidase (*e.g.*, a recombinant human sialidase) that comprises at least one mutation relative to a wild-type sialidase, *e.g.*, a substitution, deletion, or addition (insertion) of at least one amino acid. The mutation may, for example, enhance resistance (decrease sensitivity) to protease (*e.g.*, trypsin) degradation. Alternatively or in addition, the sialidase may include a mutation, or a combination of mutations, that can improve the expression, activity or both the expression and activity of the sialidase.

[0074] The invention further provides fusion proteins and/or antibody conjugates comprising a mutant sialidase enzyme and an antibody or portion thereof, *e.g.*, an immunoglobulin Fc domain and/or an antigen-binding domain. The sialidase enzyme portion of the fusion protein and/or antibody conjugate comprises at least one mutation relative to a wild-type sialidase (for example, a mutation that increases resistance to protease (*e.g.*, trypsin) degradation). The sialidase can also include one or more of the other mutations described herein that improve expression and/or activity of the sialidase.

[0075] The invention further relates to pharmaceutical compositions and methods of using fusion proteins and/or antibody conjugates to treat cancer, *e.g.*, a solid tumor, soft tissue tumor, hematopoietic tumor, metastatic lesion, or an epithelial cell cancer.

I. Recombinant Human Sialidases

[0076] As used herein, the term "sialidase" refers to any enzyme, or a functional fragment thereof, that cleaves a terminal sialic acid residue from a substrate, for example, a glycoprotein or a glycolipid. The term sialidase includes variants having one or more amino acid substitutions, deletions, or insertions relative to a wild-type sialidase sequence, and/or fusion proteins or conjugates including a sialidase. Sialidases are also called neuraminidases, and, unless indicated otherwise, the two terms are used interchangeably herein. As used herein, the term "functional fragment" of a sialidase refers to fragment of a full-length sialidase that retains, for example, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the enzymatic activity of the corresponding full-length, naturally occurring sialidase. Sialidase enzymatic activity may be assayed by any method known in the art, including, for example,

by measuring the release of sialic acid from the fluorogenic substrate 4-methylumbelliferyl-N-acetylneuraminic acid (4MU-NeuAc). In certain embodiments, the functional fragment comprises at least 100, 150, 200, 250, 300, 310, 320, 330, 340, 350, 360, or 370 consecutive amino acids present in a full-length, naturally occurring sialidase.

[0077] Four sialidases have been found in the human genome and are referred to as Neu1, Neu2, Neu3 and Neu4.

[0078] Human Neu1 is a lysosomal neuraminidase enzyme which functions in a complex with beta-galactosidase and cathepsin A. The amino acid sequence of human Neu1 is depicted in SEQ ID NO: 7, and a nucleotide sequence encoding human Neu1 is depicted in SEQ ID NO: 23.

[0079] Human Neu2 is a cytosolic sialidase enzyme. The amino acid sequence of human Neu2 is depicted in SEQ ID NO: 1, and a nucleotide sequence encoding human Neu2 is depicted in SEQ ID NO: 24. Unless stated otherwise, as used herein, wild-type human Neu2 refers to human Neu2 having the amino acid sequence of SEQ ID NO: 1.

[0080] Human Neu3 is a plasma membrane sialidase with an activity specific for gangliosides. Human Neu3 has two isoforms: isoform 1 and isoform 2. The amino acid sequence of human Neu3, isoform 1 is depicted in SEQ ID NO: 8, and a nucleotide sequence encoding human Neu3, isoform 1 is depicted in SEQ ID NO: 25. The amino acid sequence of human Neu3, isoform 2 is depicted in SEQ ID NO: 9, and a nucleotide sequence encoding human Neu3, isoform 2 is depicted in SEQ ID NO: 34.

[0081] Human Neu4 has two isoforms: isoform 1 is a peripheral membrane protein and isoform 2 localizes to the lysosome lumen. The amino acid sequence of human Neu4, isoform 1 is depicted in SEQ ID NO: 10, and a nucleotide sequence encoding human Neu4, isoform 1 is depicted in SEQ ID NO: 26. The amino acid sequence of human Neu4, isoform 2 is depicted in SEQ ID NO: 11, and a nucleotide sequence encoding human Neu4, isoform 2 is depicted in SEQ ID NO: 35.

[0082] Four sialidases have also been found in the mouse genome and are referred to as Neu1, Neu2, Neu3 and Neu4. The amino acid sequence of mouse Neu1 is depicted in SEQ ID NO: 38, and a nucleotide sequence encoding mouse Neu1 is depicted in SEQ ID NO: 42. The amino acid sequence of mouse Neu2 is depicted in SEQ ID NO: 39 and a nucleotide sequence encoding mouse Neu2 is depicted in SEQ ID NO: 43. The amino acid sequence of mouse Neu3 is depicted in SEQ ID NO: 40, and a nucleotide sequence encoding mouse Neu3

is depicted in SEQ ID NO: 44. The amino acid sequence of mouse Neu4 is depicted in SEQ ID NO: 41, and a nucleotide sequence encoding mouse Neu4 is depicted in SEQ ID NO: 45.

[0083] Exemplary prokaryotic sialidases include sialidases from *Salmonella typhimurium* and *Vibrio cholera*. The amino acid sequence of *Salmonella typhimurium* sialidase (St-sialidase) is depicted in SEQ ID NO: 30, and a nucleotide sequence encoding *Salmonella typhimurium* sialidase is depicted in SEQ ID NO: 6. The amino acid sequence of *Vibrio cholera* sialidase is depicted in SEQ ID NO: 36, and a nucleotide sequence encoding *Vibrio cholera* sialidase is depicted in SEQ ID NO: 37.

[0084] In certain embodiments, a recombinant mutant sialidase (*e.g.*, human sialidase) has at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, about 100%, or more than 100% of the enzymatic activity of a corresponding (or template) wild-type sialidase (*e.g.*, human sialidase).

[0085] In certain embodiments, a recombinant mutant sialidase (*e.g.*, human sialidase) has about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, or more than 100% of the enzymatic activity of a corresponding (or template) wild-type sialidase (*e.g.*, human sialidase).

[0086] In certain embodiments, the recombinant mutant sialidase (*e.g.*, human sialidase) has the same substrate specificity as the corresponding wild-type sialidase (*e.g.*, human sialidase). In other embodiments, the recombinant mutant sialidase (*e.g.*, human sialidase) has a different substrate specificity than the corresponding wild-type sialidase (*e.g.*, human sialidase). For example, in certain embodiments the recombinant mutant human sialidase can cleave α2,3, α2,6, and/or α2,8 linkages. In certain embodiments the sialidase can cleave α2,3 and α2,8 linkages.

[0087] In certain embodiments, the expression yield of the recombinant mutant sialidase (*e.g.*, human sialidase) sialidase in mammalian cells, *e.g.*, HEK293 cells, CHO cells, murine myeloma cells (*e.g.*, NS0, Sp2/0), or human fibrosarcoma cells (*e.g.*, HT-1080), is greater than about 10%, about 20%, about 50%, about 75%, about 100%, about 150%, about 200%,

about 250%, about 300%, about 400%, about 500%, about 600%, about 700%, about 800%, about 900%, or about 1,000% of the expression yield of the corresponding wild-type sialidase (*e.g.*, human sialidase).

[0088] In certain embodiments, the recombinant mutant sialidase (*e.g.*, human sialidase) has about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, or more than 100% of the enzymatic activity of a corresponding wild-type sialidase (*e.g.*, human sialidase), and the expression yield of the recombinant mutant sialidase (*e.g.*, human sialidase) in mammalian cells, *e.g.,* HEK293 cells, is greater than about 10%, about 20%, about 50%, about 75%, about 100%, about 150%, about 200%, about 250%, about 300%, about 400%, about 500%, about 600%, about 700%, about 800%, about 900%, or about 1,000% of the expression yield of a corresponding sialidase (*e.g.*, human sialidase) human sialidase.

[0089] In certain embodiments, the amino acid sequence of the recombinant mutant sialidase (*e.g.*, human sialidase) has at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of a corresponding wild-type sialidase (*e.g.*, human sialidase).

a. Substitutions of Residues to Decrease Proteolytic Cleavage

[0090] It has been discovered that certain sialidases (*e.g.,* human Neu2) are susceptible to cleavage by a protease (*e.g.,* trypsin). As a result, proteolytic cleavage of the sialidase may occur during recombinant protein production, harvesting, purification, or formulation, during administration to a subject, or after administration to a subject. Accordingly, in certain embodiments, the recombinant mutant sialidase (*e.g.*, human sialidase) comprises a substitution of at least one wild-type amino acid residue, wherein the substitution decreases cleavage of the sialidase by a protease (*e.g.,* trypsin) relative to a sialidase without the substitution.

[0091] In certain embodiments, the protease is a trypsin (*e.g.*, a mammalian trypsin, a bovine trypsin, a human trypsin such as trypsin 1, trypsin 2, or mesotrypsin, a cod trypsin, a *Streptomyces griseus* trypsin, a *Saccharopolyspora erythraeus* trypsin, a *Streptomyces exfoliatus* trypsin, and a *Streptomyces albidoflavus* trypsin), α-lytic protease, or a serine protease such as kallikreins, elastase and chymotrypsin.

[0092] In certain embodiments, incubation of the recombinant mutant sialidase (*e.g.*, human sialidase) with a protease (*e.g.,* trypsin) results in from about 1% to about 50%, from about 1% to about 40%, from about 1%, to about 30%, from about 1% to about 20%, from about 1% to about 10%, from about 1% to about 5%, from about 5% to about 50%, from about 5% to about 40%, from about 5% to about 30%, from about 5% to about 20%, from about 5% to about 10%, from about 10% to about 50%, from about 10% to about 40%, from about 10% to about 30%, from about 10% to about 20%, from about 20% to about 50%, from about 20% to about 40%, from about 20% to about 30%, from about 30% to about 50%, from about 30% to about 40%, or from about 40% to about 50% of the proteolytic cleavage of a corresponding sialidase (*e.g.*, wild-type sialidase) without the mutation when incubated with the protease under the same conditions. In certain embodiments, incubation of the recombinant mutant sialidase (*e.g.*, human sialidase) with a protease (*e.g.,* trypsin) results in less than 50%, less than 40%, less than 30%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the proteolytic cleavage of a corresponding sialidase (*e.g.*, wild-type sialidase) without the mutation(s) when incubated with the protease under the same conditions. Proteolytic cleavage can be assayed by any method known in the art, including for example, by SDS-PAGE as described in Example 5 herein.

[0093] As shown in **FIGURE 27A**, the arginine residue at a position corresponding to position 243 of wild-type human Neu2 (SEQ ID NO: 1) is conserved among many different sialidases. Accordingly, it is believed that mutating amino acids nearby this conserved arginine residue can reduce proteolytic cleavage of the sialidase. Thus, in certain embodiments, mutations within about 5 amino acid, about 4 amino acids, about 3 amino acids, or about 2 amino acids of the arginine residue at a position corresponding to position 243 of wild-type human Neu2 (SEQ ID NO: 1) can be substituted to increase resistance to proteolytic cleavage.

[0094] Exemplary substitutions that increase resistance to proteolytic cleavage include: (i) a substitution of an alanine residue at a position corresponding to position 242 of wild-type human Neu2 (SEQ ID NO: 1), *e.g.*, a substitution by cysteine (A242C), phenylalanine (A242F), glycine (A242G), histidine (A242H), isoleucine (A242I), lysine (A242K), leucine (A242L), methionine (A242M), asparagine (A242N), glutamine (A242Q), arginine (A242R), serine (A242S), valine (A242V), tryptophan (A242W), or tyrosine (A242Y); (ii) a substitution of an arginine residue at a position corresponding to position 243 of wild-type human Neu2 (SEQ ID NO: 1), *e.g.,* a substitution by glutamic acid (R243E), histidine

(R243H), asparagine (R243N), glutamine (R243Q), or lysine (R243K); (iii) a substitution of a valine residue at a position corresponding to position 244 of wild-type human Neu2 (SEQ ID NO: 1), *e.g.,* a substitution by isoleucine (V244I), lysine (V244K), or proline (V244P); or (iv) a combination of any of the foregoing. In certain embodiments, the alanine at a position corresponding to position 242 of wild-type human Neu2 is substituted by an aromatic amino acid, *e.g.,* tryptophan (A242W), tyrosine (A242Y), or phenylalanine (A242F). In certain embodiments, the alanine at a position corresponding to position 242 of wild-type human Neu2 is substituted by cysteine (A242C). In certain embodiments, the recombinant mutant human sialidase or the recombinant non-human sialidase comprises a substitution or combination of substitutions corresponding to a substitution or combination of substitutions listed in **TABLE 1** (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)).

TABLE 1

Wild Type Human Neu2 (SEQ ID NO: 1) Amino Acid	**Exemplary Substitution(s) at Specified Position(s)**
A242	C, F, G, H, I, K, L, M, N, P, Q, R, S, V, W, Y
R243	E, H, N, Q, K
V244	I, K, P

[0095] Additional exemplary substitutions that increase resistance to proteolytic cleavage (and/or increase expression yield and/or enzymatic activity) include: (i) a substitution of a leucine residue at a position corresponding to position 240 of wild-type human Neu2 (SEQ ID NO: 1), *e.g.*, a substitution by aspartic acid (L240D), asparagine (L240N), or tyrosine (L240Y); (ii) a substitution of an alanine residue at a position corresponding to position 213 of wild-type human Neu2 (SEQ ID NO: 1), *e.g.*, a substitution by cysteine (A213C), asparagine (A213N), serine (A213S), or threonine (A213T); (iii) a substitution of an arginine residue at a position corresponding to position 241 of wild-type human Neu2 (SEQ ID NO: 1), *e.g.*, a substitution by alanine (R241A), aspartic acid (R241D), leucine (R241L), glutamine (R241Q). or tyrosine (R241Y); (iv) a substitution of a serine residue at a position corresponding to position 258 of wild-type human Neu2 (SEQ ID NO: 1), *e.g.*, a substitution by cysteine (S258C); (v) a substitution of a leucine residue at a position corresponding to position 260 of wild-type human Neu2 (SEQ ID NO: 1), *e.g.*, a substitution by aspartic acid

(L260D), phenylalanine (L260F), glutamine (L260Q), or threonine (L260T); (vi) a substitution of a valine residue at a position corresponding to position 265 of wild-type human Neu2 (SEQ ID NO: 1), *e.g.*, a substitution by phenylalanine (V265F); or (vii) a combination of any of the foregoing. It is contemplated that, in certain embodiments, a substitution or a combination of substitutions at these positions may improve hydrophobic and/or aromatic interaction between secondary structure elements in the sialidase (*e.g.*, between an α-helix and the nearest β-sheet) thereby stabilizing the structure and improving resistance to proteolytic cleavage.

[0096] In certain embodiments, the recombinant mutant sialidase or the recombinant non-human sialidase comprises a mutation at position L240. In certain embodiments, the recombinant mutant sialidase comprises a combination of mutations at positions (i) A213 and A242, (ii) A213, A242, and S258, (iii) L240 and L260, (iv) R241 and A242, (v) A242 and L260, (vi) A242 and V265, or (vii) L240 and A242. In certain embodiments, the recombinant mutant human sialidase comprises a combination of substitutions selected from (i) A213C, A242F, and S258C, (ii) A213C and A242F, (iii) A213T and A242F, (iv) R241Y and A242F, and (v) L240Y and A242F. In certain embodiments, the recombinant mutant human sialidase or the recombinant non-human sialidase comprises a substitution or combination of substitutions corresponding to a substitution or combination of substitutions listed in **TABLE 2** (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)).

TABLE 2

Substitution(s)
A242C, V244P
A242R, V244R
A242R, V244H
A242Y, V244P
A242T, V244P
A242N, V244P
A213C, A242F
A213S, A242F
A213T, A242F
A213N, A242F
A213C, A242F, S258C

Substitution(s)
A242F, L260F
A242F, V265F
L240Y
L240Y, L260F
L240D, L260T
L240N, L260T
L240N, L260D
L240N, L260Q
L240Y, A242F
R241A, A242F
R241Y, A242F

b. Substitution of Cysteine Residues

[0097] In certain embodiments, the recombinant mutant human sialidase further comprises a substitution of at least one cysteine (cys, C) residue. It has been discovered that certain cysteine residues in sialidases may inhibit expression of functional protein as a result of protein aggregation. Accordingly, in certain embodiments, the recombinant mutant human sialidase contains at least one mutation to remove a free cysteine (*e.g.*, for Neu1 (SEQ ID NO: 7), a mutation of, for example, one or more of C111, C117, C171, C183, C218, C240, C242, and C252; for Neu2 (SEQ ID NO: 1), a mutation of, for example, one or more of C125, C196, C219, C272, C332, and C352; for Neu3 (SEQ ID NO: 8), a mutation of, for example, one or more of C7, C90, C99, C106, C127, C136, C189, C194, C226, C242, C250, C273, C279, C295, C356, C365, C368, C384, C383, C394, and C415; and for Neu4 (SEQ ID NO: 10), a mutation of, for example, one or more of C88, C125, C126, C186, C191, C211, C223, C239, C276, C437, C453, C480, and C481). Free cysteines can be substituted with any amino acid. In certain embodiments, the free cysteine is substituted with serine (ser, S), isoleucine (iso, I), valine (val, V), phenylalanine (phe, F), leucine (leu, L), or alanine (ala, A). Exemplary cysteine substitutions in Neu2 include C125A, C125I, C125S, C125V, C196A, C196L, C196V, C272S, C272V, C332A, C332S, C332V, C352L, and C352V. In certain embodiments, the cysteine at a position corresponding to position 332 of wild-type human Neu2 is substituted by a hydrophobic amino acid, *e.g.,* alanine (C332A), valine (C332V), isoleucine (C332I), or leucine (C332L). In certain embodiments, the cysteine at a position corresponding to position 332 of wild-type human Neu2 is substituted by alanine (C332A).

[0098] In certain embodiments, the recombinant mutant human sialidase comprises two or more cysteine substitutions. Exemplary double or triple cysteine substitutions in Neu2 include: C125S and C332S; C272V and C332A; C272V and C332S; C332A and C352L; C125S and C196L; C196L and C352L; C196L and C332A; C332A and C352L; and C196L, C332A and C352L.

[0099] In certain embodiments, the recombinant mutant human sialidase is a Neu2 sialidase and comprises the substitutions C322A and C352L.

[00100] In certain embodiments, the sialidase contains an amino acid substitution at 2, 3, 4, 5, or 6 cysteines typically present in a human sialidase, e.g., Neu2 or Neu3.

[00101] In certain embodiments, the recombinant mutant human sialidase comprises a substitution or combination of substitutions corresponding to a substitution or combination of substitutions listed in TABLE 3 (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)).

TABLE 3

Substitution(s)
C125A
C125I
C125S
C125V
C196A
C196L
C196V
C272S
C272V
C332A
C332S
C332V
C352L
C352V
C125S + C332S
C272V + C332A
C272V + C332S
C332A + C352L
C125S + C196L
C196L + C352L
C196L + C332A
C196L + C332A + C352L

c. Substitutions of Residues to Increase pI and/or Decrease Hydrophobicity

[00102] In addition the sialidase (*e.g.*, human sialidase) may further comprise one or more substitutions that modify pI (*e.g.,* increase pI) and/or hydrophobicity (*e.g.,* decrease hydrophobicity) of the sialidase.

[00103] The isoelectric point (pI) of a protein is the pH at which the net charge is zero. The pI also generally indicates the pH at which the protein is least soluble, which may affect the ability to express and purify the protein. Generally, a protein has good solubility if its pI is greater than 2 units above the pH of the solution. Human Neu2 has a predicted pI of 7.5. Thus, human Neu2 is least soluble around neutral pH, which is undesirable because expression and physiological systems are at neutral pH. In contrast, the sialidase from *Salmonella typhimurium* (St-sialidase), which exhibits good solubility and recombinant expression, has a pI of 9.6. Accordingly, to increase expression of human Neu2 or the other human sialidases, a recombinant mutant human sialidase may be designed to contain one or more amino acid substitution(s) wherein the substitution(s) increase(s) the pI of the sialidase relative to a sialidase without the substitution. Additionally, decreasing the number of hydrophobic amino acids on the surface of a sialidase may improve expression of sialidase by, for example, reducing aggregation. Accordingly, to increase expression of human Neu2 or the other human sialidases, a recombinant mutant human sialidase may be designed to contain one or more amino acid substitution(s) wherein the substitution(s) decrease(s) the hydrophobicity of a surface of the sialidase relative to a sialidase without the substitution(s).

[00104] Accordingly, in certain embodiments, the recombinant mutant human sialidase comprises at least one amino acid substitution, wherein the substitution increases the isoelectric point (pI) of the sialidase and/or decreases the hydrophobicity of the sialidase relative to a sialidase without the substitution. This may be achieved by introducing one or more charged amino acids, for example, positively or negatively charged amino acids, into the recombinant sialidase. In certain embodiments, the amino acid substitution is to a charged amino acid, for example, a positively charged amino acid such as lysine (lys, K), histidine (his, H), or arginine (arg, R), or a negatively charged amino acid such as aspartic acid (asp, D) or glutamic acid (glu, E). In certain embodiments, the amino acid substitution is to a lysine residue. In certain embodiments, the substitution increases the pI of the sialidase to about 7.75, about 8, about 8.25, about 8.5, about 8.75, about 9, about 9.25, about 9.5, or about 9.75.

[00105] In certain embodiments, the amino acid substitution occurs at a surface exposed D or E amino acid, in a helix or loop, or in a position that has a K or R in the corresponding position of St-sialidase. In certain embodiments, the amino acid substitution occurs at an amino acid that is remote from the catalytic site or otherwise not involved in catalysis, an amino acid that is not conserved with the other human Neu proteins or with St-Sialidase or Clostridium NanH, or an amino acid that is not located in a domain important for function (e.g., an Asp-box or beta strand).

[00106] Exemplary amino acid substitutions in Neu2 that increase the isoelectric point (pI) of the sialidase and/or decrease the hydrophobicity of the sialidase relative to a sialidase without the substitution include A2E, A2K, D215K, V325E, V325K, E257K, and E319K. In certain embodiments, the recombinant mutant human sialidase comprises two or more amino acid substitutions, including, for example, A2K and V325E, A2K and V325K, E257K and V325K, A2K and E257K, and E257K and A2K and V325K.

[00107] In certain embodiments, the recombinant mutant human sialidase comprises a substitution or combination of substitutions corresponding to a substitution or combination of substitutions listed in TABLE 4 (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)).

TABLE 4

Substitution(s)
A2K
E72K
D215K
E257K
V325K
A2K + E257K
A2K + V325E
A2K + V325K
E257K + V325K

d. Addition of N-terminal Peptides and N- or C-terminal Substitutions

[00108] In addition, the sialidase (e.g., human sialidase) may further comprise an N-terminal peptide and/or N- or C-terminal substitutions.

[00109] It has been discovered that the addition of a peptide sequence of two or more amino acids to the N-terminus of a human sialidase can improve expression and/or activity of the

sialidase. In certain embodiments, the peptide is at least 2 amino acids in length, for example, from 2 to 20, from 2 to 10, from 2 to 5, or 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids in length. In certain embodiments, the peptide may form, or have a propensity to form, an α-helix.

[00110] In mice, a Neu2 isoform (type B) found in thymus contains six amino acids not present in the canonical isoform of Neu2 found in skeletal muscle. In certain embodiments herein, the N-terminal six amino acids of the mouse thymus Neu2 isoform, MEDLRP (SEQ ID NO: 4), or variations thereof, can be added onto a human Neu, e.g., human Neu2. In certain embodiments, the recombinant mutant human sialidase comprises a peptide at least two amino acid residues in length covalently associated with an N-terminal amino acid of the sialidase. In certain embodiments the recombinant mutant human sialidase comprises the peptide MEDLRP (SEQ ID NO: 4) or EDLRP (SEQ ID NO: 3) covalently associated with an N-terminal amino acid of the sialidase. In certain embodiments, the sialidase may further comprise a cleavage site, e.g., a proteolytic cleavage site, located between the peptide, e.g., MEDLRP (SEQ ID NO: 4) or EDLRP (SEQ ID NO: 3), and the remainder of the sialidase. In certain embodiments, the peptide, e.g., MEDLRP (SEQ ID NO: 4) or EDLRP (SEQ ID NO: 3), may be post-translationally cleaved from the remainder of the sialidase.

[00111] Alternatively to, or in combination with, the N-terminal addition, 1-5 amino acids of the 12 amino acid N-terminal region of the recombinant mutant human sialidase may be removed, e.g., the N-terminal methionine can be removed. In certain embodiments, if the recombinant mutant human sialidase is Neu2, the N-terminal methionine can be removed, the first five amino acids (MASLP; SEQ ID NO: 12) can be removed, or the second through fourth amino acids (ASLP; SEQ ID NO: 13) can be removed.

[00112] In certain embodiments, 1-5 amino acids of the 12 amino acid N-terminal region of the recombinant mutant human sialidase are substituted with MEDLRP (SEQ ID NO: 4), EDLRP (SEQ ID NO: 3), or TVEKSVVF (SEQ ID NO: 14). For example, in certain embodiments, if the recombinant mutant human sialidase is Neu2, the amino acids MASLP (SEQ ID NO: 12), ASLP (SEQ ID NO: 13) or M are substituted with MEDLRP (SEQ ID NO: 4), EDLRP (SEQ ID NO: 3) or TVEKSVVF (SEQ ID NO: 14).

[00113] Human sialidases have a β-propeller structure, characterized by 6 blade-shaped β-sheets arranged toroidally around a central axis. Generally, hydrophobic interactions between the blades of a β-propeller, including between the N- and C-terminal blades, enhance

stability. Accordingly, in order to increase expression of human Neu2 or the other human sialidases, a recombinant mutant human sialidase can be designed comprising an amino acid substitution that increases hydrophobic interactions and/or hydrogen bonding between the N- and C-terminal β-propeller blades of the sialidase.

[00114] Accordingly, in certain embodiments, the recombinant mutant human sialidase comprises a substitution of at least one wild-type amino acid residue, wherein the substitution increases hydrophobic interactions and/or hydrogen bonding between the N- and C-termini of the sialidase relative to a sialidase without the substitution. In certain embodiments, the wild-type amino acid is substituted with asparagine (asn, N), lysine (lys, K), tyrosine (tyr, Y), phenylalanine (phe, F), or tryptophan (trp, W). Exemplary substitutions in Neu2 that increase hydrophobic interactions and/or hydrogen bonding between the N- and C-termini include L4N, L4K, V6Y, L7N, L4N and L7N, L4N and V6Y and L7N, V12N, V12Y, V12L, V6Y, V6F, or V6W. In certain embodiments, the valine at a position corresponding to position 6 of wild-type human Neu2 is substituted by an aromatic amino acid, e.g., tryptophan (V6W), tyrosine (V6Y), or phenylalanine (V6F). In certain embodiments, the sialidase comprises the V6Y substitution.

[00115] In certain embodiments, the recombinant mutant human sialidase comprises a combination of the above substitutions. For example, a recombinant mutant human Neu2 sialidase can comprise the additional amino acids MEDLRP (SEQ ID NO: 4), EDLRP (SEQ ID NO: 3), or TVEKSVVF (SEQ ID NO: 14) at the N-terminus and, in combination, can comprise at least one L4N, L4K, V6Y, L7N, L4N and L7N, L4N and V6Y and L7N, V12N, V12Y, V12L, V6Y, V6F, or V6W substitution. In certain embodiments, the amino acids MASLP (SEQ ID NO: 12), ASLP (SEQ ID NO: 13) or M of a recombinant mutant human Neu2 sialidase are replaced with MEDLRP (SEQ ID NO: 4), EDLRP (SEQ ID NO: 3) or TVEKSVVF (SEQ ID NO: 14) and the recombinant mutant human Neu2 sialidase also comprises at least one L4N, L4K, V6Y, L7N, L4N and L7N, L4N and V6Y and L7N, V12N, V12Y, V12L, V6Y, V6F, or V6W substitution.

[00116] In certain embodiments, the recombinant mutant human sialidase comprises a mutation or combination of mutations corresponding to a mutation or combination of mutations listed in TABLE 5 (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)).

TABLE 5

Mutation(s)
Substitute M at the N-terminus with EDLRP (SEQ ID NO: 3)
Substitute M at the N-terminus with MEDLRP (SEQ ID NO: 4)
Insert MEDLRP (SEQ ID NO: 4) at the N-terminus
Substitute MASLP (SEQ ID NO: 12) at the N-terminus with MEDLRP (SEQ ID NO: 4)
L4N
V6Y
L7N
V6F
V6W

[00117] Additionally, in certain embodiments, the sialidase comprises a substitution or deletion of an N-terminal methionine at the N-terminus of the sialidase. For example, in certain embodiments, the sialidase comprises a substitution of a methionine residue at a position corresponding to position 1 of wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, the methionine at a position corresponding to position 1 of wild-type human Neu2 is substituted by alanine (M1A). In certain embodiments, the methionine at a position corresponding to position 1 of wild-type human Neu2 is substituted by a negatively charged amino acid, e.g., glutamic acid (M1E) or aspartic acid (M1D). In certain embodiments, the methionine at a position corresponding to position 1 of wild-type human Neu2 is substituted by aspartic acid (M1D). In other embodiments, the sialidase comprises a deletion of a methionine residue at a position corresponding to position 1 (ΔM1) of wild-type human Neu2 (SEQ ID NO: 1).

[00118] In certain embodiments, the recombinant mutant human sialidase comprises a substitution or combination of substitutions corresponding to a substitution or combination of substitutions listed in TABLE 6 (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)).

TABLE 6

Mutation(s)
Deletion of M1, V6Y, I187K
M1R, V6Y, I187K
M1H, V6Y, I187K
M1K, V6Y, I187K
M1D, V6Y, I187K
M1T, V6Y, I187K

Mutation(s)
M1N, V6Y, I187K
M1Q, V6Y, I187K
M1G, V6Y, I187K
M1A, V6Y, I187K
M1V, V6Y, I187K
M1L, V6Y, I187K
M1F, V6Y, I187K
M1Y, V6Y, I187K

e. Other Substitutions

[00119] In addition, the sialidase may further comprise at least one of the following substitutions: A328E, K370N, or H210N. In certain embodiments, the isoleucine at a position corresponding to position 187 of wild-type human Neu2 is substituted by a positively charged amino acid, e.g., lysine (I187K) or arginine (I187R). In certain embodiments, the isoleucine at a position corresponding to position 187 of wild-type human Neu2 is substituted by lysine (I187K). In certain embodiments, a recombinant mutant human Neu2 comprises the substitution of the amino acids GDYDAPTHQVQW (SEQ ID NO: 15) with the amino acids SMDQGSTW (SEQ ID NO: 16) or STDGGKTW (SEQ ID NO: 17). In certain embodiments, a recombinant mutant human Neu2 comprises the substitution of the amino acids PRPPAPEA (SEQ ID NO: 18) with the amino acids QTPLEAAC (SEQ ID NO: 19). In certain embodiments, a recombinant mutant human Neu2 comprises the substitution of the amino acids NPRPPAPEA (SEQ ID NO: 20) with the amino acids SQNDGES (SEQ ID NO: 21).

[00120] The invention further provides a recombinant mutant human sialidase comprising at least one substitution at a position corresponding to V212, A213, Q214, D215, T216, L217, E218, C219, Q220, V221, A222, E223, V224, E225, or T225.

[00121] The invention further provides a recombinant mutant human sialidase comprising an amino acid substitution at a position identified in TABLE 7 (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, the sialidase comprises an amino acid substitution identified in TABLE 7. In certain embodiments, the sialidase comprises a combination of any amino acid substitutions identified in TABLE 7.

TABLE 7

Wild Type Human Neu2 (SEQ ID NO: 1) Amino Acid	**Exemplary Substitution(s) at Specified Position(s)**
M1	D
L4	S, T, Y, L, F, A, P, V, I, N, D, or H
P5	G
V6	Y
L7	F, Y, S, I, T, or N
K9	D
V12	L, A, P, V, N, D, or H
F13	S, N, R, K, T, G, D, E, or A
I22	S, N, R, K, T, G, D, E, A, Y, L, F, P, V, I, or H
A24	S, N, R, K, T, G, D, E, A, Y, L, F, P, V, I, or H
L34	S, T, Y, L, F, A, P, V, I, N, D, or H
A36	S, T, Y, L, F, A, P, V, I, N, D, or H
A42	R or D
K44	R or E
K45	A, E, or R
L54	M
P62	H, G, N, T, S, F, I, D, or E
H64	F, Y, S, I, T, or N
Q69	H
R78	K
D80	P
P89	S, T, Y, L, F, A, P, V, I, N, D, H, or M
A93	E or K
G107	D
Q108	H
Q112	E, R, or K
C125	Y, F, or L
Q126	E, F, H, I, L, or Y
A150	V
T156	R, N, D, C, G, H, I, L, F, S, Y, V, A, P, or T

Wild Type Human Neu2 (SEQ ID NO: 1) Amino Acid	Exemplary Substitution(s) at Specified Position(s)
F157	R, N, D, C, G, H, I, L, F, S, Y, V, A, or P
A158	R, N, D, C, G, H, I, L, F, S, Y, V, A, P, or T
V159	R, N, D, C, G, H, I, L, F, S, Y, V, A, or P
G160	R, N, D, C, G, H, I, L, F, S, Y, V, A, P, or T
P161	R, N, D, C, G, H, I, L, F, S, Y, V, A, or P
G162	R, N, D, C, G, H, I, L, F, S, Y, V, A, P, or T
H163	R, N, D, C, G, H, I, L, F, S, Y, V, A, or P
C164	R, N, D, C, G, H, I, L, F, S, Y, V, A, P, or T
L165	R, N, D, C, G, H, I, L, F, S, Y, V, A, or P
R170	P
A171	G
V176	R, N, D, C, G, H, I, L, F, S, Y, V, P, or A
P177	S, T, Y, L, F, A, P, V, I, N, D, or H
A178	S, T, Y, L, F, A, P, V, I, N, D, or H
L184	S, N, R, K, T, G, D, E, A, F, H, I, L, P, V, or Y
H185	S, N, R, K, T, G, D, E, or A
P186	S, N, R, K, T, G, D, E, A, F, H, I, L, P, V, or Y
I187	S, N, R, K, T, G, D, E, or A
Q188	P, S, N, R, K, T, G, D, E, or A
R189	P
P190	F, M, A, D, G, H, N, P, R, S, or T
I191	M, A, D, F, H, I, L, N, P, S, T, V, Y, E, G, K, or R
A194	S, T, Y, L, F, A, P, V, I, N, D, or H
A213	C, N, S, or T
L217	R, N, D, C, G, H, I, L, F, S, Y, or V
C219	R, N, D, C, G, H, I, L, F, S, Y, or V
A222	D
E225	P or C
H239	P
L240	D, N, or Y
R241	A, D, L, Q, or Y

Wild Type Human Neu2 (SEQ ID NO: 1) Amino Acid	Exemplary Substitution(s) at Specified Position(s)
A242	C, F, G, H, I, K, L, M, N, Q, R, S, V, W, or Y
V244	I or P
T249	A
D251	G
E257	P
S258	C
L260	D, F, Q, or T
V265	F
Q270	S, T, A, H, P, or F
G271	S, N, R, K, T, G, D, E, or A
C272	S, N, R, K, T, G, D, E, A, C, H, Y, F, H, L, P, or V
A290	C
W292	R
S301	A, D, E, F, G, H, I, K, L, M, N, P, Q, T, V, W, Y, C, or R
W302	A, D, E, F, G, H, I, L, M, N, P, Q, R, S, T, V, Y, or K
E319	D
V325	F, Y, S, I, T, N, A, D, H, L, P, or V
L326	F, Y, S, I, T, N, A, D, H, L, P, or V
L327	F, Y, S, I, T, N, A, D, H, L, P, or V
C332	A, D, G, H, N, P, R, S, or T
Y359	A or S
V363	R, S, T, Y, L, F, A, P, V, I, N, D, or H
L365	K, Q, F, Y, S, I, T, N, A, D, H, L, P, or V

[00122] For example, in certain embodiments, the recombinant mutant human sialidase comprises: (a) a substitution of a proline residue at a position corresponding to position 5 of wild-type human Neu2 (P5); (b) a substitution of a lysine residue at a position corresponding to position 9 of wild-type human Neu2 (K9); (c) a substitution of an alanine residue at a position corresponding to position 42 of wild-type human Neu2 (A42); (d) a substitution of a lysine residue at a position corresponding to position 44 of wild-type human Neu2 (K44); (e)

a substitution of a lysine residue at a position corresponding to position 45 of wild-type human Neu2 (K45); (f) a substitution of a leucine residue at a position corresponding to position 54 of wild-type human Neu2 (L54); (g) a substitution of a proline residue at a position corresponding to position 62 of wild-type human Neu2 (P62); (h) a substitution of a glutamine residue at a position corresponding to position 69 of wild-type human Neu2 (Q69); (i) a substitution of an arginine residue at a position corresponding to position 78 of wild-type human Neu2 (R78); (j) a substitution of an aspartic acid residue at a position corresponding to position 80 of wild-type human Neu2 (D80); (k) a substitution of an alanine residue at a position corresponding to position 93 of wild-type human Neu2 (A93); (l) a substitution of a glycine residue at a position corresponding to position 107 of wild-type human Neu2 (G107); (m) a substitution of a glutamine residue at a position corresponding to position 108 of wild-type human Neu2 (Q108); (n) a substitution of a glutamine residue at a position corresponding to position 112 of wild-type human Neu2 (Q112); (o) a substitution of a cysteine residue at a position corresponding to position 125 of wild-type human Neu2 (C125); (p) a substitution of a glutamine residue at a position corresponding to position 126 of wild-type human Neu2 (Q126); (q) a substitution of an alanine residue at a position corresponding to position 150 of wild-type human Neu2 (A150); (r) a substitution of a cysteine residue at a position corresponding to position 164 of wild-type human Neu2 (C164); (s) a substitution of an arginine residue at a position corresponding to position 170 of wild-type human Neu2 (R170); (t) a substitution of an alanine residue at a position corresponding to position 171 of wild-type human Neu2 (A171); (u) a substitution of a glutamine residue at a position corresponding to position 188 of wild-type human Neu2 (Q188); (v) a substitution of an arginine residue at a position corresponding to position 189 of wild-type human Neu2 (R189); (w) a substitution of an alanine residue at a position corresponding to position 213 of wild-type human Neu2 (A213); (x) a substitution of a leucine residue at a position corresponding to position 217 of wild-type human Neu2 (L217); (y) a substitution of a glutamic acid residue at a position corresponding to position 225 of wild-type human Neu2 (E225); (z) a substitution of a histidine residue at a position corresponding to position 239 of wild-type human Neu2 (H239); (aa) a substitution of a leucine residue at a position corresponding to position 240 of wild-type human Neu2 (L240); (bb) a substitution of an arginine residue at a position corresponding to position 241 of wild-type human Neu2 (R241); (cc) a substitution of an alanine residue at a position corresponding to position 242 of wild-type human Neu2 (A242); (dd) a substitution of a valine residue at a position corresponding to position 244 of wild-type human Neu2 (V244); (ee) a substitution

of a threonine residue at a position corresponding to position 249 of wild-type human Neu2 (T249); (ff) a substitution of an aspartic acid residue at a position corresponding to position 251 of wild-type human Neu2 (D251); (gg) a substitution of a glutamic acid residue at a position corresponding to position 257 of wild-type human Neu2 (E257); (hh) a substitution of a serine residue at a position corresponding to position 258 of wild-type human Neu2 (S258); (ii) a substitution of a leucine residue at a position corresponding to position 260 of wild-type human Neu2 (L260); (jj) a substitution of a valine residue at a position corresponding to position 265 of wild-type human Neu2 (V265); (kk) a substitution of a glutamine residue at a position corresponding to position 270 of wild-type human Neu2 (Q270); (ll) a substitution of an alanine residue at a position corresponding to position 290 of wild-type human Neu2 (A290); (mm) a substitution of a tryptophan residue at a position corresponding to position 292 of wild-type human Neu2 (W292); (nn) a substitution of a serine residue at a position corresponding to position 301 of wild-type human Neu2 (S301); (oo) a substitution of a tryptophan residue at a position corresponding to position 302 of wild-type human Neu2 (W302); (pp) a substitution of a valine residue at a position corresponding to position 363 of wild-type human Neu2 (V363); or (qq) a substitution of a leucine residue at a position corresponding to position 365 of wild-type human Neu2 (L365); or a combination of any of the foregoing substitutions. For example, the sialidase may comprise a substitution of K9, A42, P62, A93, Q216, A242, Q270, S301, W302, V363, or L365, or a combination of any of the foregoing substitutions.

[00123] In certain embodiments, in the sialidase: (a) the proline residue at a position corresponding to position 5 of wild-type human Neu2 is substituted by histidine (P5H); (b) the lysine residue at a position corresponding to position 9 of wild-type human Neu2 is substituted by aspartic acid (K9D); (c) the alanine residue at a position corresponding to position 42 of wild-type human Neu2 is substituted by a positively charged amino acid, *e.g.*, arginine (A42R) or lysine (A42K), or is substituted by aspartic acid (A42D); (d) the lysine residue at a position corresponding to position 44 of wild-type human Neu2 is substituted by arginine (K44R) or glutamic acid (K44E); (e) the lysine residue at a position corresponding to position 45 of wild-type human Neu2 is substituted by alanine (K45A), arginine (K45R), or glutamic acid (K45E); (f) the leucine residue at a position corresponding to position 54 of wild-type human Neu2 is substituted by methionine (L54M); (g) the proline residue at a position corresponding to position 62 of wild-type human Neu2 is substituted by asparagine (P62N), aspartic acid (P62D), histidine (P62H), glutamic acid (P62E), glycine (P62G), serine

(P62S), or threonine (P62T); (h) the glutamine residue at a position corresponding to position 69 of wild-type human Neu2 is substituted by histidine (Q69H); (i) the arginine residue at a position corresponding to position 78 of wild-type human Neu2 is substituted by lysine (R78K); (j) the aspartic acid residue at a position corresponding to position 80 of wild-type human Neu2 is substituted by proline (D80P); (k) the alanine residue at a position corresponding to position 93 of wild-type human Neu2 is substituted by a negatively charged amino acid, *e.g.*, aspartic acid (A93D) or glutamic acid (A93E), or is substituted by lysine (A93K); (l) the glycine residue at a position corresponding to position 107 of wild-type human Neu2 is substituted by aspartic acid (G107D); (m) the glutamine residue at a position corresponding to position 108 of wild-type human Neu2 is substituted by histidine (Q108H); (n) the glutamine residue at a position corresponding to position 112 of wild-type human Neu2 is substituted by glutamic acid (Q112E), arginine (Q112R), or lysine (Q112K); (o) the cysteine residue at a position corresponding to position 125 of wild-type human Neu2 is substituted by leucine (C125L); (p) the glutamine residue at a position corresponding to position 126 of wild-type human Neu2 is substituted by an aromatic amino acid, *e.g.*, phenylalanine (Q126F), tyrosine (Q126Y), or tryptophan (Q126W), or is substituted by leucine (Q126L), glutamic acid (Q126E), histidine (Q126H), or isoleucine (Q126I); (q) the alanine residue at a position corresponding to position 150 of wild-type human Neu2 is substituted by valine (A150V); (r) the cysteine residue at a position corresponding to position 164 of wild-type human Neu2 is substituted by glycine (C164G); (s) the arginine residue at a position corresponding to position 170 of wild-type human Neu2 is substituted by proline (R170P); (t) the alanine residue at a position corresponding to position 171 of wild-type human Neu2 is substituted by glycine (A171G); (u) the glutamine residue at a position corresponding to position 188 of wild-type human Neu2 is substituted by proline (Q188P); (v) the arginine residue at a position corresponding to position 189 of wild-type human Neu2 is substituted by proline (R189P); (w) the alanine residue at a position corresponding to position 213 of wild-type human Neu2 is substituted by cysteine (A213C), asparagine (A213N), serine (A213S), or threonine (A213T); (x) the leucine residue at a position corresponding to position 217 of wild-type human Neu2 is substituted by alanine (L217A) or valine (L217V); (y) the threonine residue at a position corresponding to position 249 of wild-type human Neu2 is substituted by alanine (T249A); (z) the aspartic acid residue at a position corresponding to position 251 of wild-type human Neu2 is substituted by glycine (D251G); (aa) the glutamic acid residue at a position corresponding to position 225 of wild-type human Neu2 is substituted by cysteine (E225C) or proline (E225P); (bb) the histidine residue at a

position corresponding to position 239 of wild-type human Neu2 is substituted by proline (H239P); (cc) the leucine residue at a position corresponding to position 240 of wild-type human Neu2 is substituted by aspartic acid (L240D), asparagine (L240N), or tyrosine (L240Y); (dd) the arginine residue at a position corresponding to position 241 of wild-type human Neu2 is substituted by alanine (R241A), aspartic acid (R241D), leucine (R241L), glutamine (R241Q). or tyrosine (R241Y); (ee) the alanine residue at a position corresponding to position 242 of wild-type human Neu2 is substituted by cysteine (A242C), phenylalanine (A242F), glycine (A242G), histidine (A242H), isoleucine (A242I), lysine (A242K), leucine (A242L), methionine (A242M), asparagine (A242N), glutamine (A242Q), arginine (A242R), serine (A242S), valine (A242V), tryptophan (A242W), or tyrosine (A242Y); (ff) the valine residue at a position corresponding to position 244 of wild-type human Neu2 is substituted by isoleucine (V244I), lysine (V244K), or proline (V244P); (gg) the glutamic acid residue at a position corresponding to position 257 of wild-type human Neu2 is substituted by proline (E257P); (hh) the serine residue at a position corresponding to position 258 is substituted by cysteine (S258C); (ii) the leucine residue at a position corresponding to position 260 of wild-type human Neu2 is substituted by aspartic acid (L260D), phenylalanine (L260F), glutamine (L260Q), or threonine (L260T); (jj) the valine residue at a position corresponding to position 265 of wild-type human Neu2 is substituted by phenylalanine (V265F); (kk) the glutamine residue at a position corresponding to position 270 of wild-type human Neu2 is substituted by a polar, uncharged amino acid, *e.g.,* serine (Q270S) or threonine (Q270T), or is substituted by alanine (Q270A), histidine (Q270H), phenylalanine (Q270F), or proline (Q270P); (ll) the alanine residue at a position corresponding to position 290 of wild-type human Neu2 is substituted by cysteine (A290C); (mm) the tryptophan residue at a position corresponding to position 292 of wild-type human Neu2 is substituted by arginine (W292R); (nn) the serine residue at a position corresponding to position 301 of wild-type human Neu2 is substituted by alanine (S301A), aspartic acid (S301D), glutamic acid (S301E), phenylalanine (S301F), histidine (S301H), lysine (S301K), leucine (S301L), methionine (S301M), asparagine (S301N), proline (S301P), glutamine (S301Q), arginine (S301R), threonine (S301T), valine (S301V), tryptophan (S301W), or tyrosine (S301Y)); (oo) the tryptophan residue at a position corresponding to position 302 of wild-type human Neu2 is substituted by alanine (W302A), aspartic acid (W302D), phenylalanine (W302F), glycine (W302G), histidine (W302H), isoleucine (W302I), lysine (W302K), leucine (W302L), methionine (W302M), asparagine (W302N), proline (W302P), glutamine (W302Q), arginine (W302R), serine (W302S), threonine (W302T), valine (W302V), or tyrosine (W302Y); (pp) the valine residue at a

position corresponding to position 363 of wild-type human Neu2 is substituted by arginine (V363R); or (qq) the leucine residue at a position corresponding to position 365 of wild-type human Neu2 is substituted by glutamine (L365Q), histidine (L365H), isoleucine (L365I), lysine (L365K) or serine (L365S); or the sialidase comprises a combination of any of the foregoing substitutions. For example, the sialidase may comprise a substitution selected from K9D, A42R, P62G, P62N, P62S, P62T, A93E, Q126Y, A242F, A242W, A242Y, Q270A, Q270T, S301A, S301R, W302K, W302R, V363R, and L365I, or a combination of any of the foregoing substitutions.

[00124] In certain embodiments, the recombinant mutant human sialidase comprises a deletion of a leucine residue at a position corresponding to position 184 of wild-type human Neu2 (ΔL184), a deletion of a histidine residue at a position corresponding to position 185 of wild-type human Neu2 (ΔH185), a deletion of a proline residue at a position corresponding to position 186 of wild-type human Neu2 (ΔP186), a deletion of an isoleucine residue at a position corresponding to position 187 of wild-type human Neu2 (ΔI187), and a deletion of a glutamine residue at a position corresponding to position 184 of wild-type human Neu2 (ΔQ188), or a combination of any of the foregoing deletions.

[00125] In certain embodiments, the recombinant mutant human sialidase comprises an insertion between a threonine residue at a position corresponding to position 216 of wild-type human Neu2 and a leucine residue at a position corresponding to position 217 of wild-type human Neu2, for example, an insertion of an amino acid selected from S, T, Y, L, F, A, P, V, I, N, D, and H.

[00126] Additional exemplary sialidase mutations, and combinations of sialidase mutations, are described in International (PCT) Patent Application Publication No. WO 2019/136167, including in the Detailed Description in the section entitled "I. Recombinant Human Sialidases," and in the Examples in Examples 1, 2, 3, 4, 5, and 6, and International (PCT) Patent Application Publication No. WO 2021/003469, including in the Detailed Description in the section entitled "I. Recombinant Human Sialidases," and in the Examples in Examples 2, 3, 4, and 5.

f. Combinations of Substitutions

[00127] The invention further provides a recombinant mutant human sialidase comprising a combination of any of the mutations contemplated herein. For example, the recombinant mutant sialidase enzyme may comprise a combination of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,

14, 15 or more of the mutations contemplated herein. It is contemplated that the recombinant mutant sialidase enzyme may comprise 1-15, 1-10, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 2-15, 2-10, 2-7, 2-6, 2-5, 2-4, 2-3, 3-15, 3-10, 3-7, 3-6, 3-5, or 3-4 of the mutations contemplated herein.

[00128] For example, alternatively or in addition to the modifications to decrease sensitivity to protease (e.g., trypsin) degradation, the recombinant mutant sialidase enzyme may comprise one or more of the following modifications described herein.

[00129] In certain embodiments, the recombinant mutant sialidase enzyme further comprises an M1 deletion (ΔM1), M1A substitution, M1D substitution, V6Y substitution, K9D substitution, P62G substitution, P62N substitution, P62S substitution, P62T substitution, A93E substitution, I187K substitution, Q270A substitution, S301R substitution, W302K substitution, C332A substitution, V363R substitution, L365I substitution, or a combination of any of the foregoing.

[00130] In certain embodiments, the recombinant mutant sialidase enzyme further comprises a M1 deletion (ΔM1), M1A substitution, M1D substitution, V6Y substitution, I187K substitution, C332A substitution, or a combination of any of the foregoing. For example, the recombinant mutant sialidase enzyme may comprise a combination of mutations selected from: M1A and V6Y; M1A and I187K; M1A and C332A; M1D and V6Y; M1D and I187K; M1D and C332A; ΔM1 and V6Y; ΔM1 and I187K; ΔM1 and C332A; V6Y and I187K; V6Y and C332A; I187K and C332A; M1A, V6Y, and I187K; M1A, V6Y, and C332A; M1A, I187K, and C332A; M1D, V6Y, and I187K; M1D, V6Y, and C332A; M1D, I187K, and C332A; ΔM1, V6Y, and I187K; ΔM1, V6Y, and C332A; ΔM1, I187K, and C332A; V6Y, I187K, and C332A; M1A, V6Y, I187K, and C332A; M1D, V6Y, I187K, and C332A; and ΔM1, V6Y, I187K, and C332A.

[00131] In certain embodiments, the recombinant mutant sialidase enzyme further comprises (i) an amino acid substitution identified in TABLE 7, or a combination of any amino acid substitutions identified in TABLE 7, and (ii) an M1 deletion (ΔM1), M1A substitution, M1D substitution, V6Y substitution, I187K substitution, C332A substitution, or a combination of any of the foregoing. For example, the recombinant mutant sialidase enzyme may comprise (i) an amino acid substitution identified in TABLE 7, or a combination of any amino acid substitutions identified in TABLE 7, and (ii) a combination of mutations selected from: M1A and V6Y; M1A and I187K; M1A and C332A; M1D and V6Y; M1D and I187K; M1D and C332A; ΔM1 and V6Y; ΔM1 and I187K; ΔM1 and C332A; V6Y and I187K; V6Y and

C332A; I187K and C332A; M1A, V6Y, and I187K; M1A, V6Y, and C332A; M1A, I187K, and C332A; M1D, V6Y, and I187K; M1D, V6Y, and C332A; M1D, I187K, and C332A; ΔM1, V6Y, and I187K; ΔM1, V6Y, and C332A; ΔM1, I187K, and C332A; V6Y, I187K, and C332A; M1A, V6Y, I187K, and C332A; M1D, V6Y, I187K, and C332A; and ΔM1, V6Y, I187K, and C332A.

[00132] In certain embodiments, the recombinant mutant sialidase enzyme comprises: (a) the M1D, V6Y, P62G, A93E, I187K, and C332A substitutions; (b) the M1D, V6Y, K9D, A93E, I187K, C332A, V363R, and L365I substitutions; (c) the M1D, V6Y, P62N, I187K, and C332A substitutions; (d) the M1D, V6Y, I187K, Q270A, S301R, W302K, and C332A substitutions; (e) the M1D, V6Y, P62S, I187K, Q270A, S301R, W302K, and C332A substitutions; (f) the M1D, V6Y, P62T, I187K, Q270A, S301R, W302K, and C332A substitutions; (g) the M1D, V6Y, P62N, I187K, Q270A, S301R, W302K, and C332A substitutions; (h) the M1D, V6Y, P62G, A93E, I187K, S301A, W302R, and C332A substitutions; (i) the M1D, V6Y, P62G, A93E, Q126Y, I187K, Q270T, and C332A substitutions; (j) the M1D, V6Y, P62G, A93E, Q126Y, I187K, and C332A substitutions; (k) the M1D, V6Y, P62G, A93E, Q126Y, I187K, A242F, Q270T, and C332A substitutions; (l) the M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, A242F, Q270T, and C332A substitutions; (m) the M1D, V6Y, P62G, A93E, Q112E, Q126Y, I187K, Q270T, A242F, and C332A; or (n) the M1D, V6Y, P62G, A93E, Q126Y, I187K, E225C, Q270T, A290C, A242F, C332A substitutions.

[00133] In certain embodiments, the recombinant mutant human sialidase further comprises a substitution of a serine residue at a position corresponding to position 301 of wild-type human Neu2 (S301) in combination with a substitution of a tryptophan residue at a position corresponding to position 302 of wild-type human Neu2 (W302). For example, the recombinant mutant human sialidase may comprise a combination of substitutions corresponding to a combination of substitutions listed in a row of TABLE 8 (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)). For example, the recombinant mutant human sialidase may comprise: the S301K and W302R substitutions; the S301K and W302K substitutions; or the S301A and W302S substitutions.

TABLE 8

Substitutions
S301A, W302R

Substitutions
S301A, W302S
S301A, W302T
S301K, W302S
S301N, W302S
S301T, W302S
S301T, W302T
S301T, W302R
S301A, W302A
S301K, W302R
S301K, W302T
S301N, W302T
S301K, W302K
S301P, W302R
S301P, W302S
S301P, W302T

[00134] In certain embodiments, the recombinant mutant human sialidase further comprises a combination of substitutions corresponding to a combination of substitutions listed in a row of **TABLE 9** (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)).

TABLE 9

Substitutions
M1D, V6Y, P62G, I187K, C332A
M1D, V6Y, K9D, I187K, C332A, V363R, L365I
M1D, V6Y, P62G, A93E, I187K, C332A
M1D, V6Y, K9D, I187K, C332A, V363R, L365K
M1D, V6Y, K9D, I187K, C332A, V363R, L365S
M1D, V6Y, K9D, I187K, C332A, V363R, L365Q
M1D, V6Y, K9D, I187K, C332A, V363R, L365H
M1D, V6Y, A93K, I187K, C332A
M1D, V6Y, A93E, I187K, C332A

Substitutions
V6Y, I187K, W292R
V6Y, G107D, I187K
V6Y, C125L
C125L, I187K
V6Y, C125L, I187K
M1D, V6Y, K45A, I187K, C332A
M1D, V6Y, Q270A, I187K, C332A
M1D, V6Y, K44R, K45R, I187K, C332A
M1D, V6Y, Q112R, I187K, C332A
M1D, V6Y, Q270F, I187K, C332A
M1D, V6Y, I187K, S301R, W302K, C332A
M1D, V6Y, K44E, K45E, I187K, C332A
M1D, V6Y, I187K, L217V, C332A
M1D, V6Y, I187K, L217A, C332A
M1D, V6Y, K44E, K45E, I187K, S301R, W302K, C332A
M1D, V6Y, Q112R, I187K, S301R, W302K, C332A
M1D, V6Y, I187K, Q270A, S301R, W302K, C332A
M1D, V6Y, K44E, K45E, Q112R, I187K, C332A
M1D, V6Y, K44E, K45E, I187K, Q270A, C332A
M1D, V6Y, K45A, I187K, Q270A, C332A
M1D, V6Y, I187K, Q270H, C332A
M1D, V6Y, I187K, Q270P, C332A
M1D, V6Y, Q112K, I187K, C332A
M1D, V6Y, P62S, I187K, Q270A, S301R, W302K, C332A
M1D, V6Y, P62T, I187K, Q270A, S301R, W302K, C332A
M1D, V6Y, P62N, I187K, Q270A, S301R, W302K, C332A
V6Y, P62H, I187K
V6Y, Q108H, I187K
M1D, V6Y, P62H, I187K, C332A
M1D, V6Y, P62G, I187K, C332A
V6Y, P62G, I187K

Substitutions
M1D, V6Y, P62H, I187K
M1D, V6Y, Q108H, I187K
M1D, V6Y, P62N, I187K, C332A
M1D, V6Y, P62D, I187K, C332A
M1D, V6Y, P62E, I187K, C332A
V6Y, C164G, I187K, T249A
V6Y, C164G, I187K
V6Y, Q126L, I187K D251G
V6Y, L54M, Q69H, R78K, A171G, I187K
V6Y, P62T, I187K
V6Y, A150V, I187K
P5H, V6Y, P62S, I187K
V6Y, C164G, I187K
Q126Y, Q170T
Q126Y, A242F, Q270T
M1D, V6Y, P62G, A93E, Q126E, I187K, C332A
M1D, V6Y, P62G, A93E, Q126I, I187K, C332A
M1D, V6Y, P62G, A93E, Q126L, I187K, C332A
M1D, V6Y, P62G, A93E, Q126Y, I187K, C332A
M1D, V6Y, P62G, A93E, Q126F, I187K, C332A
M1D, V6Y, P62G, A93E, Q126H, I187K, C332A
M1D, V6Y, P62G, A93E, I187K, Q270S, C332A
M1D, V6Y, P62G, A93E, I187K, Q270T, C332A
M1D, V6Y, P62G, A93E, Q126Y, I187K, Q270T, C332A
M1D, V6Y, P62G, A93E, Q126Y, I187K, A242F, Q270T, C332A
M1D, V6Y, P62G, D80P, A93E, I187K, C332A
M1D, V6Y, P62G, A93E, R170P, I187K, C332A
M1D, V6Y, P62G, A93E, I187K, Q188P, C332A
M1D, V6Y, P62G, A93E, I187K, R189P, C332A
M1D, V6Y, P62G, A93E, I187K, E225P, C332A
M1D, V6Y, P62G, A93E, I187K, H239P, C332A

Substitutions
M1D, V6Y, P62G, A93E, I187K, E257P, C332A
M1D, V6Y, P62G, A93E, I187K, S301A, C332A
M1D, V6Y, P62G, A93E, I187K, S301D, C332A
M1D, V6Y, P62G, A93E, I187K, S301E, C332A
M1D, V6Y, P62G, A93E, I187K, S301F, C332A
M1D, V6Y, P62G, A93E, I187K, S301H, C332A
M1D, V6Y, P62G, A93E, I187K, S301K, C332A
M1D, V6Y, P62G, A93E, I187K, S301L, C332A
M1D, V6Y, P62G, A93E, I187K, S301M, C332A
M1D, V6Y, P62G, A93E, I187K, S301N, C332A
M1D, V6Y, P62G, A93E, I187K, S301P, C332A
M1D, V6Y, P62G, A93E, I187K, S301Q, C332A
M1D, V6Y, P62G, A93E, I187K, S301R, C332A
M1D, V6Y, P62G, A93E, I187K, S301T, C332A
M1D, V6Y, P62G, A93E, I187K, S301V, C332A
M1D, V6Y, P62G, A93E, I187K, S301W, C332A
M1D, V6Y, P62G, A93E, I187K, S301Y, C332A
M1D, V6Y, P62G, A93E, I187K, W302A, C332A
M1D, V6Y, P62G, A93E, I187K, W302D, C332A
M1D, V6Y, P62G, A93E, I187K, W302F, C332A
M1D, V6Y, P62G, A93E, I187K, W302G, C332A
M1D, V6Y, P62G, A93E, I187K, W302H, C332A
M1D, V6Y, P62G, A93E, I187K, W302I, C332A
M1D, V6Y, P62G, A93E, I187K, W302L, C332A
M1D, V6Y, P62G, A93E, I187K, W302M, C332A
M1D, V6Y, P62G, A93E, I187K, W302N, C332A
M1D, V6Y, P62G, A93E, I187K, W302P, C332A
M1D, V6Y, P62G, A93E, I187K, W302Q, C332A
M1D, V6Y, P62G, A93E, I187K, W302R, C332A
M1D, V6Y, P62G, A93E, I187K, W302S, C332A
M1D, V6Y, P62G, A93E, I187K, W302T, C332A

Substitutions
M1D, V6Y, P62G, A93E, I187K, W302V, C332A
M1D, V6Y, P62G, A93E, I187K, W302Y, C332A
M1D, V6Y, P62G, A93E, I187K, S301A, W302A, C332A
M1D, V6Y, P62G, A93E, I187K, S301A, W302R, C332A
M1D, V6Y, P62G, A93E, I187K, S301A, W302S, C332A
M1D, V6Y, P62G, A93E, I187K, S301A, W302T, C332A
M1D, V6Y, P62G, A93E, I187K, S301K, W302S, C332A
M1D, V6Y, P62G, A93E, I187K, S301K, W302R, C332A
M1D, V6Y, P62G, A93E, I187K, S301K, W302T, C332A
M1D, V6Y, P62G, A93E, I187K, S301N, W302S, C332A
M1D, V6Y, P62G, A93E, I187K, S301N, W302T, C332A
M1D, V6Y, P62G, A93E, I187K, S301T, W302R, C332A
Q126Y, Q270T
Q126Y, A242F, Q270T
M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, A242F, Q270T, C332A
M1D, V6Y, P62G, A93E, Q112E, Q126Y, I187K, Q270T, A242F, C332A
M1D, V6Y, P62G, A93E, Q126Y, I187K, E225C, Q270T, A290C, A242F, C332A
V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F, C332A
M1D, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F, C332A
M1D, V6Y, P62G, A93E, Q126Y, I187K, Q270T, A242F, C332A
M1D, V6Y, A42R, A93E, Q126Y, I187K, Q270T, A242F, C332A
M1D, V6Y, A42R, P62G, Q126Y, I187K, Q270T, A242F, C332A
M1D, V6Y, A42R, P62G, A93E, I187K, Q270T, A242F, C332A
M1D, V6Y, A42R, P62G, A93E, Q126Y, Q270T, A242F, C332A
M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, C332A
M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, A242F, C332A
M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F

[00135] In certain embodiments, the sialidase comprises a substitution of M1, A42, and Q270, or a combination of any of the foregoing substitutions. These substitutions were found to, for example, improve the activity of the enzyme (see, Example 11). In certain embodiments, the sialidase comprises a substitution at each of M1, A42, and Q270. In

certain embodiments, the sialidase comprises a substitution selected from M1D, A42R, and Q270T, or a combination of any of the foregoing substitutions. In certain embodiments, the sialidase comprises each of the M1D, A42R, and Q270T substitutions.

[00136] In certain embodiments, the sialidase comprises a substitution of V6, P62, A93, Q126, and I187, or a combination of any of the foregoing substitutions. These substitutions were found to, for example, improve the expression/yield of the enzyme (see, Example 11). In certain embodiments, the sialidase comprises a substitution at each of V6, P62, A93, Q126, and I187. In certain embodiments, the sialidase comprises a substitution selected from V6Y, P62G, A93E, Q126Y, and I187K, or a combination of any of the foregoing substitutions. In certain embodiments, the sialidase comprises each of the V6Y, P62G, A93E, Q126Y, and I187K substitutions.

[00137] In certain embodiments, the sialidase comprises a substitution of M1, A42, A242, and Q270, or a combination of any of the foregoing substitutions. These substitutions were found to, for example, improve the stability of the enzyme (see, Example 11). In certain embodiments, the sialidase comprises a substitution at each of M1, A42, A242, and Q270. In certain embodiments, the sialidase comprises a substitution selected from M1D, A42R, A242F, and Q270T, or a combination of any of the foregoing substitutions. In certain embodiments, the sialidase comprises each of the M1D, A42R, A242F, and Q270T substitutions.

[00138] In certain embodiments, the recombinant mutant sialidase enzyme comprises: (a) the V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F, and C332A substitutions; (b) the ΔM1 deletion and the V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F, and C332A substitutions; (c) the M1D, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F, and C332A substitutions; (d) the M1D, V6Y, P62G, A93E, Q126Y, I187K, Q270T, A242F, and C332A substitutions; (e) the M1D, V6Y, A42R, A93E, Q126Y, I187K, Q270T, A242F, and C332A substitutions; (f) the M1D, V6Y, A42R, P62G, Q126Y, I187K, Q270T, A242F, and C332A substitutions; (g) the M1D, V6Y, A42R, P62G, A93E, I187K, Q270T, A242F, and C332A substitutions; (h) the M1D, V6Y, A42R, P62G, A93E, Q126Y, Q270T, A242F, and C332A substitutions; (i) the M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, and C332A substitutions; (j) the M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, A242F, and C332A substitutions; or (k) the M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, and A242F substitutions.

[00139] In certain embodiments, the sialidase comprises a substitution of M1, V6, A42, P62, A93, Q126, I187, A242, Q270, C332A, or a combination of any of the foregoing substitutions. In certain embodiments, the sialidase comprises a substitution at each of M1, V6, A42, P62, A93, Q126, I187, A242, Q270, and C332. In certain embodiments, the sialidase comprises a substitution selected from M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, A242F, Q270T, and C332A, or a combination of any of the foregoing substitutions. In certain embodiments, the sialidase comprises each of the M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, A242F, Q270T, and C332A substitutions.

[00140] In certain embodiments, the recombinant mutant human sialidase comprises the amino acid sequence of any one of SEQ ID NOs: 48-54, 149, 154, 159, 191, or 198, or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 48-54, 149, 154, 159, 191, or 198. In certain embodiments, the recombinant mutant human sialidase is then modified, or has been modified, to include one or more modifications to decrease protease sensitivity.

[00141] In certain embodiments, the recombinant mutant human sialidase comprises the amino acid sequence of

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_7SX_8X_9DEHAELIVX_{10}R$
$RGDYDAX_{11}THQVQWX_{12}AQEVVAQAX_{13}LX_{14}GHRSMNPCPLYDX_{15}QTGTLFLFFIAIPX_{16}X_{17}$
$VTEX_{18}QQLQTRANVTRLX_{19}X_{20}VTSTDHGRTWSSPRDLTDAAIGPX_{21}YREWSTFAVGPGHX_{22}$
$LQLHDX_{23}X_{24}RSLVVPAYAYRKLHPX_{25}X_{26}X_{27}PIPSAFX_{28}FLSHDHGRTWARGHFVX_{29}QDTX$
$_{30}ECQVAEVX_{31}TGEQRVVTLNARSX_{32}X_{33}X_{34}X_{35}RX_{36}QAQSX_{37}NX_{38}GLDFQX_{39}X_{40}QX_{41}VKK$
$LX_{42}EPPPX_{43}GX_{44}QGSVISFPSPRSGPGSPAQX_{45}LLYTHPTHX_{46}X_{47}QRADLGAYLNPRPPA$
$PEAWSEPX_{48}LLAKGSX_{49}AYSDLQSMGTGPDGSPLFGX_{50}LYEANDYEEIX_{51}FX_{52}MFTLKQAF$
PAEYLPQ (SEQ ID NO: 199),

wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Ala or Lys, X_3 is Asn or Leu, X_4 is Pro or His, X_5 is Phe, Trp, Tyr or Val, X_6 is Lys or Asp, X_7 is Ala or Arg, X_8 is Lys, Arg, or Glu, X_9 is Lys, Ala, Arg, or Glu, X_{10} is Leu or Met, X_{11} is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_{12} is Gln or His, X_{13} is Arg or Lys, X_{14} is Asp or Pro, X_{15} is Ala, Glu or Lys, X_{16} is Gly or Asp, X_{17} is Gln or His, X_{18} is Gln, Arg, or Lys, X_{19} is Ala, Cys, Ile, Ser, Val, or Leu, X_{20} is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_{21} is Ala or Val, X_{22} is Cys or Gly, X_{23} is Arg or Pro, X_{24} is Ala or Gly, X_{25} is Arg, Ile, or Lys, X_{26} is Gln or Pro, X_{27} is Arg or Pro, X_{28} is Ala, Cys, Leu, or Val, X_{29} is Ala, Cys, Asn, Ser, or Thr, X_{30} is Leu, Ala, or Val, X_{31} is Glu or Pro, X_{32} is His or Pro, X_{33} is Leu, Asp, Asn, or Tyr, X_{34} is Arg, Ala, Asp, Leu, Gln, or Tyr, X_{35} is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_{36} is Val, Ile, or Lys, X_{37} is Thr or Ala, X_{38} is Asp or

Gly, X_{39} is Glu, Lys, or Pro, X_{40} is Ser or Cys, X_{41} is Leu, Asp, Phe, Gln, or Thr, X_{42} is Val or Phe, X_{43} is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{44} is Cys or Val, X_{45} is Trp or Arg, X_{46} is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{47} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{48} is Lys or Val, X_{49} is Ala, Cys, Ser, or Val, X_{50} is Cys, Leu, or Val, X_{51} is Val or Arg, and X_{52} is Leu, Gln, His, Ile, Lys, or Ser, and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, the recombinant mutant human sialidase is then modified, or has been modified, to include one or more modifications to decrease protease sensitivity.

[00142] In certain embodiments, the recombinant mutant human sialidase comprises the amino acid sequence of

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_4SKKDEHAELIVLRRGDYD
AX_5THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_6QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCX_7VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX_8QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX_9RV
QAQSTNDGLDFQESQLVKKLVEPPPX$_{10}$GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX$_{11}$X$_{12}$
QRADLGAYLNPRPPAPEAWSEPVLLAKGSX$_{13}$AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX
$_{14}$FX$_{15}$MFTLKQAFPAEYLPQ (SEQ ID NO: 200),

wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Phe, Trp, Tyr or Val, X_3 is Lys or Asp, X_4 is Arg or Ala, X_5 is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_6 is Ala, Glu, or Lys, X_7 is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_8 is Arg, Ile, or Lys, X_9 is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_{10} is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{11} is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{12} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{13} is Ala, Cys, Ser, or Val, X_{14} is Val or Arg, and X_{15} is Leu, Gln, His, Ile, Lys, or Ser, and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, X_1 is Ala, Asp, Met, or not present, X_2 is Tyr or Val, X_3 is Lys or Asp, X_4 is Arg or Ala, X_5 is Pro, Asn, Gly, Ser or Thr, X_6 is Ala or Glu, X_7 is Gln or Tyr, X_8 is Ile or Lys, X_9 is Ala or Thr, X_{10} is Gln, Ala, or Thr, X_{11} is Ser, Arg, or Ala, X_{12} is Trp, Lys, or Arg, X_{13} is Ala or Cys, X_{14} is Val or Arg, and X_{15} is Leu or Ile. In certain embodiments, the recombinant mutant human sialidase is then modified, or has been modified, to include one or more modifications to decrease protease sensitivity.

[00143] In certain embodiments, the recombinant mutant human sialidase comprises the amino acid sequence of

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX_7X_8DEHAELIVX_9RR$
$GDYDAX_{10}THQVQWX_{11}AQEVVAQAX_{12}LDGHRSMNPCPLYDX_{13}QTGTLFLFFIAIPX_{14}X_{15}VT$
$EX_{16}QQLQTRANVTRLX_{17}X_{18}VTSTDHGRTWSSPRDLTDAAIGPX_{19}YREWSTFAVGPGHX_{20}LQ$
$LHDRX_{21}RSLVVPAYAYRKLHPX_{22}QRPIPSAFX_{23}FLSHDHGRTWARGHFVAQDTX_{24}ECQVAE$
$VETGEQRVVTLNARSHLRARVQAQSX_{25}NX_{26}GLDFQX_{27}SQLVKKLVEPPPX_{28}GX_{29}QGSVISF$
$PSPRSGPGSPAQX_{30}LLYTHPTHX_{31}X_{32}QRADLGAYLNPRPPAPEAWSEPX_{33}LLAKGSX_{34}AYS$
$DLQSMGTGPDGSPLFGX_{35}LYEANDYEEIX_{36}FX_{37}MFTLKQAFPAEYLPQ$

(SEQ ID NO: 47), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Ala or Lys, X_3 is Asn or Leu, X_4 is Pro or His, X_5 is Phe, Trp, Tyr or Val, X_6 is Lys or Asp; X_7 is Lys, Arg, or Glu. X_8 is Lys, Ala, Arg, or Glu, X_9 is Leu or Met, X_{10} is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_{11} is Gln or His, X_{12} is Arg or Lys, X_{13} is Ala, Glu or Lys, X_{14} is Gly or Asp, X_{15} is Gln or His, X_{16} is Gln, Arg, or Lys, X_{17} is Ala, Cys, Ile, Ser, Val, or Leu, X_{18} is Gln or Leu, X_{19} is Ala or Val, X_{20} is Cys or Gly, X_{21} is Ala or Gly, X_{22} is Arg, Ile, or Lys, X_{23} is Ala, Cys, Leu, or Val, X_{24} is Leu, Ala, or Val, X_{25} is Thr or Ala, X_{26} is Asp or Gly, X_{27} is Glu or Lys, X_{28} is Gln, Ala, His, Phe, or Pro, X_{29} is Cys or Val, X_{30} is Trp or Arg, X_{31} is Ser or Arg, X_{32} is Trp or Lys, X_{33} is Lys or Val, X_{34} is Ala, Cys, Ser, or Val, X_{35} is Cys, Leu, or Val, X_{36} is Val or Arg, and X_{37} is Leu, Gln, His, Ile, Lys, or Ser, and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, the recombinant mutant human sialidase is then modified, or has been modified, to include one or more modifications to decrease protease sensitivity.

[00144] In certain embodiments, the recombinant mutant human sialidase comprises the amino acid sequence of

$X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD$
$AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV$
$TRLCQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK$
$LHPX_6QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQ$
$AQSTNDGLDFQESQLVKKLVEPPPX_7GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX_8X_9QRA$
$DLGAYLNPRPPAPEAWSEPVLLAKGSX_{10}AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX_{11}FX$
$_{12}MFTLKQAFPAEYLPQ$

(SEQ ID NO: 46), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Phe, Trp, Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_5 is Ala, Glu, or Lys, X_6 is Arg, Ile, or Lys, X_7 is Gln, Ala, His, Phe, or Pro, X_8 is Ser or Arg, X_9 is Trp or Lys, X_{10} is Ala, Cys, Ser, or Val, X_{11} is Val or Arg, and X_{12} is Leu, Gln, His, Ile, Lys, or Ser, and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, X_1 is Ala, Asp, Met, or not present, X_2 is Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Gly, Ser or Thr, X_5 is Ala or Glu, X_6 is Ile or Lys, X_7 is Gln or Ala, X_8 is Ser or Arg, X_9 is Trp or Lys, X_{10} is Ala or

Cys, X_{11} is Val or Arg, and X_{12} is Leu or Ile. In certain embodiments, the recombinant mutant human sialidase is then modified, or has been modified, to include one or more modifications to decrease protease sensitivity.

[00145] In certain embodiments, the recombinant mutant human sialidase comprises the amino acid sequence of

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX_7X_8DEHAELIVX_9RR$
$GDYDAX_{10}THQVQWX_{11}AQEVVAQAX_{12}LX_{13}GHRSMNPCPLYDX_{14}QTGTLFLFFIAIPX_{15}X_{16}V$
$TEX_{17}QQLQTRANVTRLX_{18}X_{19}VTSTDHGRTWSSPRDLTDAAIGPX_{20}YREWSTFAVGPGHX_{21}L$
$QLHDX_{22}X_{23}RSLVVPAYAYRKLHPX_{24}X_{25}X_{26}PIPSAFX_{27}FLSHDHGRTWARGHFVX_{28}QDTX_{29}$
$ECQVAEVX_{30}TGEQRVVTLNARSX_{31}X_{32}X_{33}X_{34}RX_{35}QAQSX_{36}NX_{37}GLDFQX_{38}X_{39}QX_{40}VKKL$
$X_{41}EPPPX_{42}GX_{43}QGSVISFPSPRSGPGSPAQX_{44}LLYTHPTHX_{45}X_{46}QRADLGAYLNPRPPAP$
$EAWSEPX_{47}LLAKGSX_{48}AYSDLQSMGTGPDGSPLFGX_{49}LYEANDYEEIX_{50}FX_{51}MFTLKQAFP$
AEYLPQ

(SEQ ID NO: 182), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Ala or Lys, X_3 is Asn or Leu, X_4 is Pro or His, X_5 is Phe, Trp, Tyr or Val, X_6 is Lys or Asp, X_7 is Lys, Arg, or Glu, X_8 is Lys, Ala, Arg, or Glu, X_9 is Leu or Met, X_{10} is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_{11} is Gln or His, X_{12} is Arg or Lys, X_{13} is Asp or Pro, X_{14} is Ala, Glu or Lys, X_{15} is Gly or Asp, X_{16} is Gln or His, X_{17} is Gln, Arg, or Lys, X_{18} is Ala, Cys, Ile, Ser, Val, or Leu, X_{19} is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_{20} is Ala or Val, X_{21} is Cys or Gly, X_{22} is Arg or Pro, X_{23} is Ala or Gly, X_{24} is Arg, Ile, or Lys, X_{25} is Gln or Pro, X_{26} is Arg or Pro, X_{27} is Ala, Cys, Leu, or Val, X_{28} is Ala, Cys, Asn, Ser, or Thr, X_{29} is Leu, Ala, or Val, X_{30} is Glu or Pro, X_{31} is His or Pro, X_{32} is Leu, Asp, Asn, or Tyr, X_{33} is Arg, Ala, Asp, Leu, Gln, or Tyr, X_{34} is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_{35} is Val, Ile, or Lys, X_{36} is Thr or Ala, X_{37} is Asp or Gly, X_{38} is Glu, Lys, or Pro, X_{39} is Ser or Cys, X_{40} is Leu, Asp, Phe, Gln, or Thr, X_{41} is Val or Phe, X_{42} is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{43} is Cys or Val, X_{44} is Trp or Arg, X_{45} is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{46} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{47} is Lys or Val, X_{48} is Ala, Cys, Ser, or Val, X_{49} is Cys, Leu, or Val, X_{50} is Val or Arg, and X_{51} is Leu, Gln, His, Ile, Lys, or Ser, and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, the recombinant mutant human sialidase is then modified, or has been modified, to include one or more modifications to decrease protease sensitivity.

[00146] In certain embodiments, the recombinant mutant human sialidase comprises the amino acid sequence of

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCX_6VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX_7QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX_8RV
QAQSTNDGLDFQESQLVKKLVEPPPX$_9$GCQGSVISFPSPRSGPGSPAQWLLYTHPTH$X_{10}X_{11}$Q
RADLGAYLNPRPPAPEAWSEPVLLAKGSX_{12}AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX_{13}
FX_{14}MFTLKQAFPAEYLPQ

(SEQ ID NO: 183), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Phe, Trp, Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_5 is Ala, Glu, or Lys, X_6 is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_7 is Arg, Ile, or Lys, X_8 is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_9 is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{10} is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{11} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{12} is Ala, Cys, Ser, or Val, X_{13} is Val or Arg, and X_{14} is Leu, Gln, His, Ile, Lys, or Ser, and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, X_1 is Ala, Asp, Met, or not present, X_2 is Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Gly, Ser or Thr, X_5 is Ala or Glu, X_6 is Gln or Tyr, X_7 is Ile or Lys, X_8 is Ala or Thr, X_9 is Gln, Ala, or Thr, X_{10} is Ser, Arg, or Ala, X_{11} is Trp, Lys, or Arg, X_{12} is Ala or Cys, X_{13} is Val or Arg, and X_{14} is Leu or Ile. In certain embodiments, the recombinant mutant human sialidase is then modified, or has been modified, to include one or more modifications to decrease protease sensitivity.

[00147] In certain embodiments, the recombinant mutant human sialidase comprises a conservative substitution relative to a recombinant mutant human sialidase sequence disclosed herein. As used herein, the term "conservative substitution" refers to a substitution with a structurally similar amino acid. For example, conservative substitutions may include those within the following groups: Ser and Cys; Leu, Ile, and Val; Glu and Asp; Lys and Arg; Phe, Tyr, and Trp; and Gln, Asn, Glu, Asp, and His. Conservative substitutions may also be defined by the BLAST (Basic Local Alignment Search Tool) algorithm, the BLOSUM substitution matrix (e.g., BLOSUM 62 matrix), or the PAM substitution:p matrix (e.g., the PAM 250 matrix).

[00148] Sequence identity may be determined in various ways that are within the skill of a person skilled in the art, e.g., using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. BLAST (Basic Local Alignment Search Tool) analysis using the algorithm employed by the programs blastp, blastn, blastx,

tblastn and tblastx (Karlin et al., (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268; Altschul, (1993) J. Mol. Evol. 36:290-300; Altschul et al., (1997) Nucleic Acids Res. 25:3389-3402, incorporated by reference herein) are tailored for sequence similarity searching. For a discussion of basic issues in searching sequence databases see Altschul et al., (1994) Nature Genetics 6:119-129, which is fully incorporated by reference herein. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. The search parameters for histogram, descriptions, alignments, expect (i.e., the statistical significance threshold for reporting matches against database sequences), cutoff, matrix and filter are at the default settings. The default scoring matrix used by blastp, blastx, tblastn, and tblastx is the BLOSUM62 matrix (Henikoff et al., (1992) Proc. Natl. Acad. Sci. USA 89:10915-10919, fully incorporated by reference herein). Four blastn parameters may be adjusted as follows: Q=10 (gap creation penalty); R=10 (gap extension penalty); wink=1 (generates word hits at every wink.sup.th position along the query); and gapw=16 (sets the window width within which gapped alignments are generated). The equivalent blastp parameter settings may be Q=9; R=2; wink=1; and gapw=32. Searches may also be conducted using the NCBI (National Center for Biotechnology Information) BLAST Advanced Option parameter (e.g.: -G, Cost to open gap [Integer]: default = 5 for nucleotides/ 11 for proteins; -E, Cost to extend gap [Integer]: default = 2 for nucleotides/ 1 for proteins; -q, Penalty for nucleotide mismatch [Integer]: default = -3; -r, reward for nucleotide match [Integer]: default = 1; -e, expect value [Real]: default = 10; -W, wordsize [Integer]: default = 11 for nucleotides/ 28 for megablast/ 3 for proteins; -y, Dropoff (X) for blast extensions in bits: default = 20 for blastn/ 7 for others; -X, X dropoff value for gapped alignment (in bits): default = 15 for all programs, not applicable to blastn; and –Z, final X dropoff value for gapped alignment (in bits): 50 for blastn, 25 for others). ClustalW for pairwise protein alignments may also be used (default parameters may include, e.g., Blosum62 matrix and Gap Opening Penalty = 10 and Gap Extension Penalty = 0.1). A Bestfit comparison between sequences, available in the GCG package version 10.0, uses DNA parameters GAP=50 (gap creation penalty) and LEN=3 (gap extension penalty). The equivalent settings in Bestfit protein comparisons are GAP=8 and LEN=2.

II. Fusion Proteins/Antibody Conjugates

[00149] To promote the selective removal of sialic acids on hypersialylated cancer cells and/or in the tumor microenvironment, it may be helpful to target a sialidase as described herein to such a cell or to such a tumor microenvironment. Additionally, in order to promote the removal of sialic acid by a sialidase in a subject, it may be helpful to extend the plasma half-life of the sialidase in the subject. These can be achieved by including the sialidase in a fusion protein and/or antibody conjugate (*e.g.*, a chemically conjugated conjugate).

[00150] Accordingly, the invention further provides fusion proteins comprising a sialidase enzyme, or a functional fragment thereof, and a portion or fragment of an antibody, such as an immunoglobulin Fc domain (also referred to herein as an Fc domain), or an immunoglobulin antigen-binding domain (also referred to herein as an antigen-binding domain). In certain embodiments, the sialidase and antibody or portion thereof (*e.g.*, immunoglobulin Fc domain or antigen-binding domain) are linked by a peptide bond or an amino acid linker.

[00151] As used herein, unless otherwise indicated, the term "fusion protein" is understood to refer to a single polypeptide chain comprising amino acid sequences based upon two or more separate proteins or polypeptide chains, where the two amino acid sequences may be fused together directly or via an intervening linker sequence, *e.g.,* via an intervening amino acid linker. A nucleotide sequence encoding a fusion protein can, for example, be created using conventional recombinant DNA technologies.

[00152] In certain embodiments, the fusion protein comprises a tag, such as a Strep tag (*e.g.*, a Strep II tag), a His tag (*e.g.*, a 10x His tag), a myc tag, or a FLAG tag. The tag can be located on the C-terminus or the N-terminus of the fusion protein. In certain embodiments, a fusion protein comprises a sialidase portion joined to a polypeptide comprising an immunoglobulin heavy chain in an N- to C-terminal orientation, wherein the sialidase portion comprises an N-terminal addition of MEDLRP (SEQ ID NO: 4), and a Strep II Tag is located on the C-terminus of the immunoglobulin heavy chain or the N-terminus of the sialidase portion.

a. Sialidase portion

[00153] The sialidase portion of the fusion protein described herein can be any sialidase, *e.g.*, a fungal, bacterial, non-human mammalian or human sialidase. In certain embodiments, the sialidase portion is a recombinant human sialidase comprising at least one mutation

relative to a wild-type human sialidase, *e.g.*, a substitution, deletion, or addition of at least one amino acid, as described above.

[00154] In certain embodiments, the sialidase is any recombinant mutant human sialidase disclosed herein, or a functional fragment thereof.

[00155] In certain embodiments, the sialidase (*e.g.*, human sialidase) is engineered to include one or more modifications, for example, an amino acid deletion, amino acid addition, or amino acid substitution, to decrease protease sensitivity, and may then, alternatively or in addition, include one or more of the following substitutions.

[00156] In certain embodiments, the sialidase portion comprises a C332A and C352L mutation. In certain embodiments, the sialidase comprises an N-terminal addition of MEDLRP (SEQ ID NO: 4) or EDLRP (SEQ ID NO: 3). In certain embodiments, the sialidase portion comprises a LSHSLST (SEQ ID NO: 22) peptide on the N-terminus. In certain embodiments, the sialidase portion comprises an N-terminal addition of MEDLRP (SEQ ID NO: 4) and an A2K substitution. In certain embodiments, the sialidase portion comprises an N-terminal addition of MEDLRP (SEQ ID NO: 4) and a C332A substitution. In certain embodiments, the sialidase portion comprises an N-terminal addition of MEDLRP (SEQ ID NO: 4), a C332A substitution, and a C352L substitution.

[00157] In certain embodiments, the sialidase portion comprises an M1 deletion (ΔM1), M1A substitution, M1D substitution, V6Y substitution, K9D substitution, A42R substitution, P62G substitution, P62N substitution, P62S substitution, P62T substitution, A93E substitution, Q126Y substitution, I187K substitution, A242F substitution, A242T substitution, Q270A substitution, Q270T substitution, S301R substitution, S301R substitution, W302K substitution, W302R substitution, C332A substitution, V363R substitution, L365I substitution, or a combination of any of the foregoing.

[00158] In certain embodiments, the sialidase portion comprises the amino acid sequence of any one of SEQ ID NOs: 48-54, 149, 154, 159, 191, or 198, or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 48-54, 149, 154, 159, 191, or 198.

b. Antibody portion

[00159] As used herein, unless otherwise indicated, the term "antibody" is understood to mean an intact antibody (*e.g.*, an intact monoclonal antibody), or a fragment thereof, such as a Fc fragment of an antibody (*e.g.*, an Fc fragment of a monoclonal antibody), or an antigen-

binding fragment of an antibody (*e.g.*, an antigen-binding fragment of a monoclonal antibody), including an intact antibody, antigen-binding fragment, or Fc fragment that has been modified, engineered, or chemically conjugated. Examples of antigen-binding fragments include Fab, Fab', $(Fab')_2$, Fv, single chain antibodies (*e.g.*, scFv), minibodies, and diabodies. Examples of antibodies that have been modified or engineered include chimeric antibodies, humanized antibodies, and multispecific antibodies (*e.g.*, bispecific antibodies). An example of a chemically conjugated antibody is an antibody conjugated to a toxin moiety.

[00160] In certain embodiments, the fusion protein comprises an immunoglobulin Fc domain. As used herein, unless otherwise indicated, the term "immunoglobulin Fc domain" refers to a fragment of an immunoglobulin heavy chain constant region which, either alone or in combination with a second immunoglobulin Fc domain, is capable of binding to an Fc receptor. An immunoglobulin Fc domain may include, *e.g.*, immunoglobulin CH2 and CH3 domains. An immunoglobulin Fc domain may include, *e.g.*, immunoglobulin CH2 and CH3 domains and an immunoglobulin hinge region. Boundaries between immunoglobulin hinge regions, CH2, and CH3 domains are well known in the art, and can be found, *e.g.*, in the PROSITE database (available on the world wide web at prosite.expasy.org).

[00161] In certain embodiments, the immunoglobulin Fc domain is derived from a human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, and IgM Fc domain. A single amino acid substitution (S228P according to Kabat numbering; designated IgG4Pro) may be introduced to abolish the heterogeneity observed in recombinant IgG4 antibody. See Angal, S. *et al.* (1993) MOL. IMMUNOL. 30:105-108.

[00162] In certain embodiments, the immunoglobulin Fc domain is derived from a human IgG1 isotype or another isotype that elicits antibody-dependent cell-mediated cytotoxicity (ADCC) and/or complement mediated cytotoxicity (CDC). In certain embodiments, the immunoglobulin Fc domain is derived from a human IgG1 isotype (*e.g.,* SEQ ID NO: 31, SEQ ID NO: 5, or SEQ ID NO: 211).

[00163] In certain embodiments, the immunoglobulin Fc domain is derived from a human IgG4 isotype or another isotype that elicits little or no antibody-dependent cell-mediated cytotoxicity (ADCC) and/or complement mediated cytotoxicity (CDC). In certain embodiments, the immunoglobulin Fc domain is derived from a human IgG4 isotype.

[00164] In certain embodiments, the immunoglobulin Fc domain comprises either a "knob" mutation, *e.g.,* T366Y, or a "hole" mutation, *e.g.,* Y407T, for heterodimerization with a

second polypeptide (residue numbers according to EU numbering, Kabat, E.A., *et al.* (1991) SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST, FIFTH EDITION, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). For example, in certain embodiments, the immunoglobulin Fc domain is derived from a human IgG1 Fc domain and comprises a Y407T mutation (e.g., the fusion protein comprises SEQ ID NO: 32, SEQ ID NO: 147, SEQ ID NO: 213, or SEQ ID NO: 215). In certain embodiments, the immunoglobulin Fc domain is derived from a human IgG1 Fc domain and comprises a T366Y mutation (e.g., the fusion protein comprises SEQ ID NO: 33, SEQ ID NO: 148, SEQ ID NO: 214, or SEQ ID NO: 216).

[00165] In certain embodiments, the immunoglobulin Fc domain is modified to prevent glycosylation of the Fc domain. For example, in certain embodiments, the immunoglobulin Fc domain is derived from a human IgG1 Fc domain and comprises a mutation at position N297, for example, an N297A mutation (residue numbers according to EU numbering, Kabat, E.A., *et al.*, *supra*). For example, in certain embodiments, the fusion protein comprises SEQ ID NO: 212, SEQ ID NO: 215, or SEQ ID NO: 216.

[00166] In certain embodiments, the fusion protein comprises an immunoglobulin antigen-binding domain. The inclusion of such a domain may improve targeting of a fusion protein to a sialylated cancer cell and/or to the tumor microenvironment. As used herein, unless otherwise indicated, the term "immunoglobulin antigen-binding domain" refers to a polypeptide that, alone or in combination with another immunoglobulin antigen-binding domain, defines an antigen-binding site. Exemplary immunoglobulin antigen-binding domains include, for example, immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region, where the variable regions together define an antigen binding site.

[00167] The immunoglobulin antigen-binding domain and/or antigen binding site can be derived from an antibody selected from, for example, adecatumumab, ascrinvacumab, cixutumumab, conatumumab, daratumumab, drozitumab, duligotumab, durvalumab, dusigitumab, enfortumab, enoticumab, epratuxumab, figitumumab, ganitumab, glembatumumab, intetumumab, ipilimumab, iratumumab, icrucumab, lexatumumab, lucatumumab, mapatumumab, narnatumab, necitumumab, nesvacumab, ofatumumab, olaratumab, panitumumab, patritumab, pritumumab, radretumab, ramucirumab, rilotumumab, robatumumab, seribantumab, tarextumab, teprotumumab, tovetumab, vantictumab, vesencumab, votumumab, zalutumumab, flanvotumab, altumomab, anatumomab,

arcitumomab, bectumomab, blinatumomab, detumomab, ibritumomab, minretumomab, mitumomab, moxetumomab, naptumomab, nofetumomab, pemtumomab, pintumomab, racotumomab, satumomab, solitomab, taplitumomab, tenatumomab, tositumomab, tremelimumab, abagovomab, atezolizumab, durvalumab, avelumab, igovomab, oregovomab, capromab, edrecolomab, nacolomab, amatuximab, bavituximab, brentuximab, cetuximab, derlotuximab, dinutuximab, ensituximab, futuximab, girentuximab, indatuximab, isatuximab, margetuximab, rituximab, siltuximab, ublituximab, ecromeximab, abituzumab, alemtuzumab, bevacizumab, bivatuzumab, brontictuzumab, cantuzumab, cantuzumab, citatuzumab, clivatuzumab, dacetuzumab, demcizumab, dalotuzumab, denintuzumab, elotuzumab, emactuzumab, emibetuzumab, enoblituzumab, etaracizumab, farletuzumab, ficlatuzumab, gemtuzumab, imgatuzumab, inotuzumab, labetuzumab, lifastuzumab, lintuzumab, lirilumab, lorvotuzumab, lumretuzumab, matuzumab, milatuzumab, moxetumomab, nimotuzumab, obinutuzumab, ocaratuzumab, otlertuzumab, onartuzumab, oportuzumab, parsatuzumab, pertuzumab, pidilizumab, pinatuzumab, polatuzumab, sibrotuzumab, simtuzumab, tacatuzumab, tigatuzumab, trastuzumab, tucotuzumab, urelumab, vandortuzumab, vanucizumab, veltuzumab, vorsetuzumab, sofituzumab, catumaxomab, ertumaxomab, depatuxizumab, ontuxizumab, blontuvetmab, tamtuvetmab, nivolumab, pembrolizumab, epratuzumab, MEDI9447, urelumab, utomilumab, hu3F8, hu14.18-IL-2, 3F8/OKT3BsAb, lirilumab, BMS-986016 pidilizumab, AMP-224, AMP-514, BMS-936559, atezolizumab, and avelumab. In certain embodiments, the immunoglobulin antigen-binding domain can be derived from an antibody selected from trastuzumab, daratumumab, girentuximab, ofatumumab, avelumab, and rituximab.

[00168] In certain embodiments, the immunoglobulin antigen-binding domain is derived from trastuzumab. The trastuzumab heavy chain amino acid sequence is depicted in SEQ ID NO: 63, and the trastuzumab light chain amino acid sequence is depicted in SEQ ID NO: 64. The amino acid sequence of an exemplary scFv derived from trastuzumab is depicted in SEQ ID NO: 65.

[00169] The immunoglobulin antigen-binding domain and/or antigen binding site can be derived from an antibody that binds a cancer antigen selected from, for example, adenosine A2a receptor (A2aR), A kinase anchor protein 4 (AKAP4), B melanoma antigen (BAGE), brother of the regulator of imprinted sites (BORIS), breakpoint cluster region Abelson tyrosine kinase (BCR/ABL), CA125, CAIX, CD19, CD20, CD22, CD30, CD33, CD52, CD73, CD137, carcinoembryonic antigen (CEA), a claudin (*e.g.* a claudin 18, *e.g.,* claudin

18.2), CS1, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), estrogen receptor binding site associated antigen 9 (EBAG9), epidermal growth factor (EGF), epidermal growth factor receptor (EGFR), EGF-like module receptor 2 (EMR2), epithelial cell adhesion molecule (EpCAM) (17-1A), FR-alpha, G antigen (GAGE), disialoganglioside GD2 (GD2), glycoprotein 100 (gp100), human epidermal growth factor receptor 2 (HER2), hepatocyte growth factor (HGF), human papillomavirus 16 (HPV-16), heat-shock protein 105 (HSP105), isocitrate dehydrogenase type 1 (IDH1), idiotype (NeuGcGM3), indoleamine-2,3-dioxygenase 1 (IDO1), IGF-1, IGF1R, IGG1K, killer cell immunoglobulin-like receptor (KIR), lymphocyte activation gene 3 (LAG-3), lymphocyte antigen 6 complex K (LY6K), Matrix-metalloproteinase-16 (MMP16), melanotransferrin (MFI2), melanoma antigen 3 (MAGE-A3), melanoma antigen C2 (MAGE-C2), melanoma antigen D4 (MAGE-D4), melanoma antigen recognized by T-cells 1 (Melan-A/MART-1), N-methyl-N'-nitroso-guanidine human osteosarcoma transforming gene (MET), mucin 1 (MUC1), mucin 4 (MUC4), mucin 16 (MUC16), New York esophageal squamous cell carcinoma 1 (NY-ESO-1), prostatic acid phosphatase (PAP), programmed cell death receptor 1 (PD-1), programmed cell death receptor ligand 1 (PD-L1), phosphatidylserine, preferentially expressed antigen of melanoma (PRAME), prostate specific antigen (PSA), protein tyrosine kinase 7 (PTK7, also known as colon carcinoma kinase 4 (CCK4)), receptor tyrosine kinase orphan receptor 1 (ROR1), scatter factor receptor kinase, sialyl-Tn, sperm-associated antigen 9 (SPAG-9), synovial sarcoma X-chromosome breakpoint 1 (SSX1), survivin, telomerase, T-cell immunoglobulin domain and mucin domain-3 (TIM-3), vascular endothelial growth factor (VEGF) (*e.g.,* VEGF-A), vascular endothelial growth factor Receptor 2 (VEGFR2), V-domain immunoglobulin-containing suppressor of T-cell activation (VISTA),Wilms' Tumor-1 (WT1), X chromosome antigen 1b (XAGE-1b), 5T4, Mesothelin, Glypican 3 (GPC3), Folate Receptor α (FRα), Prostate Specific Membrane Antigen (PSMA), cMET, CD38, B Cell Maturation Antigen (BCMA), CD123, CLDN6, CLDN9, LRRC15, PRLR (Prolactin Receptor), RING finger protein 43 (RNF43), Uroplakin-1 B (UPK1 B), tumor necrosis factor superfamily member 9 (TNFSF9), tumor necrosis factor receptor superfamily member 21 (TNFSRF21), bone morphogenetic protein receptor type-1B (BMPR1B), Kringle domain-containing transmembrane protein 2 (KREMEN2), Delta-like protein 3 (DLL3), Siglec7 and Siglec9. Additional exemplary cancer antigens include those found on cancer stem cells, *e.g.,* SSEA3, SSEA4, TRA-1-60, TRA-1-81, SSEA1, CD133 (AC133), CD90 (Thy-1), CD326 (EpCAM), Cripto-1 (TDGF1), PODXL-1 (Podocalyxin-like protein 1), ABCG2, CD24,

CD49f (Integrin α6), Notch2, CD146 (MCAM), CD10 (Neprilysin), CD117 (c-KIT), CD26 (DPP-4), CXCR4, CD34, CD271, CD13 (Alanine aminopeptidase), CD56 (NCAM), CD105 (Endoglin), LGR5, CD114 (CSF3R), CD54 (ICAM-1), CXCR1, 2, TIM-3 (HAVCR2), CD55 (DAF), DLL4 (Delta-like ligand 4), CD20 (MS4A1), and CD96.

[00170] The invention further provides antibody conjugates containing one or more of the fusion proteins disclosed herein. As used herein, unless otherwise indicated, the term "antibody conjugate" is understood to refer to an antibody, or a functional fragment thereof, that comprises antigen-binding activity and/or Fc receptor-binding activity, conjugated (*e.g.*, covalently coupled) to an additional functional moiety. In certain embodiments, the antibody or functional antibody fragment is conjugated to a sialidase enzyme, *e.g.*, a recombinant mutant human sialidase enzyme disclosed herein. In certain embodiments, an antibody conjugate comprises a single polypeptide chain. In certain embodiments, an antibody conjugate comprises two, three, four, or more polypeptide chains that are covalently or non-covalently associated together to produce a multimeric complex, *e.g.*, a dimeric, trimeric or tetrameric complex.

[00171] **TABLE 10** shows antibodies and antibody-drug conjugates suitable for use in accordance with the present invention, the antigen bound by the antibody or antibody-drug conjugate, and for certain antibodies, the type of cancer targeted by the antibody or antibody-drug conjugate.

TABLE 10

Antibody or antibody-drug conjugate	**Cancer Antigen**	**Cancer Type**
oregovomab	CA125	
girentuximab	CAIX	
obinutuzumab	CD20	
ofatumumab	CD20	
rituximab	CD20	
alemtuzumab	CD52	
Ipilimumab	cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)	
tremelimumab	CTLA-4	
Cetuximab	epidermal growth factor receptor (EGFR)	
necitumumab	EGFR	
panitumumab	EGFR	
zalutumumab	EGFR	

Antibody or antibody-drug conjugate	Cancer Antigen	Cancer Type
edrecolomab	epithelial cell adhesion molecule (EpCAM) (17-1A)	
farletuzumab	FR-alpha	
Pertuzumab	human epidermal growth factor receptor 2 (HER2)	
trastuzumab	HER2	
rilotumumab	HGF	
figitumumab	IGF-1	
Ganitumab	IGF1R	
durvalumab	IGG1K	
bavituximab	Phosphatidylserine	
onartuzumab	scatter factor receptor kinase	
bevacizumab	vascular endothelial growth factor-A (VEGF-A)	
ramucirumab	vascular endothelial growth factor Receptor 2 (VEGFR2)	
blinatumomab	CD19	acute lymphoblastic leukemia (ALL)
Rituximab; ofatumumab; ibritumomab (*e.g.*, ^{90}Y-ibritumomab; tositumomab (*e.g.*, ^{131}I-tositumomab	CD20	non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL) B-cell NHL pre-B ALL
brentuximab (*e.g.*, brentuximab vedotin	CD30	Hodgkin's lymphoma
gemtuzumab (*e.g.*, gemtuzumab ozogamicin	CD33	acute myelogenous leukemia (AML)
Alemtuzumab	CD52	CLL
Ipilimumab	cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)	Unresectable or metastatic melanoma
cetuximab; panitumumab	epidermal growth factor receptor (EGFR)	colorectal cancer (CRC) Head and Neck
Catumaxomab	epithelial cell adhesion molecule (EpCAM)	Malignant ascites
trastuzumab; pertuzumab	human epidermal growth factor receptor 2 (HER2)	Breast
nivolumab; pembrolizumab	programmed cell death receptor 1 (PD-1)	Metastatic melanoma, non-small cell lung cancer (NSCLC)
Bevacizumab	vascular endothelial growth factor (VEGF)	Breast, Cervical CRC, NSCLC renal cell carcinoma (RCC), Ovarian Glioblastoma

Antibody or antibody-drug conjugate	Cancer Antigen	Cancer Type
Ramucirumab	vascular endothelial growth factor receptor 2 (VEGF-R2)	Gastric NSCLC
Epratuzumab; moxetumomab; inotuzumab (*e.g.*, inotuzumab ozogamicin)	CD22	acute lymphoblastic leukemia (ALL)
MEDI9447	CD73	Advanced solid tumors
Urelumab; utomilumab (PF-05082566)	CD137	Advanced solid tumors
Elotuzumab	CD2 subset 1 (CS1)	Multiple myeloma
Tremelimumab	cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)	Malignant mesothelioma
Necitumumab	epidermal growth factor receptor (EGFR)	non-small cell lung cancer (NSCLC)
dinutuximab; hu3F8; hu14.18-IL-2; 3F8/OKT3BsAb	disialoganglioside GD2 (GD2)	Neuroblastoma Retinoblastoma Melanoma other solid tumors
Racotumomab	Idiotype (NeuGcGM3)	NSCLC, Breast Melanoma
Lirilumab	killer cell immunoglobulin-like receptor (KIR)	Lymphoma
BMS-986016	lymphocyte activation gene 3 (LAG-3)	Breast, Hematological, Advanced solid tumors
Onartuzumab	N-methyl-N'-nitroso-guanidine human osteosarcoma transforming gene (MET)	NSCLC
abagovomab; oregovomab	mucin 16 (MUC16)	Ovarian
pidilizumab; AMP-224; AMP-514	programmed cell death receptor 1 (PD-1)	B-cell lymphoma Melanoma, CRC
BMS-936559; atezolizumab; durvalumab; avelumab	programmed cell death receptor ligand 1 (PD-L1)	NSCLC, renal cell carcinoma (RCC) Bladder, Breast Melanoma, squamous cell carcinoma of the head and neck (SCCHN)
naptumomab (*e.g.*, naptumomab estafenatox)	5T4	RCC, CRC Prostate

c. Linker

[00172] In certain embodiments, the sialidase portion of the fusion protein can be linked or fused directly to the antibody portion (*e.g.*, immunoglobulin Fc domain and/or

immunoglobulin antigen-binding domain) of the fusion protein. In other embodiments, the sialidase portion can be covalently bound to the antibody portion by a linker.

[00173] The linker may couple, with one or more natural amino acids, the sialidase, or functional fragment thereof, and the antibody portions or fragments, where the amino acid (for example, a cysteine amino acid) may be introduced by site-directed mutagenesis. The linker may include one or more unnatural amino acids. It is contemplated that, in certain circumstances, a linker containing for example, one or more sulfhydryl reactive groups (*e.g.*, a maleimide) may covalently link a cysteine in the sialidase portion or the antibody portion that is a naturally occurring cysteine residue or is the product of site-specific mutagenesis.

[00174] The linker may be a cleavable linker or a non-cleavable linker. Optionally or in addition, the linker may be a flexible linker or an inflexible linker.

[00175] The linker should be a length sufficiently long to allow the sialidase and the antibody portions to be linked without steric hindrance from one another and sufficiently short to retain the intended activity of the fusion protein. The linker preferably is sufficiently hydrophilic to avoid or minimize instability of the fusion protein. The linker preferably is sufficiently hydrophilic to avoid or minimize insolubility of the fusion protein. The linker should be sufficiently stable *in vivo* (*e.g.*, it is not cleaved by serum, enzymes, *etc.*) to permit the fusion protein to be operative *in vivo*.

[00176] The linker may be from about 1 angstroms (Å) to about 150 Å in length, or from about 1 Å to about 120 Å in length, or from about 5 Å to about 110 Å in length, or from about 10 Å to about 100 Å in length. The linker may be greater than about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 27, 30 or greater angstroms in length and/or less than about 110, 100, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, or fewer Å in length. Furthermore, the linker may be about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, and 120 Å in length.

[00177] In certain embodiments, the linker comprises a polypeptide linker that connects or fuses the sialidase portion of the fusion protein to the antibody portion (*e.g.*, immunoglobulin Fc domain and/or immunoglobulin antigen-binding domain) of the fusion protein. For example, it is contemplated that a gene encoding a sialidase portion linked directly or indirectly (for example, via an amino acid containing linker) to an antibody portion can be created and expressed using conventional recombinant DNA technologies. For example, the amino terminus of a sialidase portion can be linked to the carboxy terminus of either the light

or the heavy chain of an antibody portion. For example, for a Fab fragment, the amino terminus or carboxy terminus of the sialidase can be linked to the first constant domain of the heavy antibody chain (CH1). When a linker is employed, the linker may comprise hydrophilic amino acid residues, such as Gln, Ser, Gly, Glu, Pro, His and Arg. In certain embodiments, the linker is a peptide containing 1-25 amino acid residues, 1-20 amino acid residues, 2-15 amino acid residues, 3-10 amino acid residues, 3-7 amino acid residues, 4-25 amino acid residues, 4-20 amino acid residues, 4-15 amino acid residues, 4-10 amino acid residues, 5-25 amino acid residues, 5-20 amino acid residues, 5-15 amino acid residues, or 5-10 amino acid residues. Exemplary linkers include glycine and serine-rich linkers, *e.g.*, $(GlyGlyPro)_n$, or $(GlyGlyGlyGlySer)_n$, where n is 1-5. In certain embodiments, the linker comprises, consists, or consists essentially of GGGGS (SEQ ID NO: 184). In certain embodiments, the linker comprises, consists, or consists essentially of GGGGSGGGGS (SEQ ID NO: 145). In certain embodiments, the linker comprises, consists, or consists essentially of EPKSS (SEQ ID NO: 146). Additional exemplary linker sequences are disclosed, *e.g.*, in George *et al.* (2003) PROTEIN ENGINEERING 15:871–879, and U.S. Patent Nos. 5,482,858 and 5,525,491.

[00178] In certain embodiments, the fusion protein comprises the amino acid sequence of any one of SEQ ID NOs: 66-85, 98-142, 150-153, 155-158, 160-163, 166-178, 185, 187, 189, 192-197, 203-210, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, or 249, or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 66-85, 98-142, 150-153, 155-158, 160-163, 166-178, 185, 187, 189, 192-197, 203-210, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, or 249.

d. Antibody Conjugates

[00179] The invention further provides antibody conjugates comprising a fusion protein disclosed herein. The antibody conjugate may comprise a single polypeptide chain (*i.e.,* a fusion protein disclosed herein) or, the antibody conjugate may comprise additional polypeptide chains (*e.g.,* one, two, or three additional polypeptide chains). For example, an antibody conjugate may comprise a first polypeptide (fusion protein) comprising a recombinant mutant human sialidase enzyme and an immunoglobulin heavy chain, and a second polypeptide comprising an immunoglobulin light chain, where, for example, the immunoglobulin heavy and light chains together define a single antigen-binding site.

[00180] In certain embodiments, the antibody conjugate can include a single sialidase. In other embodiments, the antibody conjugate can include more than one (*e.g.,* two) sialidases. If more than one sialidase is included, the sialidases can be the same or different. In certain embodiments, the antibody conjugate can include a single antigen-binding site. In other embodiments, the antibody conjugate can include more than one (*e.g.*, two) antigen-binding sites. If two antigen-binding sites are used, they can be the same or different. In certain embodiments, the antibody conjugate comprises an immunoglobulin Fc fragment.

[00181] In certain embodiments, the antibody conjugate comprises one or two immunoglobulin heavy chains, or a functional fragment thereof. In certain embodiments, the antibody conjugate comprises one or two immunoglobulin light chains, or a functional fragment thereof. In certain embodiments, the antibody conjugate comprises a sialidase fused to the N- or C-terminus of an immunoglobulin heavy chain or an immunoglobulin light chain.

[00182] **FIGURE 9** depicts exemplary antibody conjugate constructs containing one or more sialidase enzymes. For example, in **FIGURE 9A**, a first antigen-binding site is depicted as 10, a second antigen-binding site is depicted as 20, a sialidase is depicted as 30, and a Fab is depicted as 40. In each of the constructs depicted in **FIGUREs 9A-9I** it is understood that the Fc may optionally be modified in some manner, *e.g.* using Knobs-into-Holes type technology, *e.g.*, as depicted by 50 in **FIGURE 9B**. Throughout **FIGURE 9** similar structures are depicted by similar schematic representations.

[00183] **FIGURE 9A** depicts antibody conjugate constructs comprising a first polypeptide comprising a first immunoglobulin light chain; a second polypeptide comprising a first immunoglobulin heavy chain; a third polypeptide comprising a second immunoglobulin heavy chain; and a fourth polypeptide comprising a second immunoglobulin light chain. The first and second polypeptides can be covalently linked together, the third and fourth polypeptides can be covalently linked together, and the second and third polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. In certain embodiments, the first polypeptide and the second polypeptide together define a first antigen-binding site as depicted as 10, and the third polypeptide and the fourth polypeptide together define a second antigen-binding site as depicted as 20. A sialidase enzyme as depicted as 30 can be conjugated to the N- or C-terminus of the first and second immunoglobulin light chain or the first and second immunoglobulin heavy chain.

[00184] **FIGURE 9B** depicts antibody conjugate constructs comprising a first polypeptide comprising a first immunoglobulin light chain; a second polypeptide comprising a first immunoglobulin heavy chain; a third polypeptide comprising a second immunoglobulin heavy chain; and a fourth polypeptide comprising a second immunoglobulin light chain. The first and second polypeptides can be covalently linked together, the third and fourth polypeptides can be covalently linked together, and the second and third polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. In certain embodiments, the first polypeptide and the second polypeptide together define a first antigen-binding site, and the third polypeptide and the fourth polypeptide together define a second antigen-binding site. A sialidase enzyme can be conjugated to the N- or C-terminus of the first immunoglobulin light chain or the first immunoglobulin heavy chain.

[00185] **FIGURE 9C** depicts antibody conjugate constructs comprising a first polypeptide comprising an immunoglobulin light chain; a second polypeptide comprising an immunoglobulin heavy chain; and a third polypeptide comprising an immunoglobulin Fc domain. The first and second polypeptides can be covalently linked together and the second and third polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. In certain embodiments, the first polypeptide and the second polypeptide together define an antigen-binding site. A sialidase enzyme can be conjugated to the N- or C-terminus of the first immunoglobulin light chain or the first immunoglobulin heavy chain.

[00186] **FIGURE 9D** depicts antibody conjugate constructs comprising a first polypeptide comprising an immunoglobulin light chain; a second polypeptide comprising an immunoglobulin heavy chain; and a third polypeptide comprising an immunoglobulin Fc domain and a first sialidase enzyme. The first and second polypeptides can be covalently linked together and the second and third polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. The third polypeptide comprises the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation. In certain embodiments, the first polypeptide and the second polypeptide together define an antigen-binding site. An optional second sialidase enzyme can be conjugated to the N- or C-terminus of the first immunoglobulin light chain or the first immunoglobulin heavy chain.

[00187] **FIGURE 9E** depicts antibody conjugate constructs comprising a first polypeptide comprising an immunoglobulin light chain; a second polypeptide comprising an immunoglobulin heavy chain; and a third polypeptide comprising an immunoglobulin Fc domain and a first sialidase enzyme. The first and second polypeptides can be covalently

linked together and the second and third polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. The third polypeptide comprises the immunoglobulin Fc domain and the sialidase in an N- to C-terminal orientation. In certain embodiments, the first polypeptide and the second polypeptide together define an antigen-binding site. An optional second sialidase enzyme can be conjugated to the N- or C-terminus of the first immunoglobulin light chain or the first immunoglobulin heavy chain.

[00188] **FIGURE 9F** depicts antibody conjugate constructs comprising a first polypeptide comprising a first immunoglobulin Fc domain, and a second polypeptide comprising a second immunoglobulin Fc domain. The first and second polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. A sialidase enzyme can be conjugated to the N- or C-terminus of the first immunoglobulin Fc domain or to the N- or C-terminus of the second immunoglobulin Fc domain. An optional second sialidase enzyme can be conjugated to the N- or C-terminus of the first immunoglobulin Fc domain or to the N- or C-terminus of the second immunoglobulin Fc domain.

[00189] **FIGURE 9G** depicts antibody conjugate constructs comprising a first polypeptide comprising an immunoglobulin light chain; and a second polypeptide comprising an immunoglobulin heavy chain variable region. The first and second polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. In certain embodiments, the first polypeptide and the second polypeptide together define an antigen-binding site. The sialidase enzyme can be conjugated to the N- or C-terminus of the immunoglobulin light chain or the immunoglobulin heavy chain variable region.

[00190] **FIGURE 9H** depicts antibody conjugate constructs comprising a first polypeptide comprising a first immunoglobulin Fc domain, and a second polypeptide comprising a second immunoglobulin Fc domain. The first and second polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. A sialidase enzyme can be conjugated to the N-terminus of the first immunoglobulin Fc domain or the second immunoglobulin Fc domain. An optional second sialidase enzyme can be conjugated to the N-terminus of the second immunoglobulin Fc domain or the first immunoglobulin Fc domain, respectively. A single chain variable fragment (scFv) can be conjugated to the C-terminus of the first immunoglobulin Fc domain or the second immunoglobulin Fc domain. An optional second single chain variable fragment (scFv) can be conjugated to the C-terminus of the first immunoglobulin Fc domain or the second immunoglobulin Fc domain, respectively.

[00191] **FIGURE 9I** depicts antibody conjugate constructs similar to those depicted in **FIGURE 9H** except that each scFv is replaced with an immunoglobulin antigen binding fragment, *e.g.*, a Fab. For example, **FIGURE 9I** depicts antibody conjugate constructs comprising a first polypeptide comprising a first immunoglobulin Fc domain, and a second polypeptide comprising a second immunoglobulin Fc domain. The first and second polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. A sialidase enzyme can be conjugated to the N-terminus of the first immunoglobulin Fc domain or the second immunoglobulin Fc domain. An optional second sialidase enzyme can be conjugated to the N-terminus of the second immunoglobulin Fc domain or the first immunoglobulin Fc domain, respectively. An antibody fragment (Fab) can be conjugated or fused to the C-terminus of the first immunoglobulin Fc domain or the second immunoglobulin Fc domain. An optional second antibody fragment (Fab) can be conjugated or fused to the C-terminus of the second immunoglobulin Fc domain or the first immunoglobulin Fc domain, respectively. In the case of a fusion, the C terminus of the Fc domain is linked (either by a bond or an amino acid linker) to a first polypeptide chain defining an immunoglobulin antigen binding fragment. In the case of antibodies that have an antigen binding site defined by a single variable region, then this may be sufficient to impart binding affinity to a target antigen. In other instances, *e.g.*, in the case of a human antibody, the first polypeptide chain defining an immunoglobulin antigen binding fragment can be conjugated (*e.g.*, covalently conjugated, *e.g.*, via a disulfide bond) to a second polypeptide chain defining an immunoglobulin antigen binding fragment, there the two antigen binding fragments together define an antigen binding site for binding the target antigen.

[00192] **FIGURE 10** depicts additional antibody conjugate constructs. For example, **FIGURE 10** depicts an antibody conjugate construct comprising a first polypeptide comprising an immunoglobulin light chain; a second polypeptide comprising an immunoglobulin heavy chain and an scFv; and a third polypeptide comprising an immunoglobulin Fc domain and a first sialidase enzyme. The first and second polypeptides can be covalently linked together and the second and third polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. The second polypeptide comprises the heavy chain and the scFv in an N- to C-terminal orientation. The third polypeptide comprises the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation. In certain embodiments, the first polypeptide and the second polypeptide together define a first antigen-binding site. In certain embodiments, the scFv

defines a second antigen-binding site. **FIGURE 10** depicts an additional antibody construct comprising a first polypeptide comprising an immunoglobulin light chain; a second polypeptide comprising an immunoglobulin heavy chain; and a third polypeptide comprising an immunoglobulin Fc domain and a first sialidase enzyme, wherein a Fab fragment is conjugated to the N-terminus of the immunoglobulin heavy chain. The first and second polypeptides can be covalently linked together and the second and third polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. The third polypeptide comprises the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation. In certain embodiments, the first polypeptide and the second polypeptide together define a first antigen-binding site. In certain embodiments, the Fab fragment defines a second antigen-binding site. In each of the constructs depicted in **FIGURE 10** it is understood that an scFv, when present, may be replaced with a Fab fragment, or a Fab fragment, when present, may be replaced with an scFv. In each of the constructs depicted in **FIGURE 10**, it is understood that the Fc may optionally be modified in some manner.

[00193] In certain embodiments, the antibody conjugate comprises a first polypeptide comprising a first immunoglobulin light chain; a second polypeptide comprising a first immunoglobulin heavy chain and a first sialidase; a third polypeptide comprising a second immunoglobulin heavy chain and a second sialidase; and a fourth polypeptide comprising a second immunoglobulin light chain. An example of this embodiment is shown in **FIGURE 11A**. The first and second polypeptides can be covalently linked together, the third and fourth polypeptides can be covalently linked together, and the second and third polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. In certain embodiments, the first polypeptide and the second polypeptide together define a first antigen-binding site, and the third polypeptide and the fourth polypeptide together define a second antigen-binding site. In certain embodiments, the second and third polypeptides comprise the first and second immunoglobulin heavy chain and the first and second sialidase, respectively, in an N- to C-terminal orientation. In certain embodiments, the second and third polypeptides comprise the first and second sialidase and the first and second immunoglobulin heavy chain, respectively, in an N- to C-terminal orientation.

[00194] In certain embodiments, the antibody conjugate comprises a first polypeptide comprising an immunoglobulin light chain; a second polypeptide comprising an immunoglobulin heavy chain; and a third polypeptide comprising an immunoglobulin Fc

domain and a sialidase. An example of this embodiment is shown in **FIGURE 11B**. The first and second polypeptides can be covalently linked together and the second and third polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. In certain embodiments, the first polypeptide and the second polypeptide together define an antigen-binding site. In certain embodiments, the third polypeptide comprises the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation, or the immunoglobulin Fc domain and the sialidase in an N- to C-terminal orientation.

[00195] In certain embodiments, the first polypeptide comprises the amino acid sequence of SEQ ID NO: 66, or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 66. In certain embodiments, the second polypeptide comprises the amino acid sequence of SEQ ID NO: 67 or 189 or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 67 or 189. In certain embodiments, the third polypeptide comprises the amino acid sequence of any one of SEQ ID NOs: 68-74, 98-112, 150, 151, 155, 156, 160, 161, 185, 187, 192, 195, 203-208, or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 68-74, 98-112, 150, 151, 155, 156, 160, 161, 185, 187, 192, 195, or 203-208.

[00196] In certain embodiments, the third polypeptide comprises the amino acid sequence of

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_7SX_8X_9DEHAELIVX_{10}R$
$RGDYDAX_{11}THQVQWX_{12}AQEVVAQAX_{13}LX_{14}GHRSMNPCPLYDX_{15}QTGTLFLFFIAIPX_{16}X_{17}$
$VTEX_{18}QQLQTRANVTRLX_{19}X_{20}VTSTDHGRTWSSPRDLTDAAIGPX_{21}YREWSTFAVGPGHX_{22}$
$LQLHDX_{23}X_{24}RSLVVPAYAYRKLHPX_{25}X_{26}X_{27}PIPSAFX_{28}FLSHDHGRTWARGHFVX_{29}QDTX_{30}$
$ECQVAEVX_{31}TGEQRVVTLNARSX_{32}X_{33}X_{34}X_{35}RX_{36}QAQSX_{37}NX_{38}GLDFQX_{39}X_{40}QX_{41}VKK$
$LX_{42}EPPPX_{43}GX_{44}QGSVISFPSPRSGPGSPAQX_{45}LLYTHPTHX_{46}X_{47}QRADLGAYLNPRPPA$
$PEAWSEPX_{48}LLAKGSX_{49}AYSDLQSMGTGPDGSPLFGX_{50}LYEANDYEEIX_{51}FX_{52}MFTLKQAF$
$PAEYLPQX_{53}DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV$
$KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT$
$ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV$
$LDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK$ (SEQ ID NO: 201),

wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Ala or Lys, X_3 is Asn or Leu, X_4 is Pro or His, X_5 is Phe, Trp, Tyr or Val, X_6 is Lys or Asp, X_7 is Ala or Arg, X_8 is Lys, Arg, or Glu, X_9 is Lys, Ala, Arg, or Glu, X_{10} is Leu or Met, X_{11} is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_{12} is Gln or His, X_{13} is Arg or Lys, X_{14} is Asp or Pro, X_{15} is Ala, Glu or Lys, X_{16} is Gly or Asp, X_{17} is Gln or His, X_{18} is Gln, Arg, or Lys, X_{19} is Ala, Cys, Ile, Ser, Val, or Leu, X_{20} is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_{21}

is Ala or Val, X_{22} is Cys or Gly, X_{23} is Arg or Pro, X_{24} is Ala or Gly, X_{25} is Arg, Ile, or Lys, X_{26} is Gln or Pro, X_{27} is Arg or Pro, X_{28} is Ala, Cys, Leu, or Val, X_{29} is Ala, Cys, Asn, Ser, or Thr, X_{30} is Leu, Ala, or Val, X_{31} is Glu or Pro, X_{32} is His or Pro, X_{33} is Leu, Asp, Asn, or Tyr, X_{34} is Arg, Ala, Asp, Leu, Gln, or Tyr, X_{35} is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_{36} is Val, Ile, or Lys, X_{37} is Thr or Ala, X_{38} is Asp or Gly, X_{39} is Glu, Lys, or Pro, X_{40} is Ser or Cys, X_{41} is Leu, Asp, Phe, Gln, or Thr, X_{42} is Val or Phe, X_{43} is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{44} is Cys or Val, X_{45} is Trp or Arg, X_{46} is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{47} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{48} is Lys or Val, X_{49} is Ala, Cys, Ser, or Val, X_{50} is Cys, Leu, or Val, X_{51} is Val or Arg, X_{52} is Leu, Gln, His, Ile, Lys, or Ser, and X_{53} is GGGGS (SEQ ID NO: 184), GGGGSGGGGS (SEQ ID NO: 145), or EPKSS (SEQ ID NO: 146), and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1).

[00197] In certain embodiments, the third polypeptide comprises the amino acid sequence of

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_4SKKDEHAELIVLRRGDYD
AX_5THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_6QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCX_7VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX_8QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX_9RV
QAQSTNDGLDFQESQLVKKLVEPPPX$_{10}$GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX$_{11}$X$_{12}$
QRADLGAYLNPRPPAPEAWSEPVLLAKGSX$_{13}$AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX
$_{14}$FX$_{15}$MFTLKQAFPAEYLPQX$_{16}$DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
K (SEQ ID NO: 202),

wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Phe, Trp, Tyr or Val, X_3 is Lys or Asp, X_4 is Arg or Ala, X_5 is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_6 is Ala, Glu, or Lys, X_7 is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_8 is Arg, Ile, or Lys, X_9 is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_{10} is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{11} is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{12} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{13} is Ala, Cys, Ser, or Val, X_{14} is Val or Arg, X_{15} is Leu, Gln, His, Ile, Lys, or Ser, and X_{16} is GGGGS (SEQ ID NO: 184), GGGGSGGGGS (SEQ ID NO: 145), or EPKSS (SEQ ID NO: 146), and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, X_1 is Ala, Asp, Met, or not present, X_2 is Tyr or Val, X_3 is Lys or Asp, X_4 is Arg or Ala, X_5 is Pro, Asn, Gly, Ser or Thr, X_6 is Ala or Glu, X_7 is

Gln or Tyr, X_8 is Ile or Lys, X_9 is Ala or Thr, X_{10} is Gln, Ala, or Thr, X_{11} is Ser, Arg, or Ala, X_{12} is Trp, Lys, or Arg, X_{13} is Ala or Cys, X_{14} is Val or Arg, and X_{15} is Leu or Ile.

[00198] In certain embodiments, the third polypeptide comprises the amino acid sequence of

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX_7X_8DEHAELIVX_9RR$
$GDYDAX_{10}THQVQWX_{11}AQEVVAQAX_{12}LDGHRSMNPCPLYDX_{13}QTGTLFLFFIAIPX_{14}X_{15}VT$
$EX_{16}QQLQTRANVTRLX_{17}X_{18}VTSTDHGRTWSSPRDLTDAAIGPX_{19}YREWSTFAVGPGHX_{20}LQ$
$LHDRX_{21}RSLVVPAYAYRKLHPX_{22}QRPIPSAFX_{23}FLSHDHGRTWARGHFVAQDTX_{24}ECQVAE$
VETGEQRVVTLNARSHLRARVQAQSX$_{25}$NX$_{26}$GLDFQX$_{27}$SQLVKKLVEPPPX$_{28}$GX$_{29}$QGSVISF
PSPRSGPGSPAQX$_{30}$LLYTHPTHX$_{31}$X$_{32}$QRADLGAYLNPRPPAPEAWSEPX$_{33}$LLAKGSX$_{34}$AYS
DLQSMGTGPDGSPLFGX$_{35}$LYEANDYEEIX$_{36}$FX$_{37}$MFTLKQAFPAEYLPQGGGGSGGGGSDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

(SEQ ID NO: 76), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Ala or Lys, X_3 is Asn or Leu, X_4 is Pro or His, X_5 is Phe, Trp, Tyr or Val, X_6 is Lys or Asp; X_7 is Lys, Arg, or Glu. X_8 is Lys, Ala, Arg, or Glu, X_9 is Leu or Met, X_{10} is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_{11} is Gln or His, X_{12} is Arg or Lys, X_{13} is Ala, Glu or Lys, X_{14} is Gly or Asp, X_{15} is Gln or His, X_{16} is Gln, Arg, or Lys, X_{17} is Ala, Cys, Ile, Ser, Val, or Leu, X_{18} is Gln or Leu, X_{19} is Ala or Val, X_{20} is Cys or Gly, X_{21} is Ala or Gly, X_{22} is Arg, Ile, or Lys, X_{23} is Ala, Cys, Leu, or Val, X_{24} is Leu, Ala, or Val, X_{25} is Thr or Ala, X_{26} is Asp or Gly, X_{27} is Glu or Lys, X_{28} is Gln, Ala, His, Phe, or Pro, X_{29} is Cys or Val, X_{30} is Trp or Arg, X_{31} is Ser or Arg, X_{32} is Trp or Lys, X_{33} is Lys or Val, X_{34} is Ala, Cys, Ser, or Val, X_{35} is Cys, Leu, or Val, X_{36} is Val or Arg, and X_{37} is Leu, Gln, His, Ile, Lys, or Ser, and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1).

[00199] In certain embodiments, the third polypeptide comprises the amino acid sequence of

$X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD$
$AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV$
$TRLCQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK$
$LHPX_6QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQ$
$AQSTNDGLDFQESQLVKKLVEPPPX_7GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX_8X_9QRA$
$DLGAYLNPRPPAPEAWSEPVLLAKGSX_{10}AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX_{11}FX$
$_{12}$MFTLKQAFPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPGK

(SEQ ID NO: 75), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Phe, Trp, Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Asp,

His, Glu, Gly, Ser or Thr, X_5 is Ala, Glu, or Lys, X_6 is Arg, Ile, or Lys, X_7 is Gln, Ala, His, Phe, or Pro, X_8 is Ser or Arg, X_9 is Trp or Lys, X_{10} is Ala, Cys, Ser, or Val, X_{11} is Val or Arg, and X_{12} is Leu, Gln, His, Ile, Lys, or Ser, and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, X_1 is Ala, Asp, Met, or not present, X_2 is Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Gly, Ser or Thr, X_5 is Ala or Glu, X_6 is Ile or Lys, X_7 is Gln or Ala, X_8 is Ser or Arg, X_9 is Trp or Lys, X_{10} is Ala or Cys, X_{11} is Val or Arg, and X_{12} is Leu or Ile.

[00200] In certain embodiments, the third polypeptide comprises the amino acid sequence of

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX_7X_8DEHAELIVX_9RR$
$GDYDAX_{10}THQVQWX_{11}AQEVVAQAX_{12}LDGHRSMNPCPLYDX_{13}QTGTLFLFFIAIPX_{14}X_{15}VT$
$EX_{16}QQLQTRANVTRLX_{17}X_{18}VTSTDHGRTWSSPRDLTDAAIGPX_{19}YREWSTFAVGPGHX_{20}LQ$
$LHDRX_{21}RSLVVPAYAYRKLHPX_{22}QRPIPSAFX_{23}FLSHDHGRTWARGHFVAQDTX_{24}ECQVAE$
$VETGEQRVVTLNARSHLRARVQAQSX_{25}NX_{26}GLDFQX_{27}SQLVKKLVEPPPX_{28}GX_{29}QGSVISF$
$PSPRSGPGSPAQX_{30}LLYTHPTHX_{31}X_{32}QRADLGAYLNPRPPAPEAWSEPX_{33}LLAKGSX_{34}AYS$
$DLQSMGTGPDGSPLFGX_{35}LYEANDYEEIX_{36}FX_{37}MFTLKQAFPAEYLPQX_{38}DKTHTCPPCPA$
PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

(SEQ ID NO: 144), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Ala or Lys, X_3 is Asn or Leu, X_4 is Pro or His, X_5 is Phe, Trp, Tyr or Val, X_6 is Lys or Asp; X_7 is Lys, Arg, or Glu. X_8 is Lys, Ala, Arg, or Glu, X_9 is Leu or Met, X_{10} is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_{11} is Gln or His, X_{12} is Arg or Lys, X_{13} is Ala, Glu or Lys, X_{14} is Gly or Asp, X_{15} is Gln or His, X_{16} is Gln, Arg, or Lys, X_{17} is Ala, Cys, Ile, Ser, Val, or Leu, X_{18} is Gln or Leu, X_{19} is Ala or Val, X_{20} is Cys or Gly, X_{21} is Ala or Gly, X_{22} is Arg, Ile, or Lys, X_{23} is Ala, Cys, Leu, or Val, X_{24} is Leu, Ala, or Val, X_{25} is Thr or Ala, X_{26} is Asp or Gly, X_{27} is Glu or Lys, X_{28} is Gln, Ala, His, Phe, or Pro, X_{29} is Cys or Val, X_{30} is Trp or Arg, X_{31} is Ser or Arg, X_{32} is Trp or Lys, X_{33} is Lys or Val, X_{34} is Ala, Cys, Ser, or Val, X_{35} is Cys, Leu, or Val, X_{36} is Val or Arg, X_{37} is Leu, Gln, His, Ile, Lys, or Ser, X_{38} is GGGGSGGGGS (SEQ ID NO: 145) or EPKSS (SEQ ID NO: 146), and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1).

[00201] In certain embodiments, the third polypeptide comprises the amino acid sequence of

$X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD$
$AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV$
$TRLCQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK$
$LHPX_6QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQ$
$AQSTNDGLDFQESQLVKKLVEPPPX_7GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX_8X_9QRA$
$DLGAYLNPRPPAPEAWSEPVLLAKGSX_{10}AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX_{11}FX$
$_{12}MFTLKQAFPAEYLPQX_{13}DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV$

DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

(SEQ ID NO: 143), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Phe, Trp, Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_5 is Ala, Glu, or Lys, X_6 is Arg, Ile, or Lys, X_7 is Gln, Ala, His, Phe, or Pro, X_8 is Ser or Arg, X_9 is Trp or Lys, X_{10} is Ala, Cys, Ser, or Val, X_{11} is Val or Arg, X_{12} is Leu, Gln, His, Ile, Lys, or Ser, and X_{13} is GGGGSGGGGS (SEQ ID NO: 145) or EPKSS (SEQ ID NO: 146), and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, X_1 is Ala, Asp, Met, or not present, X_2 is Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Gly, Ser or Thr, X_5 is Ala or Glu, X_6 is Ile or Lys, X_7 is Gln or Ala, X_8 is Ser or Arg, X_9 is Trp or Lys, X_{10} is Ala or Cys, X_{11} is Val or Arg, and X_{12} is Leu or Ile.

[00202] In certain embodiments, the third polypeptide comprises the amino acid sequence of

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX_7X_8DEHAELIVX_9RR$
$GDYDAX_{10}THQVQWX_{11}AQEVVAQAX_{12}LX_{13}GHRSMNPCPLYDX_{14}QTGTLFLFFIAIPX_{15}X_{16}V$
$TEX_{17}QQLQTRANVTRLX_{18}X_{19}VTSTDHGRTWSSPRDLTDAAIGPX_{20}YREWSTFAVGPGHX_{21}L$
$QLHDX_{22}X_{23}RSLVVPAYAYRKLHPX_{24}X_{25}X_{26}PIPSAFX_{27}FLSHDHGRTWARGHFVX_{28}QDTX_{29}$
$ECQVAEVX_{30}TGEQRVVTLNARSX_{31}X_{32}X_{33}X_{34}RX_{35}QAQSX_{36}NX_{37}GLDFQX_{38}X_{39}QX_{40}VKKL$
$X_{41}EPPPX_{42}GX_{43}QGSVISFPSPRSGPGSPAQX_{44}LLYTHPTHX_{45}X_{46}QRADLGAYLNPRPPAP$
$EAWSEPX_{47}LLAKGSX_{48}AYSDLQSMGTGPDGSPLFGX_{49}LYEANDYEEIX_{50}FX_{51}MFTLKQAFP$
AEYLPQX$_{52}$DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

(SEQ ID NO: 165), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Ala or Lys, X_3 is Asn or Leu, X_4 is Pro or His, X_5 is Phe, Trp, Tyr or Val, X_6 is Lys or Asp, X_7 is Lys, Arg, or Glu, X_8 is Lys, Ala, Arg, or Glu, X_9 is Leu or Met, X_{10} is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_{11} is Gln or His, X_{12} is Arg or Lys, X_{13} is Asp or Pro, X_{14} is Ala, Glu or Lys, X_{15} is Gly or Asp, X_{16} is Gln or His, X_{17} is Gln, Arg, or Lys, X_{18} is Ala, Cys, Ile, Ser, Val, or Leu, X_{19} is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_{20} is Ala or Val, X_{21} is Cys or Gly, X_{22} is Arg or Pro, X_{23} is Ala or Gly, X_{24} is Arg, Ile, or Lys, X_{25} is Gln or Pro, X_{26} is Arg or Pro, X_{27} is Ala, Cys, Leu, or Val, X_{28} is Ala, Cys, Asn, Ser, or Thr, X_{29} is Leu, Ala, or Val, X_{30} is Glu or Pro, X_{31} is His or Pro, X_{32} is Leu, Asp, Asn, or Tyr, X_{33} is Arg, Ala, Asp, Leu, Gln, or Tyr, X_{34} is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_{35} is Val, Ile, or Lys, X_{36} is Thr or Ala, X_{37} is Asp or Gly, X_{38} is Glu, Lys, or Pro, X_{39} is Ser or Cys, X_{40} is Leu, Asp, Phe, Gln, or Thr, X_{41} is Val or Phe, X_{42} is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{43} is Cys or Val, X_{44} is Trp or Arg, X_{45} is

Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{46} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{47} is Lys or Val, X_{48} is Ala, Cys, Ser, or Val, X_{49} is Cys, Leu, or Val, X_{50} is Val or Arg, X_{51} is Leu, Gln, His, Ile, Lys, or Ser, X_{52} is GGGGS (SEQ ID NO: 184), GGGGSGGGGS (SEQ ID NO: 145), or EPKSS (SEQ ID NO: 146), and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1).

[00203] In certain embodiments, the third polypeptide comprises the amino acid sequence of

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCX_6VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX_7QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX_8RV
QAQSTNDGLDFQESQLVKKLVEPPPX$_9$GCQGSVISFPSPRSGPGSPAQWLLYTHPTH$X_{10}X_{11}$Q
RADLGAYLNPRPPAPEAWSEPVLLAKGSX_{12}AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX_{13}
FX_{14}MFTLKQAFPAEYLPQX_{15}DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

(SEQ ID NO: 164), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Phe, Trp, Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_5 is Ala, Glu, or Lys, X_6 is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_7 is Arg, Ile, or Lys, X_8 is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_9 is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{10} is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{11} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{12} is Ala, Cys, Ser, or Val, X_{13} is Val or Arg, X_{14} is Leu, Gln, His, Ile, Lys, or Ser, X_{15} is GGGGS (SEQ ID NO: 184), GGGGSGGGGS (SEQ ID NO: 145), or EPKSS (SEQ ID NO: 146), and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, X_1 is Ala, Asp, Met, or not present, X_2 is Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Gly, Ser or Thr, X_5 is Ala or Glu, X_6 is Gln or Tyr, X_7 is Ile or Lys, X_8 is Ala or Thr, X_9 is Gln, Ala, or Thr, X_{10} is Ser, Arg, or Ala, X_{11} is Trp, Lys, or Arg, X_{12} is Ala or Cys, X_{13} is Val or Arg, and X_{14} is Leu or Ile.

[00204] In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 68. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 69. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second

polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 70. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 71. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 72. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 73. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 74. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 98. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 99. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 100. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 101. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 102. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 103. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 104. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 105. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 106. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 107. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 108. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 109. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second

polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 110. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 111. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 112. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 150. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 151. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 155. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 156. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 160. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 161. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 192. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 67, and the third polypeptide comprises SEQ ID NO: 195. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 189, and the third polypeptide comprises SEQ ID NO: 185. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 189, and the third polypeptide comprises SEQ ID NO: 187. In certain embodiments, the first polypeptide comprises SEQ ID NO: 66, the second polypeptide comprises SEQ ID NO: 189, and the third polypeptide comprises SEQ ID NO: 205.

[00205] In certain embodiments, the antibody conjugate comprises a first polypeptide comprising a first sialidase, a first immunoglobulin Fc domain, and a first single chain variable fragment (scFv) (it is also understood that the scFv may be replaced by a first polypeptide chain of an immunoglobulin antigen binding fragment, *e.g.*, Fab fragment); and a second polypeptide comprising a second sialidase, a second immunoglobulin Fc domain, and

a second single chain variable fragment (scFv) (it is also understood that the scFv may be replaced by a second polypeptide chain of an immunoglobulin antigen binding fragment, *e.g.*, Fab fragment). An example of this embodiment is shown in **FIGURE 11C** (in the construct depicted in **FIGURE 11C** it is understood that an scFv, when present, may be replaced with a Fab fragment, or a Fab fragment, when present, may be replaced with an scFv). The first and second polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. In certain embodiments, the first scFv defines a first antigen-binding site, and the second scFv defines a second antigen-binding site. In certain embodiments, the first polypeptide comprises the first sialidase, the first immunoglobulin Fc domain, and the first scFv in an N- to C-terminal orientation. In certain embodiments, the first polypeptide comprises the first scFv, the first immunoglobulin Fc domain, and the first sialidase in an N- to C-terminal orientation. In certain embodiments, the second polypeptide comprises the second sialidase, the second immunoglobulin Fc domain, and the second scFv in an N- to C-terminal orientation. In certain embodiments, the second polypeptide comprises the second scFv, the second immunoglobulin Fc domain, and the second sialidase in an N- to C-terminal orientation.

[00206] In certain embodiments, the first polypeptide comprises the amino acid sequence of any one of SEQ ID NOs: 77-83, 166-178, 194, 197, 244, or 249, or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 77-83, 166-178, 194, 197, 244, or 249. In certain embodiments, the second polypeptide comprises the amino acid sequence of any one of SEQ ID NOs: 77-83, 166-178, 194, 197, 244, or 249, or an amino acid sequence that has at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 77-83, 166-178, 194, 197, 244, or 249.

[00207] In certain embodiments, the first and/or second polypeptide comprises the amino acid sequence of

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_7SX_8X_9DEHAELIVX_{10}R$
$RGDYDAX_{11}THQVQWX_{12}AQEVVAQAX_{13}LX_{14}GHRSMNPCPLYDX_{15}QTGTLFLFFIAIPX_{16}X_{17}$
$VTEX_{18}QQLQTRANVTRLX_{19}X_{20}VTSTDHGRTWSSPRDLTDAAIGPX_{21}YREWSTFAVGPGHX_{22}$
$LQLHDX_{23}X_{24}RSLVVPAYAYRKLHPX_{25}X_{26}X_{27}PIPSAFX_{28}FLSHDHGRTWARGHFVX_{29}QDTX_{30}ECQVAEVX_{31}TGEQRVVTLNARSX_{32}X_{33}X_{34}X_{35}RX_{36}QAQSX_{37}NX_{38}GLDFQX_{39}X_{40}QX_{41}VKK$
$LX_{42}EPPPX_{43}GX_{44}QGSVISFPSPRSGPGSPAQX_{45}LLYTHPTHX_{46}X_{47}QRADLGAYLNPRPPA$
$PEAWSEPX_{48}LLAKGSX_{49}AYSDLQSMGTGPDGSPLFGX_{50}LYEANDYEEIX_{51}FX_{52}MFTLKQAF$
$PAEYLPQX_{53}DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV$
$KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT$
$ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV$

LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGG
GGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTR
YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSG
GGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLI
YSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

(SEQ ID NO: 248), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Ala or Lys, X_3 is Asn or Leu, X_4 is Pro or His, X_5 is Phe, Trp, Tyr or Val, X_6 is Lys or Asp, X_7 is Ala or Arg, X_8 is Lys, Arg, or Glu, X_9 is Lys, Ala, Arg, or Glu, X_{10} is Leu or Met, X_{11} is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_{12} is Gln or His, X_{13} is Arg or Lys, X_{14} is Asp or Pro, X_{15} is Ala, Glu or Lys, X_{16} is Gly or Asp, X_{17} is Gln or His, X_{18} is Gln, Arg, or Lys, X_{19} is Ala, Cys, Ile, Ser, Val, or Leu, X_{20} is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_{21} is Ala or Val, X_{22} is Cys or Gly, X_{23} is Arg or Pro, X_{24} is Ala or Gly, X_{25} is Arg, Ile, or Lys, X_{26} is Gln or Pro, X_{27} is Arg or Pro, X_{28} is Ala, Cys, Leu, or Val, X_{29} is Ala, Cys, Asn, Ser, or Thr, X_{30} is Leu, Ala, or Val, X_{31} is Glu or Pro, X_{32} is His or Pro, X_{33} is Leu, Asp, Asn, or Tyr, X_{34} is Arg, Ala, Asp, Leu, Gln, or Tyr, X_{35} is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_{36} is Val, Ile, or Lys, X_{37} is Thr or Ala, X_{38} is Asp or Gly, X_{39} is Glu, Lys, or Pro, X_{40} is Ser or Cys, X_{41} is Leu, Asp, Phe, Gln, or Thr, X_{42} is Val or Phe, X_{43} is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{44} is Cys or Val, X_{45} is Trp or Arg, X_{46} is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{47} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{48} is Lys or Val, X_{49} is Ala, Cys, Ser, or Val, X_{50} is Cys, Leu, or Val, X_{51} is Val or Arg, X_{52} is Leu, Gln, His, Ile, Lys, or Ser, and X_{53} is GGGGS (SEQ ID NO: 184), GGGGSGGGGS (SEQ ID NO: 145), or EPKSS (SEQ ID NO: 146), and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1).

[00208] In certain embodiments, the first and/or second polypeptide comprises the amino acid sequence of

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_4SKKDEHAELIVLRRGDYD
AX_5THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_6QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCX_7VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX_8QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX_9RV
QAQSTNDGLDFQESQLVKKLVEPPPX$_{10}$GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX$_{11}$X$_{12}$
QRADLGAYLNPRPPAPEAWSEPVLLAKGSX$_{13}$AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX
$_{14}$FX$_{15}$MFTLKQAFPAEYLPQX$_{16}$DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
KGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLE

WVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMD
YWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAW
YQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPT
FGQGTKVEIK

(SEQ ID NO: 247), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Phe, Trp, Tyr or Val, X_3 is Lys or Asp, X_4 is Arg or Ala, X_5 is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_6 is Ala, Glu, or Lys, X_7 is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_8 is Arg, Ile, or Lys, X_9 is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_{10} is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{11} is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{12} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{13} is Ala, Cys, Ser, or Val, X_{14} is Val or Arg, X_{15} is Leu, Gln, His, Ile, Lys, or Ser, and X_{16} is GGGGS (SEQ ID NO: 184), GGGGSGGGGS (SEQ ID NO: 145), or EPKSS (SEQ ID NO: 146), and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, X_1 is Ala, Asp, Met, or not present, X_2 is Tyr or Val, X_3 is Lys or Asp, X_4 is Arg or Ala, X_5 is Pro, Asn, Gly, Ser or Thr, X_6 is Ala or Glu, X_7 is Gln or Tyr, X_8 is Ile or Lys, X_9 is Ala or Thr, X_{10} is Gln, Ala, or Thr, X_{11} is Ser, Arg, or Ala, X_{12} is Trp, Lys, or Arg, X_{13} is Ala or Cys, X_{14} is Val or Arg, and X_{15} is Leu or Ile.

[00209] In certain embodiments, the first and/or second polypeptide comprises the amino acid sequence of

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX_7X_8DEHAELIVX_9RR$
$GDYDAX_{10}THQVQWX_{11}AQEVVAQAX_{12}LDGHRSMNPCPLYDX_{13}QTGTLFLFFIAIPX_{14}X_{15}VT$
$EX_{16}QQLQTRANVTRLX_{17}X_{18}VTSTDHGRTWSSPRDLTDAAIGPX_{19}YREWSTFAVGPGHX_{20}LQ$
$LHDRX_{21}RSLVVPAYAYRKLHPX_{22}QRPIPSAFX_{23}FLSHDHGRTWARGHFVAQDTX_{24}ECQVAE$
$VETGEQRVVTLNARSHLRARVQAQSX_{25}NX_{26}GLDFQX_{27}SQLVKKLVEPPPX_{28}GX_{29}QGSVISF$
$PSPRSGPGSPAQX_{30}LLYTHPTHX_{31}X_{32}QRADLGAYLNPRPPAPEAWSEPX_{33}LLAKGSX_{34}AYS$
DLQSMGTGPDGSPLFGX$_{35}$LYEANDYEEIX$_{36}$FX$_{37}$MFTLKQAFPAEYLPQGGGGSGGGGSDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEVQLVESGG
GLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTIS
ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPS
RFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

(SEQ ID NO: 85), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Ala or Lys, X_3 is Asn or Leu, X_4 is Pro or His, X_5 is Phe, Trp, Tyr or Val, X_6 is Lys or Asp; X_7 is Lys, Arg, or Glu. X_8 is Lys, Ala, Arg, or Glu, X_9 is Leu or

Met, X_{10} is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_{11} is Gln or His, X_{12} is Arg or Lys, X_{13} is Ala, Glu or Lys, X_{14} is Gly or Asp, X_{15} is Gln or His, X_{16} is Gln, Arg, or Lys, X_{17} is Ala, Cys, Ile, Ser, Val, or Leu, X_{18} is Gln or Leu, X_{19} is Ala or Val, X_{20} is Cys or Gly, X_{21} is Ala or Gly, X_{22} is Arg, Ile, or Lys, X_{23} is Ala, Cys, Leu, or Val, X_{24} is Leu, Ala, or Val, X_{25} is Thr or Ala, X_{26} is Asp or Gly, X_{27} is Glu or Lys, X_{28} is Gln, Ala, His, Phe, or Pro, X_{29} is Cys or Val, X_{30} is Trp or Arg, X_{31} is Ser or Arg, X_{32} is Trp or Lys, X_{33} is Lys or Val, X_{34} is Ala, Cys, Ser, or Val, X_{35} is Cys, Leu, or Val, X_{36} is Val or Arg, and X_{37} is Leu, Gln, His, Ile, Lys, or Ser, and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1).

[00210] In certain embodiments, the first and/or second polypeptide comprises the amino acid sequence of

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX_6QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQ
AQSTNDGLDFQESQLVKKLVEPPPX$_7$GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX$_8$X$_9$QRA
DLGAYLNPRPPAPEAWSEPVLLAKGSX$_{10}$AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX$_{11}$FX
$_{12}$MFTLKQAFPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPGKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPG
KGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNT
AVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYT
TPPTFGQGTKVEIK

(SEQ ID NO: 84), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Phe, Trp, Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_5 is Ala, Glu, or Lys, X_6 is Arg, Ile, or Lys, X_7 is Gln, Ala, His, Phe, or Pro, X_8 is Ser or Arg, X_9 is Trp or Lys, X_{10} is Ala, Cys, Ser, or Val, X_{11} is Val or Arg, and X_{12} is Leu, Gln, His, Ile, Lys, or Ser, and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, X_1 is Ala, Asp, Met, or not present, X_2 is Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Gly, Ser or Thr, X_5 is Ala or Glu, X_6 is Ile or Lys, X_7 is Gln or Ala, X_8 is Ser or Arg, X_9 is Trp or Lys, X_{10} is Ala or Cys, X_{11} is Val or Arg, and X_{12} is Leu or Ile.

[00211] In certain embodiments, the first and/or second polypeptide comprises the amino acid sequence of

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX_7X_8DEHAELIVX_9RR$
$GDYDAX_{10}THQVQWX_{11}AQEVVAQAX_{12}LX_{13}GHRSMNPCPLYDX_{14}QTGTLFLFFIAIPX_{15}X_{16}V$
$TEX_{17}QQLQTRANVTRLX_{18}X_{19}VTSTDHGRTWSSPRDLTDAAIGPX_{20}YREWSTFAVGPGHX_{21}L$
$QLHDX_{22}X_{23}RSLVVPAYAYRKLHPX_{24}X_{25}X_{26}PIPSAFX_{27}FLSHDHGRTWARGHFVX_{28}QDTX_{29}$
$ECQVAEVX_{30}TGEQRVVTLNARSX_{31}X_{32}X_{33}X_{34}RX_{35}QAQSX_{36}NX_{37}GLDFQX_{38}X_{39}QX_{40}VKKLX$
$_{41}EPPPX_{42}GX_{43}QGSVISFPSPRSGPGSPAQX_{44}LLYTHPTHX_{45}X_{46}QRADLGAYLNPRPPAPE$
$AWSEPX_{47}LLAKGSX_{48}AYSDLQSMGTGPDGSPLFGX_{49}LYEANDYEEIX_{50}FX_{51}MFTLKQAFPA$
$EYLPQX_{52}DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF$
$NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS$
$KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD$
$SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGG$
$SEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYA$
$DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSGGG$
$GSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYS$
$ASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK$

(SEQ ID NO: 180), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Ala or Lys, X_3 is Asn or Leu, X_4 is Pro or His, X_5 is Phe, Trp, Tyr or Val, X_6 is Lys or Asp, X_7 is Lys, Arg, or Glu, X_8 is Lys, Ala, Arg, or Glu, X_9 is Leu or Met, X_{10} is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_{11} is Gln or His, X_{12} is Arg or Lys, X_{13} is Asp or Pro, X_{14} is Ala, Glu or Lys, X_{15} is Gly or Asp, X_{16} is Gln or His, X_{17} is Gln, Arg, or Lys, X_{18} is Ala, Cys, Ile, Ser, Val, or Leu, X_{19} is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_{20} is Ala or Val, X_{21} is Cys or Gly, X_{22} is Arg or Pro, X_{23} is Ala or Gly, X_{24} is Arg, Ile, or Lys, X_{25} is Gln or Pro, X_{26} is Arg or Pro, X_{27} is Ala, Cys, Leu, or Val, X_{28} is Ala, Cys, Asn, Ser, or Thr, X_{29} is Leu, Ala, or Val, X_{30} is Glu or Pro, X_{31} is His or Pro, X_{32} is Leu, Asp, Asn, or Tyr, X_{33} is Arg, Ala, Asp, Leu, Gln, or Tyr, X_{34} is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_{35} is Val, Ile, or Lys, X_{36} is Thr or Ala, X_{37} is Asp or Gly, X_{38} is Glu, Lys, or Pro, X_{39} is Ser or Cys, X_{40} is Leu, Asp, Phe, Gln, or Thr, X_{41} is Val or Phe, X_{42} is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{43} is Cys or Val, X_{44} is Trp or Arg, X_{45} is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{46} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{47} is Lys or Val, X_{48} is Ala, Cys, Ser, or Val, X_{49} is Cys, Leu, or Val, X_{50} is Val or Arg, X_{51} is Leu, Gln, His, Ile, Lys, or Ser, X_{52} is GGGGS (SEQ ID NO: 184), GGGGSGGGGS (SEQ ID NO: 145), or EPKSS (SEQ ID NO: 146), and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1).

[00212] In certain embodiments, the first and/or second polypeptide comprises the amino acid sequence of

$X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD$
$AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV$
$TRLCX_6VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK$

LHPX$_7$QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX$_8$RV
QAQSTNDGLDFQESQLVKKLVEPPPX$_9$GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX$_{10}$X$_{11}$Q
RADLGAYLNPRPPAPEAWSEPVLLAKGSX$_{12}$AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX$_{13}$
FX$_{14}$MFTLKQAFPAEYLPQX$_{15}$DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKG
GGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWV
ARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW
GQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQ
QKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFG
QGTKVEIK

(SEQ ID NO: 179), wherein X_1 is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X_2 is Phe, Trp, Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X_5 is Ala, Glu, or Lys, X_6 is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X_7 is Arg, Ile, or Lys, X_8 is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X_9 is Gln, Ala, His, Phe, Pro, Ser, or Thr, X_{10} is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X_{11} is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X_{12} is Ala, Cys, Ser, or Val, X_{13} is Val or Arg, X_{14} is Leu, Gln, His, Ile, Lys, or Ser, X_{15} is GGGGS (SEQ ID NO: 184), GGGGSGGGGS (SEQ ID NO: 145), or EPKSS (SEQ ID NO: 146), and the sialidase comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1). In certain embodiments, X_1 is Ala, Asp, Met, or not present, X_2 is Tyr or Val, X_3 is Lys or Asp, X_4 is Pro, Asn, Gly, Ser or Thr, X_5 is Ala or Glu, X_6 is Gln or Tyr, X_7 is Ile or Lys, X_8 is Ala or Thr, X_9 is Gln, Ala, or Thr, X_{10} is Ser, Arg, or Ala, X_{11} is Trp, Lys, or Arg, X_{12} is Ala or Cys, X_{13} is Val or Arg, and X_{14} is Leu or Ile.

[00213] In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 77. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 78. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 79. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 80. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 81. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 82. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 83. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 166. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 167. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 168. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 169. In certain

embodiments, the first and second polypeptide comprise SEQ ID NO: 170. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 171. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 172. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 173. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 174. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 175. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 176. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 177. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 178. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 194. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 197. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 244. In certain embodiments, the first and second polypeptide comprise SEQ ID NO: 249.

[00214] In certain embodiments, the antibody conjugate comprises: a first polypeptide comprising an immunoglobulin light chain; a second polypeptide comprising an immunoglobulin heavy chain and a single chain variable fragment (scFv) (it is also understood that the scFv may be replaced by a first polypeptide chain of an immunoglobulin antigen binding fragment, *e.g.*, Fab fragment); and a third polypeptide comprising an immunoglobulin Fc domain and a sialidase. An example of this embodiment is shown in **FIGURE 11D**. The first and second polypeptides can be covalently linked together and the second and third polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. In certain embodiments, the first polypeptide and the second polypeptide together define a first antigen-binding site (i.e., the immunoglobulin light chain and immunoglobulin heavy chain together define a first antigen-binding site). In certain embodiments, the scFv defines a second antigen-binding site. In certain embodiments, the second polypeptide comprises the immunoglobulin heavy chain and the scFv in an N- to C-terminal orientation, or the scFv and the immunoglobulin heavy chain in an N- to C-terminal orientation. In certain embodiments, the third polypeptide comprises the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation, or the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation.

[00215] In certain embodiments, the antibody conjugate comprises a first polypeptide comprising a first immunoglobulin light chain; a second polypeptide comprising a first sialidase, a first immunoglobulin Fc domain, and a first immunoglobulin heavy chain variable

region; a third polypeptide comprising a second sialidase, a second immunoglobulin Fc domain, and a second immunoglobulin heavy chain variable region; and a fourth polypeptide comprising a second immunoglobulin light chain. It is also understood that an immunoglobulin light chain may be replaced by an immunoglobulin heavy chain variable region and an immunoglobulin heavy chain variable region may be replaced by an immunoglobulin light chain (*e.g.,* the antibody conjugate may comprise a first polypeptide comprising a first immunoglobulin heavy chain variable region; a second polypeptide comprising a first sialidase, a first immunoglobulin Fc domain, and a first immunoglobulin light chain; a third polypeptide comprising a second sialidase, a second immunoglobulin Fc domain, and a second immunoglobulin light chain; and a fourth polypeptide comprising a second immunoglobulin heavy chain variable region). An example of this embodiment is shown in **FIGURE 11E**. The second and third polypeptides can be covalently linked together. The covalent linkages can be disulfide bonds. In certain embodiments, the first and second polypeptides define a first antigen-binding site, and the third and fourth polypeptides define a second antigen-binding site. In certain embodiments, the second polypeptide comprises the first sialidase, the first immunoglobulin Fc domain, and the first immunoglobulin heavy chain variable region in an N- to C-terminal orientation. In certain embodiments, the third polypeptide comprises the second sialidase, the second immunoglobulin Fc domain, and the second immunoglobulin heavy chain variable region in an N- to C-terminal orientation.

[00216] In certain embodiments, the antibody conjugate has a molecular weight from about 135 kDa to about 165 kDa, *e.g.,* about 140 kDa. In other embodiments, the antibody conjugate has a molecular weight from about 215 kDa to about 245 kDa, *e.g.,* about 230 kDa.

[00217] In certain embodiments, the antibody conjugate comprises two polypeptides that each comprise an immunoglobulin Fc domain, and the first polypeptide has either a "knob" mutation, *e.g.,* T366Y, or a "hole" mutation, *e.g.,* Y407T, for heterodimerization with the second polypeptide, and the second polypeptide has either a respective "knob" mutation, *e.g.,* T366Y, or a "hole" mutation, *e.g.,* Y407T, for heterodimerization with the first polypeptide (residue numbers according to EU numbering, Kabat, E.A., *et al.* (1991) *supra*). For example, in certain embodiments, the antibody comprises two polypeptides that each comprise an immunoglobulin Fc domain derived from human IgG1 Fc domain, and the first polypeptide comprises a Y407T mutation (*e.g.,* the first polypeptide comprises SEQ ID NO: 32, SEQ ID NO: 147, SEQ ID NO: 213, or SEQ ID NO: 215), and the second polypeptide

comprises a T366Y mutation (*e.g.,* the second polypeptide comprises SEQ ID NO: 33, SEQ ID NO: 148, SEQ ID NO: 214, or SEQ ID NO: 216).

[00218] As used herein, the term "multispecific antibody" is understood to mean an antibody that specifically binds to at least two different antigens, *i.e.,* an antibody that comprises at least two antigen-binding sites that bind to at least two different antigens. As used herein, the term "bispecific antibody" is understood to mean an antibody that specifically binds to two different antigens, *i.e.,* an antibody that comprises two antigen-binding sites each of which bind to separate and distinct antigens. In other words, a first binding site binds a first antigen and a second binding site binds a second, different antigen. A multispecific or bispecific antibody may, for example, be a human or humanized antibody, and/or be a full length antibody or an antibody fragment (*e.g.*, a $F(ab')_2$ bispecific antibody).

[00219] The present invention encompasses antibody conjugates comprising antibody fragments, which may be generated by traditional means, such as enzymatic digestion, or by recombinant techniques. For a review of certain antibody fragments, see Hudson *et al.* (2003) *supra.*

[00220] In certain embodiments, the antibody conjugate or fusion protein can be covalently or non-covalently associated with a biological modifier, wherein the biological modifier can be used to enhance the solubility of the antibody, increase binding specificity, decrease immunogenicity or toxicity or modify the pharmacokinetic profile of the antibody. For example, the biological modifier can be used to increase the molecular weight of the antibody to increase its circulating half-life.

[00221] It is contemplated that the antibody conjugate or fusion protein may be covalently bound to one or more (for example, 2, 3, 4, 5, 6, 8, 9, 10 or more) biological modifiers that may comprise linear or branched polymers. Exemplary biological modifiers may include, for example, a variety of polymers, such as those described in U.S. Patent No. 7,842,789. Particularly useful are polyalkylene ethers such as polyethylene glycol (PEG) and derivatives thereof (for example, alkoxy polyethylene glycol, for example, methoxypolyethylene glycol, ethoxypolyethylene glycol and the like); block copolymers of polyoxyethylene and polyoxypropylene (Pluronics); polymethacrylates; carbomers; and branched or unbranched polysaccharides which comprise the saccharide monomers such as D-mannose, D- and L-galactose, fucose, fructose, D-xylose, L-arabinose, and D-glucuronic acid.

[00222] In other embodiments, the biological modifier can be a hydrophilic polyvinyl polymer such as polyvinyl alcohol and polyvinylpyrrolidone (PVP)-type polymers. The biological modifier can be a functionalized polyvinylpyrrolidone, for example, carboxy or amine functionalized on one (or both) ends of the polymer (as available from PolymerSource). Alternatively, the biological modifier can include Poly N-(2-hydroxypropyl)methacrylamide (HPMA), or functionalized HPMA (amine, carboxy, *etc.*), Poly(N-isopropylacrylamide) or functionalized poly(N-isopropylacrylamide). Alternatively, the biological modifier can include Poly N-(2-hydroxypropyl)methacrylamide (HPMA), or functionalized HPMA (amine, carboxy, *etc.*), Poly(N-isopropylacrylamide) or functionalized poly(N-isopropylacrylamide). The modifier prior to conjugation need not be, but preferably is, water soluble, but the final conjugate should be water soluble.

[00223] In general, the biological modifier may have a molecular weight from about 2 kDa to about 5 kDa, from about 2 kDa to about 10 kDa, from about 2 kDa to about 20 kDa, from about 2 kDa to about 30 kDa, from about 2 kDa to about 40 kDa, from about 2 kDa to about 50 kDa, from about 2 kDa to about 60 kDa, from about 2 kDa to about 70 kDa, from about 2 kDa to about 80 kDa, from about 2 kDa to about 90 kDa, from about 2 kDa to about 100 kDa, from about 2 kDa to about 150 kDa, from about 5 kDa to about 10 kDa, from about 5 kDa to about 20 kDa, from about 5 kDa to about 30 kDa, from about 5 kDa to about 40 kDa, from about 5 kDa to about 50 kDa, from about 5 kDa to about 60 kDa, from about 5 kDa to about 70 kDa, from about 5 kDa to about 80 kDa, from about 5 kDa to about 90 kDa, from about 5 kDa to about 100 kDa, from about 5 kDa to about 150 kDa, from about 10 kDa to about 20 kDa, from about 10 kDa to about 30 kDa, from about 10 kDa to about 40 kDa, from about 10 kDa to about 50 kDa, from about 10 kDa to about 60 kDa, from about 10 kDa to about 70 kDa, from about 10 kDa to about 80 kDa, from about 10 kDa to about 90 kDa, from about 10 kDa to about 100 kDa, from about 10 kDa to about 150 kDa, from about 20 kDa to about 30 kDa, from about 20 kDa to about 40 kDa, from about 20 kDa to about 50 kDa, from about 20 kDa to about 60 kDa, from about 20 kDa to about 70 kDa, from about 20 kDa to about 80 kDa, from about 20 kDa to about 90 kDa, from about 20 kDa to about 100 kDa, from about 20 kDa to about 150 kDa, from about 30 kDa to about 40 kDa, from about 30 kDa to about 50 kDa, from about 30 kDa to about 60 kDa, from about 30 kDa to about 70 kDa, from about 30 kDa to about 80 kDa, from about 30 kDa to about 90 kDa, from about 30 kDa to about 100 kDa, from about 30 kDa to about 150 kDa, from about 40 kDa to about 50 kDa, from about 40 kDa to about 60 kDa, from about 40 kDa to about 70 kDa, from about 40 kDa to

about 80 kDa, from about 40 kDa to about 90 kDa, from about 40 kDa to about 100 kDa, from about 40 kDa to about 150 kDa, from about 50 kDa to about 60 kDa, from about 50 kDa to about 70 kDa, from about 50 kDa to about 80 kDa, from about 50 kDa to about 90 kDa, from about 50 kDa to about 100 kDa, from about 50 kDa to about 150 kDa, from about 60 kDa to about 70 kDa, from about 60 kDa to about 80 kDa, from about 60 kDa to about 90 kDa, from about 60 kDa to about 100 kDa, from about 60 kDa to about 150 kDa, from about 70 kDa to about 80 kDa, from about 70 kDa to about 90 kDa, from about 70 kDa to about 100 kDa, from about 70 kDa to about 150 kDa, from about 80 kDa to about 90 kDa, from about 80 kDa to about 100 kDa, from about 80 kDa to about 150 kDa, from about 90 kDa to about 100 kDa, from about 90 kDa to about 150 kDa, or from about 100 kDa to about 150 kDa.

[00224] It is contemplated that the antibody conjugate or fusion protein is attached to about 10 or fewer polymer molecules (*e.g.,* 9, 8, 7, 6, 5, 4, 3, 2, or 1), each polymer molecule having a molecular weight of at least about 20,000 D, or at least about 30,000 D, or at least about 40,000 D.

[00225] Although a variety of polymers can be used as biological modifiers, it is contemplated that the antibody conjugates or fusion proteins described herein may be attached to polyethylene glycol (PEG) polymers. In one embodiment, the antibody conjugate or fusion protein described herein is covalently attached to at least one PEG having an actual MW of at least about 20,000 D. In another embodiment, the antibody conjugate or fusion protein described herein is covalently attached to at least one PEG having an actual MW of at least about 30,000 D. In another embodiment, the antibody conjugate or fusion protein described herein is covalently attached to at least one PEG having an actual MW of at least about 40,000 D. In certain embodiments, the PEG is methoxyPEG(5000)-succinimidylpropionate (mPEG-SPA), methoxyPEG(5000)-succinimidylsuccinate (mPEG-SS). Such PEGS are commercially available from Nektar Therapeutics or SunBiowest.

[00226] Attachment sites on an antibody conjugate or fusion protein for a biological modifier include the N-terminal amino group and epsilon amino groups found on lysine residues, as well as other amino, imino, carboxyl, sulfhydryl, hydroxyl or other hydrophilic groups. The polymer may be covalently bonded directly to the antibody conjugate or fusion protein with or without the known use of a multifunctional (ordinarily bifunctional) crosslinking agent using chemistries and used in the art. For example, sulfhydryl groups can be derivatized by coupling to maleimido-substituted PEG (*e.g.* alkoxy-PEG amine plus

sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate), or PEG-maleimide commercially available from Shearwater Polymers, Inc., Huntsville, Ala.).

III. Methods of Making a Recombinant Sialidase, Fusion Protein, or Antibody Conjugate

[00227] Methods for producing recombinant sialidases (*e.g.*, human sialidases), fusion proteins, *e.g.,* those disclosed herein, antibodies, or antibody conjugates, *e.g.,* those disclosed herein, are known in the art. For example, DNA molecules encoding light chain variable regions and/or heavy chain variable regions can be synthesized chemically or by recombinant DNA methodologies. For example, the sequences of the antibodies can be cloned from hybridomas by conventional hybridization techniques or polymerase chain reaction (PCR) techniques, using the appropriate synthetic nucleic acid primers. The resulting DNA molecules encoding the variable regions of interest can be ligated to other appropriate nucleotide sequences, including, for example, constant region coding sequences, and expression control sequences, to produce conventional gene expression constructs (*i.e.*, expression vectors) encoding the desired antibodies. Production of defined gene constructs is within routine skill in the art.

[00228] Nucleic acids encoding desired recombinant human sialidases, fusion proteins, and/or antibody conjugates can be incorporated (ligated) into expression vectors, which can be introduced into host cells through conventional transfection or transformation techniques. Exemplary host cells are *E. coli* cells, Chinese hamster ovary (CHO) cells, human embryonic kidney 293 (HEK 293) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), and myeloma cells that do not otherwise produce IgG protein. Transformed host cells can be grown under conditions that permit the host cells to express the genes that encode the immunoglobulin light and/or heavy chain variable regions.

[00229] Specific expression and purification conditions will vary depending upon the expression system employed. For example, if a gene is to be expressed in *E. coli*, it is first cloned into an expression vector by positioning the engineered gene downstream from a suitable bacterial promoter, *e.g.*, Trp or Tac, and a prokaryotic signal sequence. The expressed protein may be secreted. The expressed protein may accumulate in refractile or inclusion bodies, which can be harvested after disruption of the cells by French press or

sonication. The refractile bodies then are solubilized, and the protein may be refolded and/or cleaved by methods known in the art.

[00230] If the engineered gene is to be expressed in eukaryotic host cells, *e.g.*, CHO cells, it is first inserted into an expression vector containing a suitable eukaryotic promoter, a secretion signal, a poly A sequence, and a stop codon. Optionally, the vector or gene construct may contain enhancers and introns. In embodiments involving fusion proteins comprising an antibody or portion thereof, the expression vector optionally contains sequences encoding all or part of a constant region, enabling an entire, or a part of, a heavy or light chain to be expressed. The gene construct can be introduced into eukaryotic host cells using conventional techniques.

[00231] The host cells express a recombinant human sialidase or a fusion protein and/or antibody conjugate comprising a sialidase and V_L or V_H fragments, V_L-V_H heterodimers, V_H-V_L or V_L-V_H single chain polypeptides, complete heavy or light immunoglobulin chains, or portions thereof, each of which may be attached to a moiety having another function (*e.g.*, cytotoxicity). In some embodiments involving fusion proteins and/or antibody conjugates, a host cell is transfected with a single vector expressing a polypeptide expressing a sialidase and an entire, or part of, a heavy chain (*e.g.*, a heavy chain variable region) or a sialidase and a light chain (*e.g.*, a light chain variable region), or a polypeptide expressing an entire, or part of, a heavy chain (*e.g.*, a heavy chain variable region) or a light chain (*e.g.*, a light chain variable region). In some embodiments, a host cell is transfected with a single vector encoding (a) a polypeptide comprising a heavy chain variable region and a polypeptide comprising a light chain variable region, or (b) an entire immunoglobulin heavy chain and an entire immunoglobulin light chain, wherein in (a) or in (b), the polypeptide may also comprise a sialidase. In some embodiments, a host cell is co-transfected with more than one expression vector (*e.g.*, one expression vector expressing a polypeptide comprising an entire, or part of, a heavy chain or heavy chain variable region, optionally comprising a sialidase fused thereto, and another expression vector expressing a polypeptide comprising an entire, or part of, a light chain or light chain variable region, optionally comprising a sialidase fused thereto).

[00232] A polypeptide comprising a sialidase or a fusion protein, *e.g.*, a fusion protein comprising an immunoglobulin heavy chain variable region or light chain variable region, can be produced by growing (culturing) a host cell transfected with an expression vector encoding such a variable region, under conditions that permit expression of the polypeptide.

Following expression, the polypeptide can be harvested and purified or isolated using techniques known in the art, *e.g.*, affinity tags such as glutathione-S-transferase (GST) or histidine tags.

[00233] In embodiments in which a fusion protein and/or antibody conjugate is produced, a sialidase fused to a monoclonal antibody, Fc domain, or an antigen-binding domain of the antibody, can be produced by growing (culturing) a host cell transfected with: (a) an expression vector that encodes a complete or partial immunoglobulin heavy chain, and a separate expression vector that encodes a complete or partial immunoglobulin light chain; or (b) a single expression vector that encodes both chains (*e.g.*, complete or partial heavy and light chains), under conditions that permit expression of both chains. The sialidase will be fused to one or more of the chains. The intact fusion protein and/or antibody conjugate can be harvested and purified or isolated using techniques known in the art, *e.g.*, Protein A, Protein G, affinity tags such as glutathione-S-transferase (GST) or histidine tags. It is within ordinary skill in the art to express the heavy chain and the light chain from a single expression vector or from two separate expression vectors.

[00234] In certain embodiments, in order to express a protein, *e.g.,* a recombinant human sialidase, as a secreted protein, a native N-terminal signal sequence of the protein is replaced, *e.g.,* with MDMRVPAQLLGLLLLWLPGARC (SEQ ID NO: 28). In certain embodiments, to express a protein, *e.g.,* a recombinant human sialidase, as a secreted protein, an N-terminal signal sequence, *e.g.,* MDMRVPAQLLGLLLLWLPGARC (SEQ ID NO: 28), is added. Additional exemplary N-terminal signal sequences include signal sequences from interleukin-2, CD-5, IgG kappa light chain, trypsinogen, serum albumin, and prolactin. In certain embodiments, in order to express a protein, *e.g.,* a recombinant human sialidase, as a secreted protein, a C terminal lysosomal signal motif, *e.g.,* YGTL (SEQ ID NO: 29) is removed.

[00235] Methods for reducing or eliminating the antigenicity of antibodies and antibody fragments are known in the art. When the antibodies are to be administered to a human, the antibodies preferably are "humanized" to reduce or eliminate antigenicity in humans. Preferably, each humanized antibody has the same or substantially the same affinity for the antigen as the non-humanized mouse antibody from which it was derived.

[00236] In one humanization approach, chimeric proteins are created in which mouse immunoglobulin constant regions are replaced with human immunoglobulin constant regions. See, *e.g.*, Morrison *et al.*, 1984, PROC. NAT. ACAD. SCI. 81:6851-6855, Neuberger *et al.*,

1984, NATURE 312:604-608; U.S. Patent Nos. 6,893,625 (Robinson); 5,500,362 (Robinson); and 4,816,567 (Cabilly).

[00237] In an approach known as CDR grafting, the CDRs of the light and heavy chain variable regions are grafted into frameworks from another species. For example, murine CDRs can be grafted into human FRs. In some embodiments, the CDRs of the light and heavy chain variable regions of an antibody are grafted into human FRs or consensus human FRs. To create consensus human FRs, FRs from several human heavy chain or light chain amino acid sequences are aligned to identify a consensus amino acid sequence. CDR grafting is described in U.S. Patent Nos. 7,022,500 (Queen); 6,982,321 (Winter); 6,180,370 (Queen); 6,054,297 (Carter); 5,693,762 (Queen); 5,859,205 (Adair); 5,693,761 (Queen); 5,565,332 (Hoogenboom); 5,585,089 (Queen); 5,530,101 (Queen); Jones *et al.* (1986) NATURE 321: 522-525; Riechmann *et al.* (1988) NATURE 332: 323-327; Verhoeyen *et al.* (1988) SCIENCE 239: 1534-1536; and Winter (1998) FEBS LETT 430: 92-94.

[00238] In an approach called "SUPERHUMANIZATION™," human CDR sequences are chosen from human germline genes, based on the structural similarity of the human CDRs to those of the mouse antibody to be humanized. See, *e.g.*, U.S. Patent No. 6,881,557 (Foote); and Tan *et al.*, 2002, J. IMMUNOL. 169:1119-1125.

[00239] Other methods to reduce immunogenicity include "reshaping," "hyperchimerization," and "veneering/resurfacing." See, *e.g.*, Vaswami *et al.*, 1998, ANNALS OF ALLERGY, ASTHMA, & IMMUNOL. 81:105; Roguska *et al.*, 1996, PROT. ENGINEER 9:895-904; and U.S. Patent No. 6,072,035 (Hardman). In the veneering/resurfacing approach, the surface accessible amino acid residues in the murine antibody are replaced by amino acid residues more frequently found at the same positions in a human antibody. This type of antibody resurfacing is described, *e.g.*, in U.S. Patent No. 5,639,641 (Pedersen).

[00240] Another approach for converting a mouse antibody into a form suitable for medical use in humans is known as ACTIVMAB™ technology (Vaccinex, Inc., Rochester, NY), which involves a vaccinia virus-based vector to express antibodies in mammalian cells. High levels of combinatorial diversity of IgG heavy and light chains can be produced. See, *e.g.*, U.S. Patent Nos. 6,706,477 (Zauderer); 6,800,442 (Zauderer); and 6,872,518 (Zauderer). Another approach for converting a mouse antibody into a form suitable for use in humans is technology practiced commercially by KaloBios Pharmaceuticals, Inc. (Palo Alto, CA). This technology involves the use of a proprietary human "acceptor" library to produce an "epitope

focused" library for antibody selection. Another approach for modifying a mouse antibody into a form suitable for medical use in humans is HUMAN ENGINEERING™ technology, which is practiced commercially by XOMA (US) LLC. See, *e.g.*, International (PCT) Publication No. WO 93/11794 and U.S. Patent Nos. 5,766,886 (Studnicka); 5,770,196 (Studnicka); 5,821,123 (Studnicka); and 5,869,619 (Studnicka).

[00241] Any suitable approach, including any of the above approaches, can be used to reduce or eliminate human immunogenicity of an antibody.

[00242] In addition, it is possible to create fully human antibodies in mice. Fully human mAbs lacking any non-human sequences can be prepared from human immunoglobulin transgenic mice by techniques referenced in, *e.g.*, Lonberg *et al.*, NATURE 368:856-859, 1994; Fishwild *et al.*, NATURE BIOTECHNOLOGY 14:845-851, 1996; and Mendez *et al.*, NATURE GENETICS 15:146-156, 1997. Fully human monoclonal antibodies can also be prepared and optimized from phage display libraries by techniques referenced in, *e.g.*, Knappik *et al.*, J. MOL. BIOL. 296:57-86, 2000; and Krebs *et al.*, J. IMMUNOL. METH. 254:67-84 2001).

[00243] The present invention encompasses fusion proteins comprising antibody fragments, which may be generated by traditional means, such as enzymatic digestion, or by recombinant techniques. For a review of certain antibody fragments, see Hudson *et al.* (2003) NAT. MED. 9:129-134.

[00244] Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, *e.g.*, Morimoto *et al.* (1992) JOURNAL OF BIOCHEMICAL AND BIOPHYSICAL METHODS 24:107-117; and Brennan *et al.* (1985) SCIENCE 229:81). However, these fragments can now be produced directly by recombinant host cells. Fab, Fv and ScFv antibody fragments can all be expressed in and secreted from *E. coli*, thus allowing the facile production of large amounts of these fragments. Antibody fragments can be isolated from the antibody phage libraries. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form $F(ab')_2$ fragments (Carter *et al.* (1992) BIO/TECHNOLOGY 10:163-167). According to another approach, $F(ab')_2$ fragments can be isolated directly from recombinant host cell culture. Fab and $F(ab')_2$ fragments with increased *in vivo* half-life comprising salvage receptor binding epitope residues are described in U.S. Patent No. 5,869,046. Other techniques for the production of antibody fragments will be apparent to the skilled

practitioner. In certain embodiments, an antibody is a single chain Fv fragment (scFv). See U.S. Patent Nos. 5,571,894 and 5,587,458.

[00245] Methods for making bispecific antibodies are known in the art. See Milstein and Cuello (1983) NATURE 305:537, International (PCT) Publication No. WO93/08829, and Traunecker *et al.* (1991) EMBO J., 10:3655. For further details of generating bispecific antibodies see, for example, Suresh *et al.* (1986) METHODS ENZYMOL. 121:210. Bispecific antibodies include cross-linked or "heteroconjugate" or "heterodimer" antibodies. For example, one of the antibodies in the heterodimer can be coupled to avidin, the other to biotin. Heterodimer antibodies may be made using any convenient cross-linking method. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Patent No. 4,676,980, along with a number of cross-linking techniques.

[00246] Examples of heterodimeric or asymmetric IgG-like molecules include but are not limited to those obtained with the following technologies or using the following formats: Triomab/Quadroma, Knobs-into-Holes, CrossMabs, electrostatically-matched antibodies, LUZ-Y, Strand Exchange Engineered Domain body, Biclonic and DuoBody.

[00247] Advantages of using antibody fragments (*e.g.,* F(ab) and F(ab')$_2$ fragments) include the elimination of non-specific binding between Fc portions of antibodies and Fc receptors on cells (such as macrophages, dendritic cells, neutrophils, NK cells and B cells). In addition, they may be able to penetrate tissues more efficiently due to their smaller size.

[00248] Heterodimeric antibodies, or asymmetric antibodies, allow for greater flexibility and new formats for attaching a variety of drugs to the antibody arms. One of the general formats for creating a heterodimeric antibody is the "knobs-into-holes" format. This format is specific to the heavy chain part of the constant region in antibodies. The "knobs" part is engineered by replacing a small amino acid with a larger one, which fits into a "hole", which is engineered by replacing a large amino acid with a smaller one. What connects the "knobs" to the "holes" are the disulfide bonds between each chain. The "knobs-into-holes" shape facilitates antibody dependent cell mediated cytotoxicity. Single chain variable fragments (scFv) are connected to the variable domain of the heavy and light chain via a short linker peptide. The linker is rich in glycine, which gives it more flexibility, and serine/threonine, which gives it specificity. Two different scFv fragments can be connected together, via a hinge region, to the constant domain of the heavy chain or the constant domain of the light chain. This gives the antibody bispecificity, allowing for the binding specificities of two

different antigens. The "knobs-into-holes" format enhances heterodimer formation but doesn't suppress homodimer formation.

[00249] Several approaches to support heterodimerization have been described, for example in International (PCT) Publication Nos. WO96/27011, WO98/050431, WO2007/110205, WO2007/147901, WO2009/089004, WO2010/129304, WO2011/90754, WO2011/143545, WO2012/058768, WO2013/157954, and WO2013/096291, and European Patent Publication No. EP1870459. Typically, in the approaches known in the art, the CH_3 domain of the first heavy chain and the CH_3 domain of the second heavy chain are both engineered in a complementary manner so that the heavy chain comprising one engineered CH_3 domain can no longer homodimerize with another heavy chain of the same structure (*e.g.* a CH_3-engineered first heavy chain can no longer homodimerize with another CH_3-engineered first heavy chain; and a CH_3-engineered second heavy chain can no longer homodimerize with another CH_3-engineered second heavy chain). Thereby the heavy chain comprising one engineered CH_3 domain is forced to heterodimerize with another heavy chain comprising the CH_3 domain, which is engineered in a complementary manner. As a result, the CH_3 domain of the first heavy chain and the CH_3 domain of the second heavy chain are engineered in a complementary manner by amino acid substitutions, such that the first heavy chain and the second heavy chain are forced to heterodimerize, whereas the first heavy chain and the second heavy chain can no longer homodimerize (*e.g.*, for steric reasons).

IV. Pharmaceutical Compositions

[00250] For therapeutic use, a recombinant sialidase (*e.g.*, human sialidase) or a fusion protein and/or antibody conjugate thereof preferably is combined with a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" as used herein refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00251] The term "pharmaceutically acceptable carrier" as used herein refers to buffers, carriers, and excipients suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable carriers include any of the standard pharmaceutical carriers, such as a phosphate

buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, see, *e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975]. Pharmaceutically acceptable carriers include buffers, solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art.

[00252] In certain embodiments, a pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrins); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants (see, *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990).

[00253] In certain embodiments, a pharmaceutical composition may contain nanoparticles, *e.g.,* polymeric nanoparticles, liposomes, or micelles (See Anselmo *et al.* (2016) BIOENG. TRANSL. MED. 1: 10-29).

[00254] In certain embodiments, a pharmaceutical composition may contain a sustained- or controlled-delivery formulation. Techniques for formulating sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. Sustained-release preparations may include, *e.g.*, porous polymeric microparticles or semipermeable polymer matrices in the form of shaped articles, *e.g.,* films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides, copolymers of L-glutamic acid and gamma ethyl-L-glutamate, poly (2-hydroxyethyl-inethacrylate), ethylene vinyl acetate, or poly-D(−)-3-hydroxybutyric acid. Sustained release compositions may also include liposomes that can be prepared by any of several methods known in the art.

[00255] Pharmaceutical compositions containing a recombinant human sialidase, a recombinant human sialidase fusion protein, or an antibody conjugate disclosed herein can be presented in a dosage unit form and can be prepared by any suitable method. A pharmaceutical composition should be formulated to be compatible with its intended route of administration. Examples of routes of administration are intravenous (IV), intradermal, inhalation, transdermal, topical, transmucosal, intrathecal and rectal administration. In certain embodiments, a recombinant human sialidase, a recombinant human sialidase fusion protein, or an antibody conjugate disclosed herein is administered by IV infusion. In certain embodiments, a recombinant human sialidase, a recombinant human sialidase fusion protein, or an antibody conjugate disclosed herein is administered by intratumoral injection. Useful formulations can be prepared by methods known in the pharmaceutical art. For example, see *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990). Formulation components suitable for parenteral administration include a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as EDTA; buffers such as acetates, citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose.

[00256] For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline

(PBS). The carrier should be stable under the conditions of manufacture and storage, and should be preserved against microorganisms. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof.

[00257] In certain embodiments, a pharmaceutical composition may contain a stabilizing agent. In certain embodiments, the stabilizing agent is a cation, such as a divalent cation. In certain embodiments, the cation is calcium or magnesium. The cation can be in the form of a salt, such as calcium chloride ($CaCl_2$) or magnesium chloride ($MgCl_2$).

[00258] In certain embodiments, the stabilizing agent is present in an amount from about 0.05 mM to about 5 mM. For example, the stabilizing agent may be present in an amount of from about 0.05 mM to about 4 mM, from about 0.05 mM to about 3 mM, from about 0.05 mM to about 2 mM, from about 0.05 mM to about 1 mM, from about 0.05 mM to about 0.5 mM, from about 0.5 mM to about 4 mM, from about 0.5 mM to about 3 mM, from about 0.5 mM to about 2 mM, from about 0.5 mM to about 1 mM, from about 1 mM to about 4 mM, from about 1 mM to about 3 mM, of from about 1 mM to about 2 mM.

[00259] Pharmaceutical formulations preferably are sterile. Sterilization can be accomplished by any suitable method, *e.g.*, filtration through sterile filtration membranes. Where the composition is lyophilized, filter sterilization can be conducted prior to or following lyophilization and reconstitution.

[00260] The compositions described herein may be administered locally or systemically. Administration will generally be parenteral administration. In a preferred embodiment, the pharmaceutical composition is administered subcutaneously and in an even more preferred embodiment intravenously. Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions.

[00261] Generally, a therapeutically effective amount of active component, for example, a recombinant human sialidase or fusion protein and/or antibody conjugate thereof, is in the range of 0.1 mg/kg to 100 mg/kg, *e.g.*, 1 mg/kg to 100 mg/kg, 1 mg/kg to 10 mg/kg. The amount administered will depend on variables such as the type and extent of disease or indication to be treated, the overall health of the patient, the *in vivo* potency of the antibody, the pharmaceutical formulation, and the route of administration. The initial dosage can be increased beyond the upper level in order to rapidly achieve the desired blood-level or tissue-level. Alternatively, the initial dosage can be smaller than the optimum, and the daily dosage

may be progressively increased during the course of treatment. Human dosage can be optimized, *e.g.*, in a conventional Phase I dose escalation study designed to run from 0.5 mg/kg to 20 mg/kg. Dosing frequency can vary, depending on factors such as route of administration, dosage amount, serum half-life of the recombinant human sialidase or fusion protein and/or antibody conjugate thereof, and the disease being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks. A preferred route of administration is parenteral, *e.g.*, intravenous infusion. In certain embodiments, a recombinant human sialidase or a fusion protein and/or antibody conjugate thereof is lyophilized, and then reconstituted in buffered saline, at the time of administration.

V. Therapeutic Uses

[00262] The compositions and methods disclosed herein can be used to treat various forms of cancer in a subject or inhibit cancer growth in a subject. The invention provides a method of treating a cancer in a subject. The method comprises administering to the subject an effective amount of a recombinant human sialidase or a fusion protein and/or antibody conjugate thereof, *e.g.*, a recombinant human sialidase, fusion protein, or antibody conjugate disclosed herein, either alone or in a combination with another therapeutic agent to treat the cancer in the subject. The term "effective amount" as used herein refers to the amount of an active agent (*e.g.*, recombinant human sialidase or fusion protein thereof according to the present invention) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route.

[00263] As used herein, "treat", "treating" and "treatment" mean the treatment of a disease in a subject, *e.g.*, in a human. This includes: (a) inhibiting the disease, *i.e.*, arresting its development; and (b) relieving the disease, *i.e.*, causing regression of the disease state. As used herein, the terms "subject" and "patient" refer to an organism to be treated by the methods and compositions described herein. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and more preferably includes humans.

[00264] Examples of cancers include solid tumors, soft tissue tumors, hematopoietic tumors and metastatic lesions. Examples of hematopoietic tumors include, leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), chronic myelocytic leukemia (CML), chronic lymphocytic leukemia

(CLL), *e.g.*, transformed CLL, diffuse large B-cell lymphomas (DLBCL), follicular lymphoma, hairy cell leukemia, myelodyplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignant lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, or Richter's Syndrome (Richter's Transformation). Examples of solid tumors include malignancies, *e.g.,* sarcomas, adenocarcinomas, and carcinomas, of the various organ systems, such as those affecting head and neck (including pharynx), thyroid, lung (small cell or non-small cell lung carcinoma (NSCLC)), breast, lymphoid, gastrointestinal (*e.g.*, oral, esophageal, stomach, liver, pancreas, small intestine, colon and rectum, anal canal), genitals and genitourinary tract (*e.g.*, renal, urothelial, bladder, ovarian, uterine, cervical, endometrial, prostate, testicular), CNS (*e.g.,* neural or glial cells, *e.g.*, neuroblastoma or glioma), or skin (*e.g.,* melanoma).

[00265] In certain embodiments the cancer is an epithelial cancer, *e.g.,* an epithelial cancer that upregulates the expression of sialylated glycans. Exemplary epithelial cancers include, but are not limited to, endometrial cancer, colon cancer, ovarian cancer, cervical cancer, vulvar cancer, uterine cancer or fallopian tube cancer, breast cancer, prostate cancer, lung cancer, pancreatic cancer, urinary cancer, bladder cancer, head and neck cancer, oral cancer and liver cancer. Epithelial cancers also include carcinomas, for example, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, baso squamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypemephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma,

melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, and carcinoma villosum.

[00266] In certain embodiments, the cancer is breast cancer. In certain embodiments, the cancer is an adenocarcinoma. In certain embodiments, the cancer is a metastatic cancer. In certain embodiments, the cancer is a refractory cancer.

[00267] In certain embodiments, the cancer is resistant to or non-responsive to treatment with an antibody, *e.g.,* an antibody with ADCC activity, *e.g.,* trastuzumab.

[00268] The methods and compositions described herein can be used alone or in combination with other therapeutic agents and/or modalities. The term administered "in combination," as used herein, is understood to mean that two (or more) different treatments are delivered to the subject during the course of the subject's affliction with the disorder, such that the effects of the treatments on the patient overlap at a point in time. In certain embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery." In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In certain embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, *e.g.*, an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In certain embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The

delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

[00269] In certain embodiments, a method or composition described herein, is administered in combination with one or more additional therapies, *e.g.*, surgery, radiation therapy, or administration of another therapeutic preparation. In certain embodiments, the additional therapy may include chemotherapy, *e.g.*, a cytotoxic agent. In certain embodiments the additional therapy may include a targeted therapy, *e.g.* a tyrosine kinase inhibitor, a proteasome inhibitor, or a protease inhibitor. In certain embodiments, the additional therapy may include an anti-inflammatory, anti-angiogenic, anti-fibrotic, or anti-proliferative compound, *e.g.*, a steroid, a biologic immunomodulator, a monoclonal antibody, an antibody fragment, an aptamer, an siRNA, an antisense molecule, a fusion protein, a cytokine, a cytokine receptor, a bronchodilator, a statin, an anti-inflammatory agent (*e.g.* methotrexate), or an NSAID. In certain embodiments, the additional therapy may include a combination of therapeutics of different classes.

[00270] In certain embodiments, a method or composition described herein is administered in combination with a checkpoint inhibitor. The checkpoint inhibitor may, for example, be selected from a PD-1 antagonist, PD-L1 antagonist, CTLA-4 antagonist, adenosine A2A receptor antagonist, B7-H3 antagonist, B7-H4 antagonist, BTLA antagonist, KIR antagonist, LAG3 antagonist, TIM-3 antagonist, VISTA antagonist, and TIGIT antagonist.

[00271] In certain embodiments, the checkpoint inhibitor is a PD-1 or PD-L1 inhibitor. PD-1 is a receptor present on the surface of T-cells that serves as an immune system checkpoint that inhibits or otherwise modulates T-cell activity at the appropriate time to prevent an overactive immune response. Cancer cells, however, can take advantage of this checkpoint by expressing ligands, for example, PD-L1, that interact with PD-1 on the surface of T-cells to shut down or modulate T-cell activity. Exemplary PD-1/PD-L1 based immune checkpoint inhibitors include antibody based therapeutics. Exemplary treatment methods that employ PD-1/PD-L1 based immune checkpoint inhibition are described in U.S. Patent Nos. 8,728,474 and 9,073,994, and EP Patent No. 1537878B1, and, for example, include the use of anti-PD-1 antibodies. Exemplary anti-PD-1 antibodies are described, for example, in U.S. Patent Nos. 8,952,136, 8,779,105, 8,008,449, 8,741,295, 9,205,148, 9,181,342, 9,102,728, 9,102,727, 8,952,136, 8,927,697, 8,900,587, 8,735,553, and 7,488,802. Exemplary anti-PD-1 antibodies include, for example, nivolumab (Opdivo®, Bristol-Myers Squibb Co.), pembrolizumab (Keytruda®, Merck Sharp & Dohme Corp.), PDR001 (Novartis

Pharmaceuticals), and pidilizumab (CT-011, Cure Tech). Exemplary anti-PD-L1 antibodies are described, for example, in U.S. Patent Nos. 9,273,135, 7,943,743, 9,175,082, 8,741,295, 8,552,154, and 8,217,149. Exemplary anti-PD-L1 antibodies include, for example, atezolizumab (Tecentriq®, Genentech), durvalumab (AstraZeneca), MEDI4736, avelumab, and BMS 936559 (Bristol Myers Squibb Co.).

[00272] In certain embodiments, a method or composition described herein is administered in combination with a CTLA-4 inhibitor. In the CTLA-4 pathway, the interaction of CTLA-4 on a T-cell with its ligands (*e.g.*, CD80, also known as B7-1, and CD86) on the surface of an antigen presenting cells (rather than cancer cells) leads to T-cell inhibition. Exemplary CTLA-4 based immune checkpoint inhibition methods are described in U.S. Patent Nos. 5,811,097, 5,855,887, 6,051,227. Exemplary anti-CTLA-4 antibodies are described in U.S. Patent Nos. 6,984,720, 6,682,736, 7,311,910; 7,307,064, 7,109,003, 7,132,281, 6,207,156, 7,807,797, 7,824,679, 8,143,379, 8,263,073, 8,318,916, 8,017,114, 8,784,815, and 8,883,984, International (PCT) Publication Nos. WO98/42752, WO00/37504, and WO01/14424, and European Patent No. EP 1212422 B1. Exemplary CTLA-4 antibodies include ipilimumab or tremelimumab.

[00273] In certain embodiments, a method or composition described herein is administered in combination with (i) a PD-1 or PD-L1 inhibitor, *e.g.,* a PD-1 or PD-L1 inhibitor disclosed herein, and (ii) CTLA-4 inhibitor, *e.g.,* a CTLA-4 inhibitor disclosed herein.

[00274] In certain embodiments, a method or composition described herein is administered in combination with an IDO inhibitor. Exemplary IDO inhibitors include 1-methyl-D-tryptophan (known as indoximod), epacadostat (INCB24360), navoximod (GDC-0919), and BMS-986205.

[00275] Exemplary cytotoxic agents that can be administered in combination with a method or composition described herein include, for example, antimicrotubule agents, topoisomerase inhibitors, antimetabolites, protein synthesis and degradation inhibitors, mitotic inhibitors, alkylating agents, platinating agents, inhibitors of nucleic acid synthesis, histone deacetylase inhibitors (HDAC inhibitors, *e.g.,* vorinostat (SAHA, MK0683), entinostat (MS-275), panobinostat (LBH589), trichostatin A (TSA), mocetinostat (MGCD0103), belinostat (PXD101), romidepsin (FK228, depsipeptide)), DNA methyltransferase inhibitors, nitrogen mustards, nitrosoureas, ethylenimines, alkyl sulfonates, triazenes, folate analogs, nucleoside analogs, ribonucleotide reductase inhibitors, vinca alkaloids, taxanes, epothilones,

intercalating agents, agents capable of interfering with a signal transduction pathway, agents that promote apoptosis and radiation, or antibody molecule conjugates that bind surface proteins to deliver a toxic agent. In one embodiment, the cytotoxic agent that can be administered with a method or composition described herein is a platinum-based agent (such as cisplatin), cyclophosphamide, dacarbazine, methotrexate, fluorouracil, gemcitabine, capecitabine, hydroxyurea, topotecan, irinotecan, azacytidine, vorinostat, ixabepilone, bortezomib, taxanes (*e.g.*, paclitaxel or docetaxel), cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, vinorelbine, colchicin, anthracyclines (*e.g.*, doxorubicin or epirubicin) daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, adriamycin, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, ricin, or maytansinoids.

[00276] The invention also provides a method of increasing the expression of HLA-DR, CD86, CD83, IFNγ, IL-1b, IL-6, TNFα, IL-17A, IL-2, or IL-6 in a cell, tissue, or subject. The method comprises contacting the cell, tissue, or subject with an effective amount of a sialidase, fusion protein, and/or antibody conjugate, *e.g.,* a sialidase, fusion protein, or antibody conjugate disclosed herein. In certain embodiments, the cell is selected from a dendritic cell and a peripheral blood mononuclear cell (PBMC).

[00277] In certain embodiments, expression of HLA-DR, CD86, CD83, IFNγ, IL-1b, IL-6, TNFα, IL-17A, IL-2, or IL-6 in the cell, tissue, or subject is increased by at least about 10%, at least about 20%, at least about 50%, at least about 75%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, or at least about 1,000%, relative to a similar or otherwise identical cell or tissue that has not been contacted with the sialidase, fusion protein, or antibody conjugate. Gene expression may be measured by any suitable method known in the art, for example, by ELISA, or by Luminex multiplex assays.

[00278] The invention also provides a method of promoting infiltration of immune cells into a tumor in a subject in need thereof. The method comprises administering to the subject an effective amount of a sialidase, fusion protein, and/or antibody conjugate, *e.g.,* a sialidase, fusion protein, or antibody conjugate disclosed herein. In certain embodiments, the immune cells are T-cells, *e.g.,* CD4+ and/or CD8+ T-cells, *e.g.,* $CD69^{+}CD8^{+}$ and/or $GzmB^{+}CD8^{+}$ T-cells. In certain embodiments, the immune cells are natural killer (NK) cells.

[00279] In certain embodiments, the infiltration of immune cells into the tumor in the subject is increased by at least about 10%, at least about 20%, at least about 50%, at least about 75%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, or at least about 1,000%, relative to a similar or otherwise identical tumor and/or subject that has not been administered the sialidase, fusion protein, or antibody conjugate. Infiltration of immune cells into a tumor may be measured by any suitable method known in the art, for example, antibody staining.

[00280] The invention also provides a method of increasing the amount of circulating natural killer (NK) cells in a subject in need thereof. The method comprises administering to the subject an effective amount of a sialidase, fusion protein, and/or antibody conjugate, *e.g.,* a sialidase, fusion protein, or antibody conjugate disclosed herein, so as to increase the number of circulating NK cells relative to prior to administration of the sialidase, fusion protein, antibody conjugate, or pharmaceutical composition.

[00281] In certain embodiments, the amount of circulating NK cells in the subject is increased by at least about 10%, at least about 20%, at least about 50%, at least about 75%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, or at least about 1,000%, relative to a similar or otherwise identical subject that has not been administered the sialidase, fusion protein, or antibody conjugate. Circulating NK cells in a subject may be measured by any suitable method known in the art, for example, antibody staining.

[00282] The invention also provides a method of increasing the amount of T-cells in the draining lymph node in a subject in need thereof. The method comprises administering to the subject an effective amount of a sialidase, fusion protein, antibody conjugate, and/or pharmaceutical composition, *e.g.,* a sialidase, fusion protein, antibody conjugate, and/or pharmaceutical composition disclosed herein, so as to increase the number of T-cells in the draining lymph node relative to prior to administration of the sialidase, fusion protein, antibody conjugate, or pharmaceutical composition. In certain embodiments, the immune cells are T-cells, *e.g.,* CD4+ and/or CD8+ T-cells.

[00283] In certain embodiments, the amount of T-cells in the draining lymph node in the subject is increased by at least about 10%, at least about 20%, at least about 50%, at least

about 75%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, or at least about 1,000%, relative to a similar or otherwise identical subject that has not been administered the sialidase, fusion protein, antibody conjugate, or pharmaceutical composition. T-cells in the draining lymph node in a subject may be measured by any suitable method known in the art, for example, antibody staining.

[00284] The invention also provides a method of increasing expression of Cd3, Cd4, Cd8, Cd274, Ctla4, Icos, Pdcd1, Lag3, Il6, Il1b, Il2, Ifng, Ifna1, Mx1, Gzmb, Cxcl9, Cxcl12, and/or Ccl5 in a cell, tissue, or subject. The method comprises contacting the cell, tissue, or subject with an effective amount of a sialidase, fusion protein, antibody conjugate, and/or pharmaceutical composition, *e.g.*, a sialidase, fusion protein, antibody conjugate, and/or pharmaceutical composition disclosed herein, so as to increase the expression of Cd3, Cd4, Cd8, Cd274, Ctla4, Icos, Pdcd1, Lag3, Il6, Il1b, Il2, Ifng, Ifna1, Mx1, Gzmb, Cxcl9, Cxcl12, and/or Ccl5 relative to the cell, tissue or subject prior to contact with the sialidase, fusion protein, antibody conjugate, or pharmaceutical composition.

[00285] In certain embodiments, expression of Cd3, Cd4, Cd8, Cd274, Ctla4, Icos, Pdcd1, Lag3, Il6, Il1b, Il2, Ifng, Ifna1, Mx1, Gzmb, Cxcl9, Cxcl12, and/or Ccl5 in the cell, tissue, or subject is increased by at least about 10%, at least about 20%, at least about 50%, at least about 75%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, or at least about 1,000%, relative to a similar or otherwise identical cell, tissue, or subject that has not been contacted with the sialidase, fusion protein, antibody conjugate, or pharmaceutical composition. Gene expression may be measured by any suitable method known in the art, for example, by ELISA, Luminex multiplex assays, or Nanostring technology.

[00286] The invention also provides a method of removing sialic acid from a cell or tissue. The method comprises contacting the cell or tissue with an effective amount of a sialidase, fusion protein, and/or antibody conjugate, *e.g.*, a sialidase, fusion protein, or antibody conjugate disclosed herein. The invention also provides a method of removing sialic acid from a cell in a subject, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising a sialidase, fusion protein, and/or

antibody conjugate, *e.g.,* a sialidase, fusion protein, or antibody conjugate disclosed herein, thereby to remove sialic acid from the cell.

[00287] In certain embodiments, the cell is tumor cell, dendritic cell (DC) or monocyte. In certain embodiments, the cell is a monocyte, and the method results in increased expression of an MHC-II molecule (*e.g.*, HLA-DR) on the monocyte. In certain embodiments, expression of an MHC-II molecule in the cell or tissue is increased by at least about 10%, at least about 20%, at least about 50%, at least about 75%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, or at least about 1,000%, relative to a similar or otherwise identical cell or tissue that has not been contacted with the sialidase, fusion protein, and/or antibody conjugate. Gene expression may be measured by any suitable method known in the art, for example, by ELISA, by Luminex multiplex assays, or by flow cytometry.

[00288] The invention also provides a method of enhancing phagocytosis of a tumor cell. The method comprises contacting the tumor cell with a sialidase, fusion protein, and/or antibody conjugate, *e.g.,* a sialidase, fusion protein, or antibody conjugate disclosed herein, in an amount effective to remove sialic acid from the tumor cell, thereby enhancing phagocytosis of the tumor cell. In certain embodiments, the disclosure relates to a method of increasing phagocytosis of a tumor cell in a subject, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising a sialidase, fusion protein, and/or antibody conjugate, *e.g.,* a sialidase, fusion protein, or antibody conjugate disclosed herein, in an amount effective to remove sialic acid from the tumor cell, thereby to increase phagocytosis of the tumor cell.

[00289] In certain embodiments, phagocytosis is increased by at least about 10%, at least about 20%, at least about 50%, at least about 75%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, or at least about 1,000%, relative to a similar or otherwise identical tumor cell or population of tumor cells that has not or have not been contacted with the sialidase, fusion protein, and/or antibody conjugate. Phagocytosis may be measured by any suitable method known in the art.

[00290] The invention also provides a method of activating a dendritic cell (DC). The method comprises contacting the DC with a tumor cell that has been treated with a sialidase, fusion protein, and/or antibody conjugate, *e.g.,* a sialidase, fusion protein, or antibody conjugate disclosed herein. In certain embodiments, the disclosure relates to a method of activating a dendritic cell (DC) or a population of DCs in a subject, the method comprising administering to the subject an amount of a pharmaceutical composition comprising a sialidase, fusion protein, and/or antibody conjugate, e.g., a sialidase, fusion protein or antibody conjugate disclosed herein, effective to remove sialic acid from a tumor cell in the subject, thereby to activate the DC or the population of DCs in the subject.

[00291] In certain embodiments, activation of the DC or a population of DCs is increased by at least about 10%, at least about 20%, at least about 50%, at least about 75%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, or at least about 1,000%, relative to a similar or otherwise identical DC or population of DCs that has not or have not been contacted with a tumor cell that has been treated with the sialidase, fusion protein, and/or antibody conjugate. Activation may be measured by any suitable method known in the art.

[00292] The invention also provides a method of reducing Siglec-15 binding activity, thereby to increase anti-tumor activity in a tumor microenvironment, the method comprising contacting a T cell with a sialidase, fusion protein, and/or antibody conjugate, *e.g.,* a sialidase, fusion protein, or antibody conjugate disclosed herein. In certain embodiments, the disclosure relates to a method of reducing Siglec-15 binding activity, thereby to increase anti-tumor activity in a tumor microenvironment of a patient, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising a sialidase, fusion protein, and/or antibody conjugate, *e.g.,* a sialidase, fusion protein, or antibody conjugate disclosed herein, thereby to increase anti-tumor activity (e.g., T cell activity) in the subject.

[00293] In certain embodiments, Siglec-15 binding activity is reduced by at least about 10%, at least about 20%, at least about 50%, at least about 75%, or about 100%, relative to Siglec-15 that has not or have not been contacted with the sialidase, fusion protein, and/or antibody conjugate. Binding may be measured by any suitable method known in the art.

[00294] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[00295] In the application, where an element or component is said to be included in and/or selected from a list of recited elements or components, it should be understood that the element or component can be any one of the recited elements or components, or the element or component can be selected from a group consisting of two or more of the recited elements or components.

[00296] Further, it should be understood that elements and/or features of a composition or a method described herein can be combined in a variety of ways without departing from the spirit and scope of the present invention, whether explicit or implicit herein. For example, where reference is made to a particular compound, that compound can be used in various embodiments of compositions of the present invention and/or in methods of the present invention, unless otherwise understood from the context. In other words, within this application, embodiments have been described and depicted in a way that enables a clear and concise application to be written and drawn, but it is intended and will be appreciated that embodiments may be variously combined or separated without parting from the present teachings and invention(s). For example, it will be appreciated that all features described and depicted herein can be applicable to all aspects of the invention(s) described and depicted herein.

[00297] It should be understood that the expression "at least one of" includes individually each of the recited objects after the expression and the various combinations of two or more of the recited objects unless otherwise understood from the context and use. The expression "and/or" in connection with three or more recited objects should be understood to have the same meaning unless otherwise understood from the context.

[00298] The use of the term "include," "includes," "including," "have," "has," "having," "contain," "contains," or "containing," including grammatical equivalents thereof, should be understood generally as open-ended and non-limiting, for example, not excluding additional

unrecited elements or steps, unless otherwise specifically stated or understood from the context.

[00299] Where the use of the term "about" is before a quantitative value, the present invention also includes the specific quantitative value itself, unless specifically stated otherwise. As used herein, the term "about" refers to a ±10% variation from the nominal value unless otherwise indicated or inferred.

[00300] It should be understood that the order of steps or order for performing certain actions is immaterial so long as the present invention remain operable. Moreover, two or more steps or actions may be conducted simultaneously.

[00301] The use of any and all examples, or exemplary language herein, for example, "such as" or "including," is intended merely to illustrate better the present invention and does not pose a limitation on the scope of the invention unless claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the present invention.

EXAMPLES

[00302] The following Examples are merely illustrative and are not intended to limit the scope or content of the invention in any way.

Example 1

[00303] This example describes the construction of recombinant human sialidases (Neu1, Neu2, and Neu3).

[00304] The human sialidases Neu1, Neu2, Neu3 (isoform 1), and Neu4 (isoform 1) were expressed as secreted proteins with a 10xHis tag. To express Neu1 as a secreted protein, the native N terminal signal peptide (MTGERPSTALPDRRWGPRILGFWGGCRVWVFAAIFLLLSLAASWSKA; SEQ ID NO: 27) was replaced by MDMRVPAQLLGLLLLWLPGARC (SEQ ID NO: 28), and the C terminal lysosomal signal motif (YGTL; SEQ ID NO: 29) was removed. To express Neu2, Neu3, and Neu4 as secreted proteins, the N terminal signal peptide MDMRVPAQLLGLLLLWLPGARC (SEQ ID NO: 28) was added to each.

[00305] Sialidases were expressed in a 200 mL transfection of HEK293F human cells in 24-well plates using the pCEP4 mammalian expression vector with an N-terminal 6xHis tag. Sialidases were purified using Ni-NTA columns, quantified with a UV-Vis

spectrophotometer (NanoDrop), and examined by SDS-PAGE as shown in **FIGURE 1**. Neu1 expressed well, with a yield of ~3 μg/ml, and was present primarily in a monomeric form. Neu2 and Neu3 expression each gave yields of ~0.15 μg/mL and each were present primarily in a dimeric form. Neu4 had no detectable expression yield as measured by NanoDrop. Bacterial sialidase from *Salmonella typhimurium* (St-sialidase; SEQ ID NO: 30), which was used as a positive control for expression, gave a comparable yield to Neu1, and was present primarily in a monomeric form.

[00306] The activity of the recombinantly expressed sialidases was assayed by measuring the release of sialic acid from the fluorogenic substrate 4-methylumbelliferyl-N-acetylneuraminic acid (4MU-NeuAc). As shown in **FIGURE 2**, Neu1 has no detectable activity above a no-enzyme control, which is consistent with previous reports indicating that Neu1 is inactive unless it is in complex with beta-galactosidase and protective protein/cathepsin A (PPCA). Neu2 and Neu3 were active. An enzyme kinetics assay was performed with Neu2 and Neu3. A fixed concentration of enzyme at 1 nM was incubated with fluorogenic substrate 4MU-NeuAc at concentrations ranging from 4000 μM to 7.8 μM. Assays were conducted at both acidic (pH 5.6) and neutral (pH 7) conditions. As shown in **FIGURE 3**, both Neu2 and Neu3 were active at acidic and neutral conditions and showed enzyme kinetics that were comparable to those previously reported.

[00307] Most of the recombinantly expressed sialidases ran as aggregates or dimers on a non-reducing SDS-PAGE gel. Subsequent treatment with the reducing agent dithiothreitol (DTT) resulted in a monomeric form of the enzyme that ran at 42 kDa on a reducing SDS-PAGE gel (**FIGURE 1**).

Example 2

[00308] This example describes the construction of recombinant human sialidases with mutations that increase expression and/or activity of the sialidase.

A. Rational Design

[00309] Structural and sequence analysis identified residues A93 and P62 of Neu2 as candidates for substitutions to increase solubility and/or expression. In particular, a comparison of homologous sialidase sequences showed a preference for D or E amino acid residues at positions corresponding to position 93 of Neu2, and a preference for G amino acid residues at positions corresponding to position 62 of Neu2.

[00310] The beta-propeller family of proteins are usually stabilized by extensive hydrogen bonding interactions at the N- and C-termini of the protein. A structural analysis revealed that Neu2, which is a member of the beta-propeller family, appears to lack these stabilizing interactions. In contrast, sialidases from Salmonella typhimurium and Micromonospora viridifaciens (the bacterial sialidase most homologous to human Neu2) have extensive hydrogen bonding interactions at their N- and C-termini. Accordingly, residues K9, V363, and L365 of Neu2 were mutated to promote hydrogen bonding between the N- and C-termini of Neu2.

B. Phage Display

[00311] Neu2 was expressed in a phage display system allowing for screening of Neu2 variants for both expression level and resistance to heat denaturation. Neu2 with V6Y and I187K substitutions was used as a template for library preparation. Designed phage display libraries 1, 2, and 3 are depicted in **TABLES 11-13**, respectively. Each library included all of the possible combinations of the mutations depicted. A fourth library included random mutations generated by error prone PCR.

TABLE 11 - Phage Library 1

Wild-Type Neu2 Amino Acid(s)	Design	Substituting Amino Acids	Codon Usage
184-188 LHPIQ	Adjust length of 5 wild-type residues from 2 to 5 and substitute each residue with one of 9 polar amino acids	S, N, R, K, T, G, D, E, A	RVM
P190, I191	Substitute with one of 5 non-polar amino acids	F, I, L, M, V	NTK
C219	Substitute with one of 12 polar or nonpolar amino acids	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
L217	Substitute with one of 12 polar or nonpolar amino acids	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
T216 and L217	Insert one of 12 polar or nonpolar amino acids between the wild-type amino acids	S, T, Y, L, F, A, P, V, I, N, D, H	NHT
G271	Substitute with one of 9 polar amino acids	S, N, R, K, T, G, D, E, A	RVM
C272	Substitute with one of 9 polar amino acids	S, N, R, K, T, G, D, E, A	RVM

TABLE 12 – Phage Library 2

Wild-Type Neu2 Amino Acid(s)	Design	Substituting Amino Acids	Codon Usage
156-165 TFAVGPGHCL	Substitute with one of 12 hydrophobic or polar amino acids	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
V176	Substitute with one of 12 hydrophobic or polar amino acids	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
P177	Substitute with one of 12 hydrophobic or polar amino acids	S, T, Y, L, F, A, P, V, I, N, D, H	NHT
A178	Substitute with one of 12 hydrophobic or polar amino acids	S, T, Y, L, F, A, P, V, I, N, D, H	NHT
A194	Substitute with one of 12 hydrophobic or polar amino acids	S, T, Y, L, F, A, P, V, I, N, D, H	NHT

TABLE 13 – Phage Library 3

Wild-Type Neu2 Amino Acid(s)	Design	Substituting Amino Acids	Codon Usage
F13	Substitute with one of 9 polar amino acids chain AAs	S, N, R, K, T, G, D, E, A	RMV
L4	Substitute with one of 12 hydrophobic or polar amino acids	S, T, Y, L, F, A, P, V, I, N, D, H	NHT
L7, V12	Substitute with one of 6 polar or aromatic amino acids	F, Y, S, I, T, N	WHT
I22, A24	Substitute with one of 9 polar amino acids	S, N, R, K, T, G, D, E, A	RMV
V325, L326, and L327	Substitute with one of 6 polar or aromatic amino acids	F, Y, S, I, T, N	WHT
L365	Substitute with one of 6 polar or aromatic amino acids	F, Y, S, I, T, N	WHT
P89	Substitute with one of 5 non-polar amino acids	F, I, L, M, V	NTK
L34, A36, and V363	Substitute with one of 12 hydrophobic or polar amino acids	S, T, Y, L, F, A, P, V, I, N, D, H	NHT

[00312] The codon usage columns in **TABLES 11-13** represent degenerate codon codes used in the design of the library, where the first, second, and third positions of a given codon encoding an amino acid are as shown in **TABLE 14** and as described in Mena *et al.* (2005) PROTEIN ENG DES SEL. 18(12):559-61.

TABLE 14

Degenerate Codon Code	Mixed bases
R	A, G
Y	C, T/U
M	A, C
K	G, T/U
S	G, C
W	A, T
H	A, C, T/U
B	G, C, T (or U)
V	A, C, G
D	A, G, T/U
N	A, C, G, T/U

[00313] The phage display libraries were screened for binding to a conformation-specific antibody and/or a sialic acid biotinylated probe after heating to enrich for thermal stability and expression. The sialic acid biotinylated probe and its synthesis is depicted in **FIGURE 4.** An exemplary phage display screening procedure is depicted in **FIGURE 5.** Briefly, phage libraries expressing the desired Neu2 variants were generated. Phage were screened for binding to immobilized anti-Neu2 antibody and/or sialic acid biotinylated probe. Following washing to remove unbound phage, bound phage were eluted from the antibody or probe and analyzed as appropriate.

C. Yeast display

[00314] Neu2 was also expressed in a yeast display system allowing for screening of Neu2 variants for both expression level and resistance to heat denaturation. Neu2 with V6Y and I187K substitutions was used as a template for library preparation. Designed yeast display libraries 1a, 1b, 1c, 1d, 2a, 2b, 2c, 3a, 3b, and 3c are depicted in **TABLES 15-24,** respectively. Each library included all of the possible combinations of the mutations depicted. Five additional sublibraries were generated by error prone PCR, at an approximate average rate of 1, 2, 3, 4, and 5 substitutions per enzyme.

TABLE 15 -Yeast Library 1a

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
L184	All	NNK
H185	All	NNK
P186	None (Wild-type)	

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
K187	None (Wild-type)	
Q188	None (Wild-type)	
P190	A, D, G, H, I, L, N, P, R, S, T, V	VNT
I191	A, D, F, H, I, L, N, P, S, T, V, Y	NHT
C219	None (Wild-type)	
G271	All	NNK
C272	All	NNK

Total Diversity: 2.30E+07

TABLE 16 - Yeast Library 1b

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
L184	A, D, F, H, I, L, N, P, S, T, V, Y	NHT
H185	All	NNK
P186	A, D, F, H, I, L, N, P, S, T, V, Y	NHT
K187	None (Wild-type)	
Q188	None (Wild-type)	
P190	A, D, G, H, I, L, N, P, R, S, T, V	VNT
I191	A, D, F, H, I, L, N, P, S, T, V, Y	NHT
C219	None (Wild-type)	
G271	A, D, E, G, K, N, R, S, T	RVM
C272	A, C, D, G, H, N, P, R, S, T	NVT

Total Diversity: 4.11E+07

5

TABLE 17 -Yeast Library 1c

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
L184	A, D, F, H, I, L, N, P, S, T, V, Y	NHT
H185	A, D, E, G, K, N, R, S, T	RVM
P186	A, D, F, H, I, L, N, P, S, T, V, Y	NHT
K187	A, D, E, G, K, N, R, S, T	RVM
Q188	None (Wild-type)	
P190	F, L, I, V	NTT
I191	A, D, F, H, I, L, N, P, S, T, V, Y	NHT
C219	None (Wild-type)	
G271	A, D, E, G, K, N, R, S, T	RVM
C272	A, D, F, H, L, P, S, V, Y	BHT

Total Diversity: 4.53E+07

TABLE 18 -Yeast Library 1d

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
L184	A, D, F, H, L, P, S, V, Y	BHT
H185	A, D, E, G, K, N, R, S, T	RVM
P186	A, D, F, H, L, P, S, V, Y	BHT

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
K187	A, D, E, G, K, N, R, S, T	RVM
Q188	A, D, F, H, L, P, S, V, Y	BHT
P190	None (Wild-type)	
I191	A, D, E, G, K, N, R, S, T	RVM
C219	None (Wild-type)	
G271	A, D, E, G, K, N, R, S, T	RVM
C272	A, D, F, H, L, P, S, V, Y	BHT

Total Diversity: 4.30E+07

TABLE 19 -Yeast Library 2a

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
T156	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
F157	None (Wild-type)	
A158	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
V159	None (Wild-type)	
G160	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
P161	None (Wild-type)	
G162	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
H163	None (Wild-type)	
C164	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
L165	None (Wild-type)	
V176	L, V, P, A, H, D	SHT
P177	L, V, P, A, H, D	SHT
A178	L, V, P, A, H, D	SHT
A194	L, V, P, A, H, D	SHT

Total Diversity: 3.22E+08

5

TABLE 20 -Yeast Library 2b

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
T156	None (Wild-type)	
F157	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
A158	None (Wild-type)	
V159	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
G160	None (Wild-type)	
P161	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
G162	None (Wild-type)	
H163	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
C164	None (Wild-type)	
L165	R, N, D, C, G, H, I, L, F, S, Y, V	NDT
V176	L, V, P, A, H, D	SHT
P177	L, V, P, A, H, D	SHT
A178	L, V, P, A, H, D	SHT
A194	L, V, P, A, H, D	SHT

Total Diversity: 3.22E+08

TABLE 21 -Yeast Library 2c

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
T156	A, D, G, H, N, P, R, S, T	VVC
F157	A, D, F, H, L, P, S, V, Y	BHT
A158	A, D, G, H, N, P, R, S, T	VVC
V159	A, D, F, H, L, P, S, V, Y	BHT
G160	A, D, G, H, N, P, R, S, T	VVC
P161	A, D, F, H, L, P, S, V, Y	BHT
G162	A, D, G, H, N, P, R, S, T	VVC
H163	A, D, F, H, L, P, S, V, Y	BHT
C164	A, D, G, H, N, P, R, S, T	VVC
L165	A, D, F, H, L, P, S, V, Y	BHT
V176	None (Wild-type)	
P177	None (Wild-type)	
A178	None (Wild-type)	
A194	None (Wild-type)	

Total Diversity: 3.49E+09

TABLE 22 -Yeast Library 3a

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
L4	S, T, Y, L, F, A, P, V, I, N, D, H	NHT
L7	F, Y, S, I, T, N	WHT
V12	None (Wild-type)	
F13	None (Wild-type)	
I22	S, N, R, K, T, G, D, E, A	RMV
A24	S, N, R, K, T, G, D, E, A	RMV
L34	None (Wild-type)	
A36	None (Wild-type)	
H64	F, Y, S, I, T, N	WHT
P89	F, I, L, V	NTT
C164	None (Wild-type)	
V325	F, Y, S, I, T, N	WHT
L326	F, Y, S, I, T, N	WHT
L327	F, Y, S, I, T, N	WHT
C332	None (Wild-type)	
V363	S, T, Y, L, F, A, P, V, I, N, D, H	NHT

Total Diversity: 3.63E+08

TABLE 23 -Yeast Library 3b

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
L4	None (Wild-type)	
L7	F, Y, S, I, T, N	WHT
V12	S, T, Y, L, F, A, P, V, I, N, D, H	NHT
F13	S, N, R, K, T, G, D, E, A	RMV

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
I22	S, N, R, K, T, G, D, E, A	RMV
A24	S, N, R, K, T, G, D, E, A	RMV
L34	S, T, Y, L, F, A, P, V, I, N, D, H	NHT
A36	S, T, Y, L, F, A, P, V, I, N, D, H	NHT
H64	None (Wild-type)	
P89	None (Wild-type)	
C164	A, G, S, T	RST
V325	None (Wild-type)	
L326	None (Wild-type)	
L327	None (Wild-type)	
C332	A, D, G, H, N, P, R, S, T	VVC
V363	None (Wild-type)	

Total Diversity: 2.72E+08

TABLE 24 -Yeast Library 3c

Wild-Type Neu2 Amino Acid(s)	Substituting Amino Acids	Codon Usage
L4	None (Wild-type)	
L7	None (Wild-type)	
V12	None (Wild-type)	
F13	None (Wild-type)	
I22	S, T, Y, L, F, A, P, V, I, N, D, H	NHT
A24	S, T, Y, L, F, A, P, V, I, N, D, H	NHT
L34	None (Wild-type)	
A36	None (Wild-type)	
H64	F, Y, S, I, T, N	WHT
P89	S, T, Y, L, F, A, P, V, I, N, D, H	NHT
C164	A, G, S, T	RST
V325	A, D, F, H, L, P, S, V, Y	BHT
L326	A, D, F, H, L, P, S, V, Y	BHT
L327	A, D, F, H, L, P, S, V, Y	BHT
C332	A, D, G, H, N, P, R, S, T	VVC
V363	None (Wild-type)	

Total Diversity: 2.72E+08

[00315] The codon usage columns in **TABLES 15-24** represent degenerate codon codes used in the design of the library, where the first, second, and third positions of a given codon encoding an amino acid are as shown herein above in **TABLE 14** and as described in Mena *et al.* (2005) PROTEIN ENG DES SEL. 18(12):559-61.

[00316] The yeast display libraries were screened for binding to a conformation-specific antibody and/or a sialic acid biotinylated probe after heating to enrich for thermal stability and expression. An exemplary yeast display screening procedure is depicted in **FIGURE 6.** Briefly, a plasmid library encoding for the desired Neu2 variants, and yeast cells expressing

the desired Neu2 variants on the surface, were generated. Yeast cells were heat shocked and then screened for binding to anti-Neu2 antibody and/or sialic acid biotinylated probe on magnetic beads. The magnetic beads were isolated to remove unbound cells, and bound cells were further analyzed for Neu2 affinity, activity, and stability as appropriate.

D. Results

[00317] Mutant sialidases including mutations identified using the rational design, phage display, and yeast display approaches described in this Example were expressed as secreted proteins with a C-terminal human Fc tag in Expi293F cells using the pCEP4 mammalian expression vector. Expression was assayed using a ForteBio Octet with anti-human Fc sensors and Western blot and enzymatic activity was assayed using the fluorogenic substrate 4MU-NeuAc as described above.

[00318] Expression and activity levels for the mutant sialidases are shown in **TABLE 25**. In **TABLE 25**, enzymatic activity is indicated as "+++," which denotes activity >2 fold higher than wild-type Neu2, "++," which denotes activity comparable to wild-type Neu2, "+," which denotes activity lower than wild-type Neu2, or "-," which denotes no detectable activity, and expression is indicated as "++++," which denotes expression > 15 fold higher than wildtype-Neu2, "+++," which denotes expression > 6 fold higher than wild-type Neu2, "++," which denotes expression 2-5 fold higher than wild-type Neu2, "+," which denotes expression comparable to wild-type Neu2, or "-,"which denotes no detectable expression.

TABLE 25

Identifier	Mutation(s)	Activity	Expression
Neu2-M104	M1D, V6Y, P62G, I187K, C332A	+	++++
Neu2-M105	M1D, V6Y, K9D, I187K, C332A, V363R, L365I	+	+++
Neu2-M106	M1D, V6Y, P62G, A93E, I187K, C332A	++	++++
Neu2-M107	M1D, V6Y, K9D, I187K, C332A, V363R, L365K	+	++++
Neu2-M108	M1D, V6Y, K9D, I187K, C332A, V363R, L365S	+	++++
Neu2-M109	M1D, V6Y, K9D, I187K, C332A, V363R, L365Q	+	++++
Neu2-M110	M1D, V6Y, K9D, I187K, C332A, V363R, L365H	+	+++
Neu2-M111	M1D, V6Y, A93K, I187K, C332A	++	++
Neu2-M112	M1D, V6Y, A93E, I187K, C332A	++	++

Identifier	Mutation(s)	Activity	Expression
Neu2-M113	V6Y, I22N, C125Y, I187K, S301C, E319D	-	+++
Neu2-M114	V6Y, P62T, C125F, I187K, A222D	-	+++
Neu2-M115	V6Y, I187K, W292R	+	+++
Neu2-M116	V6Y, G107D, I187K	+	+++
Neu2-M117	C125L	+	+
Neu2-M118	V6Y, C125L	+	++
Neu2-M119	C125L, I187K	++	++
Neu2-M120	V6Y, C125L, I187K	+	+++
Neu2-M121	M1D, V6Y, K45A, I187K, C332A	++	++
Neu2-M122	M1D, V6Y, Q270A, I187K, C332A	++	+++
Neu2-M123	M1D, V6Y, K44R, K45R, I187K, C332A	+	++
Neu2-M124	M1D, V6Y, Q112R, I187K, C332A	+	++
Neu2-M125	M1D, V6Y, Q270F, I187K, C332A	+	++
Neu2-M126	M1D, V6Y, I187K, S301R, W302K, C332A	++	+++
Neu2-M127	M1D, V6Y, K44E, K45E, I187K, C332A	++	+
Neu2-M128	M1D, V6Y, I187K, L217V, C332A	+	++
Neu2-M129	M1D, V6Y, I187K, L217A, C332A	+	++
Neu2-M130	M1D, V6Y, I187K, C332A, Y359A	-	+++
Neu2-M131	M1D, V6Y, I187K, C332A, Y359S	-	+++
Neu2-M132	M1D, V6Y, K44E, K45E, I187K, S301R, W302K, C332A	++	++
Neu2-M133	M1D, V6Y, Q112R, I187K, S301R, W302K, C332A	++	+++
Neu2-M134	M1D, V6Y, I187K, Q270A, S301R, W302K, C332A	++	+++
Neu2-M135	M1D, V6Y, K44E, K45E, Q112R, I187K, C332A	+	+
Neu2-M136	M1D, V6Y, K44E, K45E, I187K, Q270A, C332A	++	++
Neu2-M137	M1D, V6Y, K45A, I187K, Q270A, C332A	++	+++
Neu2-M138	M1D, V6Y, I187K, Q270H, C332A	++	+++
Neu2-M139	M1D, V6Y, I187K, Q270P, C332A	+	+++
Neu2-M140	M1D, V6Y, Q112K, I187K, C332A	++	++
Neu2-M141	M1D, V6Y, P62S, I187K, Q270A, S301R, W302K, C332A	+	+++
Neu2-M142	M1D, V6Y, P62T, I187K, Q270A, S301R, W302K, C332A	+	+++
Neu2-M143	M1D, V6Y, P62N, I187K, Q270A, S301R, W302K, C332A	+	+++
Neu2-M144	V6Y, P62H, I187K	+	+++

Identifier	Mutation(s)	Activity	Expression
Neu2-M145	V6Y, Q108H, I187K	+	++
Neu2-M146	M1D, V6Y, P62H, I187K, C332A	++	+++
Neu2-M147	M1D, V6Y, P62G, I187K, C332A	++	++
Neu2-M148	V6Y, P62G, I187K	+	++
Neu2-M149	M1D, V6Y, P62H, I187K	++	++
Neu2-M150	M1D, V6Y, Q108H, I187K	++	++
Neu2-M151	M1D, V6Y, P62F, I187K, C332A	+	-
Neu2-M152	M1D, V6Y, P62I, I187K, C332A	+	-
Neu2-M153	M1D, V6Y, P62N, I187K, C332A	++	+++
Neu2-M154	M1D, V6Y, P62D, I187K, C332A	++	+
Neu2-M155	M1D, V6Y, P62E, I187K, C332A	++	+++
Neu2-M156	V6Y, C164G, I187K, T249A	+	+
Neu2-M157	V6Y, C164G, I187K	+	+
Neu2-M158	V6Y, Q126L, I187K D251G	+	++
Neu2-M159	V6Y, L54M, Q69H, R78K, A171G, I187K	+	+
Neu2-M160	V6Y, P62T, I187K	+	++
Neu2-M161	V6Y, A150V, I187K	+	++
Neu2-M162	P5H, V6Y, P62S, I187K	+	++
Neu2-M163	V6Y, C164G, I187K	+	+

[00319] To confirm these results, Neu2-M106 (with amino acid sequence SEQ ID NO: 48, encoded by nucleotide sequence SEQ ID NO: 89) was expressed and purified with a protein A column. **FIGURE 7A** is an image of an SDS-PAGE gel showing recombinant wildtype human Neu2 and Neu2 variant M106 (each with a C-terminal human Fc tag) under non-reducing and reducing conditions. **FIGURE 7B** is an SEC-HPLC trace for recombinant wildtype human Neu2 and Neu2 variant M106 (each with a C-terminal human Fc tag). While Neu2-Fc had a yield of 0.3 mg/liter following protein-A purification, and monomer content of 7% as determined by SEC, Neu2-M106 had a yield of 20 mg/liter, and a monomer content of 85%.

[00320] The enzyme kinetics of Neu2-M106 were assayed by measuring the release of sialic acid from the fluorogenic substrate 4-methylumbelliferyl-N-acetylneuraminic acid (4MU-NeuAc) as described above. A fixed concentration of enzyme at 2 μg/well was incubated with fluorogenic substrate 4MU-NeuAc at concentrations ranging from 4mM to 0.03μM. **FIGURE 8** depicts the enzyme activity of Neu2 variant M106. Enzymatic activity of Neu2-M106 was comparable to wildtype Neu2, with a K_M determined to be 230μM.

[00321] Together, these results show that the mutations identified by rational design, phage display, and/or yeast display approaches described herein can increase stability and/or expression of a sialidase.

Example 3

[00322] This Example describes the construction and expression of antibody-sialidase genetic fusion proteins, and antibody sialidase conjugates (ASCs) containing the fusion proteins, with mutated human sialidases.

[00323] The architecture for five types of exemplary ASCs is depicted in **FIGURE 11**. The first type of ASC, referred to as "Raptor," includes an antibody (with two heavy chains and two light chains) with a sialidase fused at the C-terminus of each heavy chain of the antibody (**FIGURE 11A**). The second type of ASC, referred to as "Janus," contains one antibody arm (with one heavy chain and one light chain), and one sialidase-Fc fusion with a sialidase fused at the N-terminus of one arm of the Fc. Each Fc domain polypeptide in the Janus ASC contains either the "knob" (T366Y) or "hole" (Y407T) mutation for heterodimerization (residue numbers according to EU numbering, Kabat, E.A., *et al.* (1991) *supra*) (**FIGURE 11B**). The third type of ASC, referred to as "Lobster," contains two Fc domain polypeptides each with a sialidase fused at the N-terminus of the Fc and a scFv fused at the C-terminus of the Fc (**FIGURE 11C**). The fourth type of ASC, referred to as "Bunk," contains one antibody arm (with one heavy chain and one light chain) with an scFv fused at the C-terminus of one arm of the Fc and one sialidase-Fc fusion with a sialidase fused at the N-terminus of the other arm of the Fc. Each Fc domain polypeptide in the Bunk ASC contains either the "knob" (T366Y) or "hole" (Y407T) mutation for heterodimerization (residue numbers according to EU numbering, Kabat, E.A., *et al.* (1991) *supra*) (**FIGURE 11D**). The fifth type of ASC, referred to as "Lobster-Fab," contains two Fc domain polypeptides each with (i) a sialidase fused at the N-terminus of the Fc and (ii) a Fab fused at the C-terminus of the Fc (**FIGURE 11E**).

[00324] Janus ASCs including Neu2 variants described in Example 2 and trastuzumab were made and tested for activity and expression. Expression was assayed using a ForteBio Octet with anti-human Fc sensors and Western blot and enzymatic activity was assayed using the fluorogenic substrate 4MU-NeuAc as described above. Expression and activity levels for the Janus ASCs are shown in **TABLE 26**. In **TABLE 26**, enzymatic activity is indicated as "+++," which denotes activity >2 fold higher than wild-type Neu2, "++," which denotes

activity comparable to wild-type Neu2, "+," which denotes activity lower than wild-type Neu2, or "-," which denotes no detectable activity, and expression is indicated as "++++," which denotes expression > 15 fold higher than wildtype-Neu2, "+++," which denotes expression > 6 fold higher than wild-type Neu2, "++," which denotes expression 2-5 fold higher than wild-type Neu2, "+," which denotes expression comparable to wild-type Neu2, or "-,"which denotes no detectable expression.

TABLE 26

Neu2 Variant	Mutation(s)	Activity	Expression
Neu2-M146	M1D, V6Y, P62H, I187K, C332A	+++	+++
Neu2-M147	M1D, V6Y, P62G, I187K, C332A	++	++
Neu2-M148	V6Y, P62G, I187K	++	+++
Neu2-M149	M1D, V6Y, P62H, I187K	+	+++
Neu2-M150	M1D, V6Y, Q108H, I187K	++	++
Neu2-M151	M1D, V6Y, P62F, I187K, C332A	++	+++
Neu2-M152	M1D, V6Y, P62I, I187K, C332A	++	+++
Neu2-M153	M1D, V6Y, P62N, I187K, C332A	++	+++
Neu2-M154	M1D, V6Y, P62D, I187K, C332A	++	++
Neu2-M155	M1D, V6Y, P62E, I187K, C332A	++	+
Neu2-M156	V6Y, C164G, I187K, T249A	+	+
Neu2-M157	V6Y, C164G, I187K	+	+
Neu2-M158	V6Y, Q126L, I187K D251G	++	++
Neu2-M159	V6Y, L54M, Q69H, R78K, A171G, I187K	+	+
Neu2-M160	V6Y, P62T, I187K	++	++
Neu2-M161	V6Y, A150V, I187K	+	++
Neu2-M162	P5H, V6Y, P62S, I187K	++	++
Neu2-M163	V6Y, C164G, I187K	+	+

[00325] Additional Janus ASCs including Neu2 variants described in Example 2 and trastuzumab were made and tested for activity and expression. Janus ASCs were expressed in Expi293F cells in 500 mL cultures and purified using protein A and ion exchange chromatography. Expression was assayed using a ForteBio Octet with anti-human Fc sensors and Western blot and enzymatic activity was assayed using the fluorogenic substrate 4MU-NeuAc as described above. Expression and activity levels for the Janus ASCs are shown in **TABLE 27**. In **TABLE 27**, enzymatic activity is indicated as "+++," which denotes activity >2 fold higher than wild-type Neu2, "++," which denotes activity comparable to wild-type Neu2, "+," which denotes activity lower than wild-type Neu2, or "-," which denotes no detectable activity, and expression is indicated as "++++," which denotes expression > 15

fold higher than wildtype-Neu2, "+++," which denotes expression > 6 fold higher than wild-type Neu2, "++," which denotes expression 2-5 fold higher than wild-type Neu2, "+," which denotes expression comparable to wild-type Neu2, or "-,"which denotes no detectable expression.

TABLE 27

Neu2 Variant	Mutation(s)	Activity	Expression
Neu2-M106	M1D, V6Y, P62G, A93E, I187K, C332A	++	++++
Neu2-M134	M1D, V6Y, I187K, Q270A, S301R, W302K, C332A	+++	++++
Neu2-M141	M1D, V6Y, P62S, I187K, Q270A, S301R, W302K, C332A	++	++++
Neu2-M142	M1D, V6Y, P62T, I187K, Q270A, S301R, W302K, C332A	++	++++
Neu2-M143	M1D, V6Y, P62N, I187K, Q270A, S301R, W302K, C332A	++	++++
Neu2-M153	M1D, V6Y, P62N, I187K, C332A	++	++++

Example 4

[00326] This example describes the construction of recombinant human sialidases with mutations that increase expression and/or activity of the sialidase.

[00327] Unless indicated otherwise, mutant sialidases in this Example were expressed as secreted proteins with a C-terminal human Fc tag in Expi293F cells using the pCEP4 mammalian expression vector. Expression was assayed using a ForteBio Octet with anti-human Fc sensors and Western blot and enzymatic activity was assayed using the fluorogenic substrate 4MU-NeuAc as described above.

[00328] Mutant Neu2 sialidases were constructed including rationally designed substitutions at position Q126. Inspection of the Neu2 crystal structure revealed that mutation of Q126 may increase interactions with neighboring amino acid residues.

[00329] Additional mutant Neu2 sialidases were constructed including rationally designed substitution at position Q270. Inspection of the Neu2 crystal structure revealed that mutation of Q270 to certain amino acids may stabilize interactions with R237 and stabilize binding in the substrate pocket.

[00330] Additional mutant Neu2 sialidases were constructed including a substitution of an amino acid residue in a beta turn with a proline (for example D80P, R189P, and/or H239P

substitutions). Substitution with a proline at these positions may, for example, stabilize the protein by influencing local protein folding.

[00331] Expression and activity levels for the resulting mutant sialidases are shown in **TABLE 28**. In **TABLE 28**, enzymatic activity is indicated as "++," which denotes activity comparable to wild-type Neu2, "+," which denotes activity lower than wild-type Neu2, or "-," which denotes no detectable activity, and expression is indicated as "+++++", which denotes expression > 40 fold higher than wildtype-Neu2, "++++", which denotes expression > 15 fold higher than wildtype-Neu2, "+++," which denotes expression > 6 fold higher than wild-type Neu2, "++," which denotes expression 2-5 fold higher than wild-type Neu2, "+," which denotes expression comparable to wild-type Neu2, or "-,"which denotes no detectable expression.

TABLE 28

Identifier	Mutation(s)	Activity	Expression
Neu2-M164	M1D, V6Y, P62G, A93E, Q126E, I187K, C332A	++	++++
Neu2-M165	M1D, V6Y, P62G, A93E, Q126I, I187K, C332A	++	++++
Neu2-M166	M1D, V6Y, P62G, A93E, Q126L, I187K, C332A	+	+++++
Neu2-M167	M1D, V6Y, P62G, A93E, Q126Y, I187K, C332A	+	+++++
Neu2-M168	M1D, V6Y, P62G, A93E, Q126F, I187K, C332A	+	+++++
Neu2-M169	M1D, V6Y, P62G, A93E, Q126H, I187K, C332A	++	++++
Neu2-M170	M1D, V6Y, P62G, A93E, I187K, Q270S, C332A	++	++++
Neu2-M171	M1D, V6Y, P62G, A93E, I187K, Q270T, C332A	++	++++
Neu2-M172	M1D, V6Y, P62G, A93E, Q126Y, I187K, Q270T, C332A	++	+++++
Neu2-M173	M1D, V6Y, P62G, A93E, Q126Y, I187K, A242F, Q270T, C332A	++	+++++
Neu2-M174	M1D, V6Y, P62G, D80P, A93E, I187K, C332A	++	++++
Neu2-M175	M1D, V6Y, P62G, A93E, R170P, I187K, C332A	++	+++
Neu2-M176	M1D, V6Y, P62G, A93E, I187K, Q188P, C332A	++	++++

Identifier	Mutation(s)	Activity	Expression
Neu2-M177	M1D, V6Y, P62G, A93E, I187K, R189P, C332A	++	++++
Neu2-M178	M1D, V6Y, P62G, A93E, I187K, E225P, C332A	+	++++
Neu2-M179	M1D, V6Y, P62G, A93E, I187K, H239P, C332A	++	++++
Neu2-M180	M1D, V6Y, P62G, A93E, I187K, E257P, C332A	++	+++

[00332] To confirm these results, Neu2-M173 (with amino acid sequence SEQ ID NO: 159, encoded by nucleotide sequence SEQ ID NO: 181) was expressed with a C-terminal human Fc tag and purified with a protein A and a ceramic hydroxyapatite (CHT) column. **FIGURE 22A** is an image of an SDS-PAGE gel showing Neu2-M173-Fc (with a C-terminal human Fc tag) under non-reducing and reducing conditions. **FIGURE 22B** is an SEC-HPLC trace for Neu2-M173-Fc (with a C-terminal human Fc tag). Neu2-M173-Fc had a yield of 120 mg/liter, and a monomer content of 90%.

[00333] The enzyme kinetics of Neu2-M173-Fc were assayed by measuring the release of sialic acid from the fluorogenic substrate 4-methylumbelliferyl-N-acetylneuraminic acid (4MU-NeuAc) as described above. A fixed concentration of enzyme at 2 μg/well was incubated with fluorogenic substrate 4MU-NeuAc at concentrations ranging from 4mM to 0.03μM. **FIGURE 23** depicts the enzyme activity of Neu2-M173-Fc. Enzymatic activity of Neu2-M173-Fc was comparable to wildtype Neu2, with a K_M determined to be 230μM.

[00334] Additional mutant Neu2 sialidases were constructed including rationally designed substitutions at positions S301 and/or W302. Mutations of S301 and/or W302 may influence interactions with neighboring amino acid residues and/or substrate.

[00335] Expression and activity levels for the mutant sialidases are shown in **TABLE 29**. In **TABLE 29**, enzymatic activity is indicated as "++," which denotes activity comparable to wild-type Neu2, "+," which denotes activity lower than wild-type Neu2, or "-," which denotes no detectable activity, and expression is indicated as "+++++", which denotes expression > 40 fold higher than wildtype-Neu2, "++++", which denotes expression > 15 fold higher than wildtype-Neu2, "+++," which denotes expression > 6 fold higher than wild-type Neu2, "++," which denotes expression 2-5 fold higher than wild-type Neu2, "+," which denotes expression comparable to wild-type Neu2, or "-,"which denotes no detectable expression.

TABLE 29

Identifier	Mutation(s)	Activity	Expression
Neu2-M182	M1D, V6Y, P62G, A93E, I187K, S301A, C332A	++	++++
Neu2-M183	M1D, V6Y, P62G, A93E, I187K, S301D, C332A	++	++++
Neu2-M184	M1D, V6Y, P62G, A93E, I187K, S301E, C332A	++	+++
Neu2-M185	M1D, V6Y, P62G, A93E, I187K, S301F, C332A	+	++++
Neu2-M186	M1D, V6Y, P62G, A93E, I187K, S301H, C332A	+	++++
Neu2-M187	M1D, V6Y, P62G, A93E, I187K, S301K, C332A	++	+++++
Neu2-M188	M1D, V6Y, P62G, A93E, I187K, S301L, C332A	++	++++
Neu2-M189	M1D, V6Y, P62G, A93E, I187K, S301M, C332A	++	++++
Neu2-M190	M1D, V6Y, P62G, A93E, I187K, S301N, C332A	++	++++
Neu2-M191	M1D, V6Y, P62G, A93E, I187K, S301P, C332A	++	++++
Neu2-M192	M1D, V6Y, P62G, A93E, I187K, S301Q, C332A	++	+++
Neu2-M193	M1D, V6Y, P62G, A93E, I187K, S301R, C332A	++	+++++
Neu2-M194	M1D, V6Y, P62G, A93E, I187K, S301T, C332A	++	++++
Neu2-M195	M1D, V6Y, P62G, A93E, I187K, S301V, C332A	++	++++
Neu2-M196	M1D, V6Y, P62G, A93E, I187K, S301W, C332A	+	++++
Neu2-M197	M1D, V6Y, P62G, A93E, I187K, S301Y, C332A	++	++++
Neu2-M198	M1D, V6Y, P62G, A93E, I187K, W302A, C332A	+	++++
Neu2-M199	M1D, V6Y, P62G, A93E, I187K, W302D, C332A	+++	+++
Neu2-M200	M1D, V6Y, P62G, A93E, I187K, W302F, C332A	+	++++
Neu2-M201	M1D, V6Y, P62G, A93E, I187K, W302G, C332A	++	++++
Neu2-M202	M1D, V6Y, P62G, A93E, I187K, W302H, C332A	+	++++
Neu2-M203	M1D, V6Y, P62G, A93E, I187K, W302I, C332A	+	++++
Neu2-M204	M1D, V6Y, P62G, A93E, I187K, W302L, C332A	++	++++

Identifier	Mutation(s)	Activity	Expression
Neu2-M205	M1D, V6Y, P62G, A93E, I187K, W302M, C332A	+	++
Neu2-M206	M1D, V6Y, P62G, A93E, I187K, W302N, C332A	+	++++
Neu2-M207	M1D, V6Y, P62G, A93E, I187K, W302P, C332A	-	++++
Neu2-M208	M1D, V6Y, P62G, A93E, I187K, W302Q, C332A	++	++++
Neu2-M209	M1D, V6Y, P62G, A93E, I187K, W302R, C332A	++	+++++
Neu2-M210	M1D, V6Y, P62G, A93E, I187K, W302S, C332A	++	++++
Neu2-M211	M1D, V6Y, P62G, A93E, I187K, W302T, C332A	++	++++
Neu2-M212	M1D, V6Y, P62G, A93E, I187K, W302V, C332A	+	++++
Neu2-M213	M1D, V6Y, P62G, A93E, I187K, W302Y, C332A	+	++++
Neu2-M214	M1D, V6Y, P62G, A93E, I187K, S301A, W302A, C332A	++	++++
Neu2-M215	M1D, V6Y, P62G, A93E, I187K, S301A, W302R, C332A	+	++++
Neu2-M216	M1D, V6Y, P62G, A93E, I187K, S301A, W302S, C332A	++	++++
Neu2-M217	M1D, V6Y, P62G, A93E, I187K, S301A, W302T, C332A	++	++++
Neu2-M218	M1D, V6Y, P62G, A93E, I187K, S301K, W302S, C332A	+	++++
Neu2-M219	M1D, V6Y, P62G, A93E, I187K, S301K, W302R, C332A	++	+++++
Neu2-M219	M1D, V6Y, P62G, A93E, I187K, S301K, W302T, C332A	++	++++
Neu2-M220	M1D, V6Y, P62G, A93E, I187K, S301N, W302S, C332A	+	++++
Neu2-M221	M1D, V6Y, P62G, A93E, I187K, S301N, W302T, C332A	++	++++
Neu2-M222	M1D, V6Y, P62G, A93E, I187K, S301T, W302R, C332A	+	++++

Example 5

[00336] This example describes the construction of recombinant human sialidases with mutations that reduce proteolytic cleavage.

[00337] Neu2-M106 (as described in Example 2, and with amino acid sequence SEQ ID NO: 48) was expressed as an Fc-fused single chain protein using a CHO cell expression

system in a large scale (10 L) high cell density production and purified with a protein A column. The resulting protein was analyzed by SDS-PAGE. Results are shown in FIGURE 24. Under reducing conditions, the protein included a mixture of full length (70 kDa, approx. 50%) and cleaved (40 kDa and 30 kDa, approx. 50%) fractions. However, in non-reducing conditions, there was no cleavage and the protein remained as a single chain (FIGURE 24). Additionally, when Neu2-M106 was expressed on a smaller scale (with a shorter duration of cell culture and lower cell density) there was no cleavage and the protein remained as a single chain. A preliminary mass spectrometry analysis showed that the 40 kDa and 30 kDa molecular weight fractions observed under reducing conditions following large scale production are a result of cleavage between amino acid residues R243 and V244 of the sialidase. The enzymatic activity of cleaved Neu2-M106 was similar to that of uncleaved Neu2-M106.

[00338] It was hypothesized that the cleavage of Neu2-M106 could be due to the activity of intracellular proteases released as a result of cell lysis during protein production, harvesting, and/or purification. To test this hypothesis, cleaved Neu2-M106 (prepared using the large scale-production described above that results in cleavage) and uncleaved Neu2-M106 (prepared using the smaller scale production described above that does not result in cleavage) were both incubated with trypsin and analyzed by SDS-PAGE under reducing conditions (FIGURE 25). Briefly, trypsin digestion reactions were performed by incubation of trypsin (5 µL, 0.005% solution in PBS) with Neu2-M106 (25 µL, 0.25 mg/mL in PBS pH 8.0) for 5 minutes on ice. Reactions were stopped by addition of LDS gel loading buffer (5 µL) and run on a reducing SDS-PAGE gel to observe trypsin mediated cleavage. The SDS-PAGE analysis showed that incubation of the uncleaved Neu2-M106 with trypsin resulted in the same cleavage pattern as that of the cleaved Neu2-M106. Additionally, incubation of the cleaved Neu2-M106 with trypsin resulted in increased intensity of the bands corresponding to the cleavage products.

[00339] Neu2-M106 was also incubated with trypsin in the presence of various protease inhibitors. Briefly, trypsin digestion reactions were performed by incubation of trypsin (0.005%) with Neu2-M106 (0.5 mg/mL) and protease inhibitor for 5 minutes on ice. Reactions were stopped by addition of LDS gel loading buffer and run on a reducing SDS-PAGE gel to observe trypsin mediated cleavage. Inhibitors used included iron citrate (at 0.3 and 5 mM), aprotinin (at 5,000 and 20,000 U/mL), AEBSF (at 0.1 and 1 mM), leupeptin (at 1

and 10 μM) or E-64 (at 1 and 10 μM). As seen in **FIGURE 26**, protease inhibitors reduced the extent of trypsin cleavage.

[00340] Together, these results confirm that cleavage of Neu2-M106 following large-scale production is due to trypsin or a member of a similar class of proteases.

[00341] Next, recombinant human sialidases with mutations that increase resistance to trypsin cleavage were rationally designed.

[00342] Unless indicated otherwise, in the remainder of this Example mutant sialidases were expressed as secreted proteins with a C-terminal human Fc tag in Expi293F cells (on a 50 mL scale) using the pCEP4 mammalian expression vector. The resulting protein was purified using a Protein A column. Expression was assayed using a ForteBio Octet with anti-human Fc sensors and Western blot and enzymatic activity was assayed using the fluorogenic substrate 4MU-NeuAc as described above. Protease cleavage was assayed by SDS-PAGE as described above.

[00343] First, R243 was mutated to different polar/charged amino acids such as K, E, H, N and Q. However, these mutations of R243 resulted in complete loss of activity and reduction in expression yields. As shown in FIGURE 27A, which provides a sequence alignment of various human and non-human sialidases, R243 is conserved among sialidases. Next, various amino residues surrounding the cleavage site were mutated and tested for expression, activity and trypsin cleavage resistance. Substitutions and combinations of substitutions that were tested are shown in FIGURE 27B. All mutations were tested in a Neu2-M106 background (i.e., including M1D, V6Y, P62G, A93E, I187K, and C332A substitutions).

[00344] Most of the mutant sialidases depicted in FIGURE 27B expressed well, however only two of the mutant sialidases (including V244I or A242C mutations) were active. The A242C mutation resulted in greater than 10 fold improved trypsin resistance and slightly lower activity (both relative to Neu2-M106). However, having an unpaired cysteine could be a potential liability, so, A242 was mutated to all 19 other amino acids and assayed for activity and trypsin resistance. As shown in FIGURE 28, mutation of A242 to aromatic amino acids such as F, W and Y resulted in a dramatic improvement in trypsin cleavage resistance compared to Neu2-M106 (FIGURE 28A) and similar enzymatic activity to Neu2-M106 (FIGURE 28B). SEC analysis showed that proteins containing each of these mutations had a similar pattern to that of Neu2-M106 and more than 95% monomer content (**FIGURE 28C**).

[00345] Structural analysis showed that replacing A242 with an aromatic amino acid could provide additional hydrophobic or stacking interactions to L260 and V265 (nonpolar amino acids located in the vicinity of the A242). Therefore, L260 and V265 were also mutated to phenylalanine. Along with these mutations several other rationally designed mutants, which could provide extra stability, for example by increasing stacking interactions, were also tested for expression, activity, and protease resistance.

[00346] Select results are shown in FIGURE 29. As shown in FIGURE 29, the combination of R241Y and A242F mutations (Neu2-M255) resulted in the most resistance to trypsin cleavage (a greater than 10 fold improved trypsin resistance relative to Neu2-M106).

[00347] Expression, activity, and protease resistance levels for the mutant sialidases are shown in TABLE 30. In TABLE 30, enzymatic activity is indicated as "++," which denotes activity comparable to wild-type Neu2, "+," which denotes activity lower than wild-type Neu2, or "-," which denotes no detectable activity, and expression is indicated as "+++++", which denotes expression > 40 fold higher than wildtype-Neu2, "++++", which denotes expression > 15 fold higher than wildtype-Neu2, "+++," which denotes expression > 6 fold higher than wild-type Neu2, "++," which denotes expression 2-5 fold higher than wild-type Neu2, "+," which denotes expression comparable to wild-type Neu2, or "-,"which denotes no detectable expression. Protease/trypsin resistance is indicated as "+++," which denotes resistance > 10 fold higher than Neu2-M106; "++," which denotes resistance ≥ 5 fold higher than Neu2-M106, "+," which denotes resistance comparable to Neu2-M106, or "-," which denotes resistance lower than Neu2-M106. NT = not tested.

TABLE 30

Identifier	Mutation(s)	Activity	Expression	Protease Resistance
Neu2-M223	M1D, V6Y, P62G, A93E, I187K, L240Y, C332A	++	+++++	+
Neu2-M224	M1D, V6Y, P62G, A93E, I187K, A242C, C332A	+	+++	+++
Neu2-M225	M1D, V6Y, P62G, A93E, I187K, A242D, C332A	-	++++	-
Neu2-M226	M1D, V6Y, P62G, A93E, I187K, A242E, C332A	-	+++	-
Neu2-M227	M1D, V6Y, P62G, A93E, I187K, A242F, C332A	++	++++	++
Neu2-M228	M1D, V6Y, P62G, A93E, I187K, A242G, C332A	+	+++	+

Identifier	Mutation(s)	Activity	Expression	Protease Resistance
Neu2-M229	M1D, V6Y, P62G, A93E, I187K, A242H, C332A	+	+++	+
Neu2-M230	M1D, V6Y, P62G, A93E, I187K, A242I, C332A	+	+++	+
Neu2-M231	M1D, V6Y, P62G, A93E, I187K, A242K, C332A	+	++++	-
Neu2-M232	M1D, V6Y, P62G, A93E, I187K, A242L, C332A	+	+++	+
Neu2-M233	M1D, V6Y, P62G, A93E, I187K, A242M, C332A	+	+++	+
Neu2-M234	M1D, V6Y, P62G, A93E, I187K, A242N, C332A	+	++++	++
Neu2-M235	M1D, V6Y, P62G, A93E, I187K, A242Q, C332A	+	+++	++
Neu2-M236	M1D, V6Y, P62G, A93E, I187K, A242R, C332A	+	++++	-
Neu2-M237	M1D, V6Y, P62G, A93E, I187K, A242S, C332A	+	+++	-
Neu2-M238	M1D, V6Y, P62G, A93E, I187K, A242T, C332A	-	+++	+
Neu2-M239	M1D, V6Y, P62G, A93E, I187K, A242V, C332A	+	+++	+
Neu2-M240	M1D, V6Y, P62G, A93E, I187K, A242W, C332A	++	++++	++
Neu2-M241	M1D, V6Y, P62G, A93E, I187K, A242Y, C332A	++	++++	++
Neu2-M242	M1D, V6Y, P62G, A93E, I187K, A242F, L260F, C332A	++	++++	++
Neu2-M243	M1D, V6Y, P62G, A93E, I187K, A242F, V265F, C332A	+	++++	++
Neu2-M244	M1D, V6Y, P62G, A93E, I187K, A242F, A213C, C332A	+	++++	++
Neu2-M245	M1D, V6Y, P62G, A93E, I187K, A242F, A213S, C332A	+	++++	++
Neu2-M246	M1D, V6Y, P62G, A93E, I187K, A242F, A213T, C332A	++	++++	++
Neu2-M247	M1D, V6Y, P62G, A93E, I187K, A242F, A213N, C332A	+	++	NT
Neu2-M248	M1D, V6Y, P62G, A93E, I187K, A242F, A213C, S258C, C332A	++	++++	++
Neu2-M249	M1D, V6Y, P62G, A93E, I187K, L240Y, L260F, C332A	++	+++++	+
Neu2-M250	M1D, V6Y, P62G, A93E, I187K, L240D, L260T, C332A	+	+	NT
Neu2-M251	M1D, V6Y, P62G, A93E, I187K, L240N, L260D, C332A	+	++	NT

Identifier	Mutation(s)	Activity	Expression	Protease Resistance
Neu2-M252	M1D, V6Y, P62G, A93E, I187K, L240N, L260T, C332A	++	++++	+
Neu2-M253	M1D, V6Y, P62G, A93E, I187K, L240N, L260Q, C332A	++	++++	+
Neu2-M254	M1D, V6Y, P62G, A93E, I187K, R241A, A242F, C332A	++	+++	++
Neu2-M255	M1D, V6Y, P62G, A93E, I187K, R241Y, A242F, C332A	++	+++	+++
Neu2-M256	M1D, V6Y, P62G, A93E, Q126Y, I187K, L240Y, A242F, Q270T, C332A	++	+++++	++
Neu2-M257	M1D, V6Y, P62G, A93E, I187K, V244I, C332A	++	++++	+
Neu2-M258	M1D, V6Y, P62G, A93E, I187K, A242C, V244K, C332A	+	+++	++

Example 6

[00348] This Example describes the construction and expression of antibody-sialidase genetic fusion proteins, and antibody sialidase conjugates (ASCs) containing the fusion proteins, with mutated human sialidases.

[00349] A Janus Antibody Sialidase Conjugate (ASC) was made using Neu2 with M1D, V6Y, P62G, A93E, I187K and C332A substitutions and Trastuzumab, referred to in this Example as "Janus Trastuzumab". This Janus Trastuzumab (including a first polypeptide chain with amino acid sequence SEQ ID NO: 66, encoded by nucleotide sequence SEQ ID NO: 86, a second polypeptide chain with amino acid sequence SEQ ID NO: 67, encoded by nucleotide sequence SEQ ID NO: 87, and a third polypeptide chain with amino acid sequence SEQ ID NO: 68, encoded by nucleotide sequence SEQ ID NO: 88) was expressed and characterized for purity using SDS-PAGE and enzymatic activity using 4MU-NeuAc as described below.

[00350] Janus Trastuzumab was expressed in a 1L transfection of Expi293 human cells using the pCEP4 mammalian expression vector. Janus Trastuzumab was purified using Protein A, followed by cation exchange chromatography (Hitrap SP-HP, GE Lifesciences). Purified proteins were analyzed by SDS-PAGE (**FIGURE 12**), and SEC-HPLC (**FIGURE 13**). Expression yield was 30mg/L, with 90% monomer purity as determined by SEC-HPLC.

[00351] The enzymatic activity of the recombinantly expressed Janus Trastuzumab was assayed by measuring the release of sialic acid from the fluorogenic substrate 4-

methylumbelliferyl-N-acetylneuraminic acid (4MU-NeuAc). Specifically, an enzyme kinetics assay was performed using a fixed concentration of enzyme at 2μg/well, which was incubated with fluorogenic substrate 4MU-NeuAc at concentrations ranging from 4000 μM to 7.8 μM. As shown in **FIGURE 14**, Janus Trastuzumab was enzymatically active, with a Km of 0.48 mM.

[00352] Janus Trastuzumab was tested for antigen (HER2) binding by using ForteBio Octet with the ASC captured on anti-Fc sensors with dipping into serial dilutions of His-tagged HER2 (50 to 0.78 nM at 1:2 dilutions). Janus Trastuzumab bound to HER2 with comparable binding affinity to trastuzumab (**FIGURE 15**).

Example 7

[00353] This Example describes the in vivo administration of antibody sialidase conjugates (ASCs) containing bacterial sialidases.

[00354] The following ASCs were made and tested in this Example: (i) a Janus ASC including Salmonella typhimurium sialidase (St-sialidase) and trastuzumab (including a first polypeptide chain with amino acid sequence SEQ ID NO: 66, encoded by nucleotide sequence SEQ ID NO: 86, a second polypeptide chain with amino acid sequence SEQ ID NO: 67, encoded by nucleotide sequence SEQ ID NO: 87, and a third polypeptide chain with amino acid sequence SEQ ID NO: 90, encoded by nucleotide sequence SEQ ID NO: 91); (ii) a Raptor ASC including St-sialidase and trastuzumab (including first and fourth polypeptide chains with amino acid sequence SEQ ID NO: 66, encoded by nucleotide sequence SEQ ID NO: 86, and second and third polypeptide chains with amino acid sequence SEQ ID NO: 92, encoded by nucleotide sequence SEQ ID NO: 93); and (iii) a Lobster ASC including St-sialidase and an scFv derived from trastuzumab (including first and second polypeptide chains with amino acid sequence SEQ ID NO: 94, encoded by nucleotide sequence SEQ ID NO: 95).

[00355] These ASCs were compared to trastuzumab in a mouse syngeneic tumor model injected with a murine breast cancer cell line expressing human HER2 (EMT6-hHER2 cells). Female BALB/c mice, 6-8 weeks of age, were inoculated subcutaneously in the right lower flank region with EMT6-HER2 tumor cells (5 x 105) in 0.1 ml of PBS for tumor development. Mice were randomly allocated to 8 groups when tumors reached 50-100 mm3, mean ~ 75-100 mm3. Treatment groups are described in TABLE 31 with dosing schedule indicated post randomization. Anti-mouse NK1.1 (Clone: PK136; BioXcell, 621717N1),

anti-mouse CD8α (Clone: 53-6.7; BioXcell, BE0004-1) and liposomal clodronate (FormuMax Scientific, Inc.) were included in treatment groups as indicated.

TABLE 31

Group	Animal No.	Treatment	Dose (mg/kg)	Dose volume(μL/g)	Route	Schedule (Days)
1	8	Vehicle (PBS)	NA	10	i.p.	0,3,7,10,14,17
2	8	Trastuzumab	10	10	i.p.	0,3,7,10,14,17
3	8	Raptor	10	10	i.p.	0,3,7,10,14,17
4	8	Janus	10	10	i.p.	0,3,7,10,14,17
5	8	Lobster	10	10	i.p.	0,3,7,10,14,17
6	8	Janus	10	10	i.p.	0,3,7,10,14,17
		anti-mouse NK1.1 (Clone: PK136)	10	10	i.p.	0,3,7,10,14,17
7	8	Janus	10	10	i.p.	0,3,7,10,14,17
		anti-mouse CD8α (Clone: 53-6.7)	10	10	i.p.	0,3,7,10,14,17
8	8	Janus	10	10	i.p.	0,3,7,10,14,17
		liposomal clodronate	0.5 mg/mouse	100 μL/mouse	i.p.	TIW x 2wks

[00356] The results from for treatment with trastuzumab, and Raptor, Janus and Lobster ASCs are shown in **FIGUREs 16A, 16B, 16C** and **16D** respectively. As can be seen, trastuzumab resulted in no complete responses in eight individual mice as treated (defined as regression below the limit of palpation at any point for the duration of the study, **FIGURE 16A**). This is in contrast to Raptor, which demonstrated 2 out of 8 animals with a complete response (**FIGURE 16B**), Janus which demonstrated 3 out of 8 animals with a complete response (**FIGURE 16C**) and Lobster which demonstrated 2 out of 8 animals with a complete response (**FIGURE 16D**).

[00357] The results of administration of Janus with NK depletion (anti-mouse NK1.1), macrophage depletion (liposomal clodronate) and CD8 T cell depletion (anti-mouse CD8α) are shown in **FIGURE 17**. As can be seen, compared to Janus treatment alone (**FIGURE 16C**), where there was a complete response in 3 out of 8 animals, NK depletion reduced the number of complete responses to 1 out of 8 animals (**FIGURE 17A**). Macrophage depletion also reduced the number of complete responses to 1 out of 8 animals (**FIGURE 17B**). CD8 T cell depletion completely reversed the effects of Janus, with no animals showing a complete response (**FIGURE 17C**). **FIGURE 17D** shows the mean tumor volume for vehicle, Janus alone, trastuzumab alone and Janus with NK, macrophage and CD8 T cell depletions. These results demonstrate that innate immunity (NK and macrophage dependent) as well as adaptive immunity (CD8 T cells) contribute to *in vivo* ASC activity.

Example 8

[00358] This Example describes the *in vivo* administration of antibody sialidase conjugates (ASCs) with bacterial sialidases.

[00359] The following ASCs were made and tested in this Example: (i) a Janus ASC including *Salmonella typhimurium* sialidase (St-sialidase) and trastuzumab (including a first polypeptide chain with amino acid sequence SEQ ID NO: 66, encoded by nucleotide sequence SEQ ID NO: 86, a second polypeptide chain with amino acid sequence SEQ ID NO: 67, encoded by nucleotide sequence SEQ ID NO: 87, and a third polypeptide chain with amino acid sequence SEQ ID NO: 90, encoded by nucleotide sequence SEQ ID NO: 91); and (ii) a Janus ASC including St-sialidase with two loss of function mutations, D100V and G231V, and trastuzumab ("Janus-LOF," including a first polypeptide chain with amino acid sequence SEQ ID NO: 66, encoded by nucleotide sequence SEQ ID NO: 86, a second polypeptide chain with amino acid sequence SEQ ID NO: 67, encoded by nucleotide sequence SEQ ID NO: 87, and a third polypeptide chain with amino acid sequence SEQ ID NO: 96, encoded by nucleotide sequence SEQ ID NO: 97).

[00360] These ASCs were tested in a mouse syngeneic orthotopic tumor model injected with an independent EMT6 cell line expressing human HER2 (EMT6-hHER2 cells as described in D'Amico *et al.* (2016) ANNALS OF ONCOLOGY, Volume 27, Issue suppl_8, 41P. Female BALB/c mice, 6-8 weeks of age, were inoculated via intra mammary implantation with EMT6-HER2 tumor cells (5×10^6). Mice were randomly allocated to 6 groups when tumors reached approximately 250 mm^3. The treatment groups are described in **TABLE 32** with

dosing schedule indicated post randomization. Anti-mouse PD1 was obtained from BioXcell (RMP1-14, Cat. # 665418F1).

TABLE 32

Group	Animal No.	Treatment	Dose (mg/kg)	Dose volume (μL/g)	Route	Schedule (Days)
1	6	Vehicle (PBS)	NA	10	i.p.	0,3,7,10
2	6	Trastuzumab	10	10	i.p.	0,3,7,10
3	6	Janus	10	10	i.p.	0,3,7,10
4	6	Janus Loss of Function (LOF)	10	10	i.p.	0,3,7,10
5	6	anti-mouse PD1	10	10	i.p.	0,3,7,10
6	6	Janus	10	10	i.p.	0,3,7,10
		anti-mouse PD1	10	10	i.p.	0,3,7,10

[00361] The results for Groups 1 through 4 (vehicle, trastuzumab, Janus and Janus LOF) are shown in **FIGURE 18A**. As can be seen, 3 out of 6 animals treated with Janus had a complete regression of tumor growth. Notably, Janus LOF and trastuzumab were both comparable to vehicle treated animals.

[00362] The 3 mice with a complete regression ("cured mice") were rechallenged with either the same EMT6-HER2 cells used originally or parental EMT6 cells (lacking engineered human HER2 expression). EMT6 cells and EMT6-HER2 cells were inoculated subcutaneously in the right or left lower flank region respectively (5×10^5) in 0.1 ml of PBS for tumor development of all three cured mice. EMT6-HER2 cells were also inoculated subcutaneously into naïve mice as a control. As can be seen in **FIGURE 18B**, neither EMT6-HER2 cells nor parental EMT6 cells resulted in tumor growth in the cured mice while EMT6-HER2 cells developed into tumors as expected in the naïve mice. These results suggest that the antibody sialidase conjugates of the present invention are capable of inducing long term memory against tumors. In addition, the long term memory is towards the tumor cell and is independent of the originally targeted cancer antigen (HER2 in this case).

[00363] The results for Groups 1, 5 and 6 (vehicle, anti-mouse PD1 and anti-mouse PD1 combined with Janus) are shown in **FIGURE 19A** and **FIGURE 19B**. While anti-mouse PD1 had good activity with 4 out of 6 mice demonstrating complete regressions (similar to

Janus alone with 3 out of 6 mice demonstrating complete regression, see **FIGURE 18A**), the combination of anti-mouse PD1 with Janus demonstrated complete regression of tumor growth in all 6 mice (**FIGURE 19B**). There was no body weight loss in any of the animals given this combination.

Example 9

[00364] This Example describes the *in vivo* administration of antibody sialidase conjugates (ASCs) with bacterial sialidases.

[00365] A Janus ASC including *Salmonella typhimurium* sialidase (St-sialidase) and trastuzumab (including a first polypeptide chain with amino acid sequence SEQ ID NO: 66, encoded by nucleotide sequence SEQ ID NO: 86, a second polypeptide chain with amino acid sequence SEQ ID NO: 67, encoded by nucleotide sequence SEQ ID NO: 87, and a third polypeptide chain with amino acid sequence SEQ ID NO: 90, encoded by nucleotide sequence SEQ ID NO: 91) was made and tested in this Example.

[00366] The ASC was tested in a mouse syngeneic tumor model injected with a B16 melanoma cell line expressing human HER2 (B16D5-HER2, Surana *et al.* CANCER IMMUNOL RES, 2(11): 1103–1112). Female C57BL/6 mice, 6-8 weeks of age, were inoculated subcutaneously in the right lower flank region with B16D5-HER2 tumor cells (5×10^5). Mice were randomly allocated to 3 groups when tumors reached approximately 50 to 100 mm^3. Treatment groups are described in **TABLE 33** with dosing schedule indicated post randomization. Anti-mouse PD1, obtained from BioXcell (RMP1-14, Cat. No. 665418F1) and anti-mouse CTLA4, obtained from BioXcell (9D9, Cat. # BE0164), were used in combination.

TABLE 33

Group	No. of Animals	Treatment	Dose (mg/kg)	Dose volume (μL/g)	Route	Schedule (Days)
1	6	Janus	NA	10	i.p.	0,3,7,10
2	6	Trastuzumab	10	10	i.p.	0,3,7,10
3	6	anti-mouse CTLA4	10	10	i.p.	0,3,7,10
		anti-mouse PD1	10	10	i.p.	0,3,7,10

[00367] The B16 melanoma mouse model is considered a difficult tumor model to treat with immuno-oncology approaches. A comparison of Janus to a combination of anti-mouse PD1 and anti-mouse CTLA4 was carried out. The results are shown in **FIGURE 20**. Anti-mouse PD1 combined with anti-mouse CTLA4 had an impact on B16D5-HER2 tumor growth, but this combination also demonstrated significant weight loss in the treated animals. By comparison, Janus demonstrated a more robust anti-tumor activity with no significant weight loss. Trastuzumab alone demonstrated marginal activity in this model.

Example 10

[00368] This Example describes the *in vivo* administration of an antibody sialidase conjugate (ASC) containing a human sialidase.

[00369] Janus Trastuzumab, as described in Example 3, including Neu2 with M1D, V6Y, P62G, A93E, I187K and C332A substitutions and Trastuzumab (including a first polypeptide chain with amino acid sequence SEQ ID NO: 66, encoded by nucleotide sequence SEQ ID NO: 86, a second polypeptide chain with amino acid sequence SEQ ID NO: 67, encoded by nucleotide sequence SEQ ID NO: 87, and a third polypeptide chain with amino acid sequence SEQ ID NO: 68, encoded by nucleotide sequence SEQ ID NO: 88) was made and tested in this Example.

[00370] Janus Trastuzumab was compared to isotype control antibody in a mouse syngeneic tumor model injected with a murine breast cancer cell line stably expressing human HER2 (EMT6-HER2). Female BALB/c mice, 6-8 weeks of age, were inoculated subcutaneously in the right lower flank region with EMT6-HER2 tumor cells (5×10^5) for tumor development. Mice were randomly allocated to groups of 8 animals each when tumors reached 50-100 mm^3, mean ~ 75-100 mm^3.

[00371] Mice were treated via intraperitoneal injection of 10 mg/kg and tumor volume (mm^3) was recorded. **FIGURE 21** shows individual tumor growth for mice that received treatment with Janus Trastuzumab or control. Significant tumor growth delay was observed following treatment with Janus Trastuzumab in this experiment.

Example 11

[00372] This example describes the construction of additional recombinant human sialidases with mutations that increase expression and/or activity of the sialidase.

[00373] Additional mutant Neu2 sialidases were constructed including rationally designed substitutions at position A42. A structural analysis of homologous sialidases revealed that transferring the G147R neuraminidase (sialidase) mutation from influenza A(H1N1)pdm09 onto human Neu2 may have stabilizing effects.

[00374] Neu2-M259-Fc (with amino acid sequence SEQ ID NO: 210, encoded by nucleotide sequence SEQ ID NO: 217, and including mutations M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, A242F, Q270T, and C332A) was expressed in a 1L transfection of Expi293 human cells using the pCEP4 mammalian expression vector. Neu2-M259-Fc was purified using protein A followed by cation exchange and ceramic hydroxyapatite (CHT) chromatography, quantified with a UV-Vis spectrophotometer (NanoDrop), and examined by SDS-PAGE.

[00375] Additional mutant Neu2 sialidases made and tested in this Example include Neu2-M260-Fc (with amino acid sequence SEQ ID NO: 220, encoded by nucleotide sequence SEQ ID NO: 221, and including mutations M1D, V6Y, P62G, A93E, Q112E, Q126Y, I187K, Q270T, A242F, and C332A), Neu2-M261-Fc (with amino acid sequence SEQ ID NO: 222, encoded by nucleotide sequence SEQ ID NO: 223, and including mutations M1D, V6Y, P62G, A93E, Q126Y, I187K, E225C, Q270T, A290C, A242F, and C332A), Neu2-M106-Fc (described in Example 2), and Neu2-173-Fc (described in Example 4).

[00376] **FIGURE 30A** is an image of an SDS-PAGE gel showing Neu2- M259-Fc under non-reducing and reducing conditions. **FIGURE 30B** is an SEC-HPLC trace for Neu2-M259-Fc, where the monomer species had a retention time of 21.7 minutes, and a monomer content of 96%.

[00377] The enzyme kinetics of Neu2-M259-Fc, Neu2-M260-Fc, Neu2-M261-Fc, Neu2-M106-Fc, and Neu2-173-Fc were assayed by measuring the release of sialic acid from the fluorogenic substrate 4-methylumbelliferyl-N-acetylneuraminic acid (4MU-NeuAc) as described above. A Michaelis-Menton kinetics characterization (measured at a variable substrate concentration) of Neu2-M259-Fc, Neu2-M106-Fc, and Neu2-M173-Fc is depicted in **FIGURE 31A**. Estimated K_M values were 0.27 mM (Neu2-M106-Fc), 0.46 mM (Neu2-M173-Fc), and 0.20 mM (Neu2-M259-Fc). Enzyme potency (measured at variable enzyme concentration) of Neu2-M259-Fc, Neu2-M106-Fc, and Neu2-M173-Fc is depicted in **FIGURE 31B.** Approximate EC_{50} values were 20.7 µg/mL (Neu2-M106-Fc), 38.3 µg/mL (Neu2-M173-Fc), and 15.18 µg/mL (Neu2-M259-Fc).

[00378] The thermal stability of Neu2-M259-Fc, Neu2-M260-Fc, Neu2-M261-Fc, Neu2-M106-Fc, and Neu2-173-Fc were assayed. Samples were prepared at 0.2 mg/mL, and incubated for 15 minutes across a temperature gradient from 37 °C to 80 °C. Enzyme activity was then measured by incubation of 2 µg of enzyme with 0.5 mM of 4-MU-Neu5Ac substrate. Tm was determined by fitting enzyme activity curves versus temperature curves. **FIGURE 32** depicts a thermal stability characterization of Neu2-M259-Fc, Neu2-M106-Fc, and Neu2-173-Fc.

[00379] A summary of certain biochemical attributes of Neu2-Fc variants M106-Fc, M173-Fc, M259-Fc, Neu2-M260-Fc, and Neu2-M261-Fc is depicted in **TABLE 34.** In **TABLE 34**, enzymatic activity is indicated as "+++," which denotes activity >2 fold higher than wild-type Neu2, or "++," which denotes activity comparable to wild-type Neu2. Together, these results show that Neu2-Fc variants M259-Fc and M260-Fc have improved expression yield and thermal stability relative to the M106-Fc and M173-Fc constructs, and M261-Fc has improved expression yield relative to the M106-Fc and M173-Fc constructs.

TABLE 34

Name	**Mutations**	**Yield (mg/L)**	**Tm (°C)**	Enzyme activity
M106-Fc	M1D, V6Y, P62G, A93E, I187K, C332A	13	49.0	+++
M173-Fc	M1D, V6Y, P62G, A93E, Q126Y, I187K, Q270T, A242F, C332A	27.2	57.1	++
M259-Fc	M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F, C332A	32	61.4	+++
M260-Fc	M1D, V6Y, P62G, A93E, Q112E, Q126Y, I187K, Q270T, A242F, C332A	34	58.7	+++
M261-Fc	M1D, V6Y, P62G, A93E, Q126Y, I187K, E225C, Q270T, A290C, A242F, C332A	66	55.7	++

[00380] The thermal stability of Neu2-M259-Fc, Neu2-M106-Fc, and Neu2-173-Fc was further assayed by incubating samples at 1 mg/mL at 37 °C for 4 hours, 24 hours, or 5 days. Enzyme activity was then measured using the 4-MU-Neu5Ac assay. Results are depicted in **FIGURE 34**, and show increased thermal stability for Neu2-M259-Fc.

[00381] A systematic analysis of the ten mutations in Neu2 variant M-259-Fc was conducted to determine the contribution of each substitution. Each of the ten mutations in Neu2 variant M-259-Fc was back-mutated to the corresponding residue in wildtype Neu2, resulting in ten variants (M262-Fc through M271-Fc) each having nine mutations. The resulting variants are described in **TABLE 35**.

TABLE 35

Name	Backmutation Relative to M259-Fc			Total Mutations	AA SEQ ID NO	Nuc SEQ ID NO
	AA #	Mut	WT			
M259-Fc		-	-	M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F, C332A	210	217
M262-Fc	1	D	M	ΔD, V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F, C332A	224	225
M263-Fc	6	Y	V	M1D, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F, C332A	226	227
M173-Fc	42	R	A	M1D, V6Y, P62G, A93E, Q126Y, I187K, Q270T, A242F, C332A	228	229
M264-Fc	62	G	P	M1D, V6Y, A42R, A93E, Q126Y, I187K, Q270T, A242F, C332A	230	231
M265-Fc	93	E	A	M1D, V6Y, A42R, P62G, Q126Y, I187K, Q270T, A242F, C332A	232	233
M266-Fc	126	Y	Q	M1D, V6Y, A42R, P62G, A93E, I187K, Q270T, A242F, C332A	234	235
M267-Fc	187	K	I	M1D, V6Y, A42R, P62G, A93E, Q126Y, Q270T, A242F, C332A	236	237
M268-Fc	242	F	A	M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, C332A	238	239
M269-Fc	270	T	Q	M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, A242F, C332A	240	241
M270-Fc	332	A	C	M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F	242	243

[00382] M259-Fc, M262-Fc through M270-Fc, and M173-Fc were expressed in Expi293 human cells using the pCEP4 mammalian expression vector, purified using a single step Protein-A purification, quantified with a UV-Vis spectrophotometer (NanoDrop), and examined by SEC-HPLC. Enzyme kinetics were assayed by measuring the release of sialic acid from the fluorogenic substrate 4-methylumbelliferyl-N-acetylneuraminic acid (4MU-NeuAc) as described above. Thermal stability was assayed by incubating samples across a temperature gradient from 37 °C to 80 °C, followed by measurement of enzyme activity, as described above. Tm was determined by fitting enzyme activity curves versus temperature curves. Results are depicted in **TABLE 36**. In **TABLE 36**, enzymatic activity is indicated as

"+++," which denotes activity >2 fold higher than wild-type Neu2, "++," which denotes activity comparable to wild-type Neu2, or "+," which denotes activity lower than wild-type Neu2.

TABLE 36

Name	SEC-HPLC Monomer %	Yield (mg/L)	Tm (°C)	Enzyme activity
M259-Fc	84%	37.8	60	+++
M262-Fc	79%	32.1	57.7	+
M263-Fc	88%	17.1	62	+++
M173-Fc	82%	35.3	56	+
M264-Fc	92%	22	62	+++
M265-Fc	81%	24.9	60	+++
M266-Fc	90%	9.6	64	+++
M267-Fc	70%	14	61	+++
M268-Fc	76%	38	57	+++
M269-Fc	79%	42.9	53	++
M270-Fc	87%	30	59	+++

[00383] Together, the results showed that removal of each of the individual mutations in M259-Fc negatively impacted at least one of monomer percentage, yield, thermal stability, or enzyme activity. In other words, each of the mutations were found to contribute to at least one of the monomer percentage, yield, stability and activity of the M259-Fc construct.

Example 12

[00384] This Example describes the *in vivo* administration of a sialidase-Fc fusion protein containing a human sialidase.

[00385] A Neu2-Fc fusion protein, including Neu2 with M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F, and C332A substitutions and a human IgG1 with a N297A mutation (having an amino acid sequence depicted in SEQ ID NO: 218, and encoded by the nucleotide sequence depicted in SEQ ID NO: 219) was made and tested in this Example. The Neu2-Fc fusion protein was the same as M259-Fc described in Example 11 but with an additional N297A mutation, and is referred to as M259-Fc-N297A.

[00386] M259-Fc-N297A was tested in a transgenic mouse engineered to express human PD-L1 and human PD-1 and where mouse PD-L1 and mouse PD-1 have been disrupted (Biocytogen Inc.). Mice, 6-8 weeks of age, were inoculated subcutaneously in the right lower flank region with a human PD-L1 expressing MC38 tumor cell line for tumor development.

Mice were randomly allocated to 3 groups of 8 animals each when tumors reached 100-130 mm^3 (mean ~ 111 mm^3) and treated as shown in **TABLE 37**.

TABLE 37

Group	Treatment	Dose	Route	Schedule
1	Isotype Control	10 mg/kg	IP	Every other day; 8 doses
2	M259-Fc-N297A	5 mg/kg		
3	Atezolizumab	5 mg/kg		

[00387] Mice were treated with intraperitoneal injections of 5 mg/kg of M259-Fc-N297A, 5 mg/kg of anti-PD-L1 antibody atezolizumab, or 10 mg/kg of isotype control every other day for 8 doses, and tumor volume (mm^3) was recorded. As shown in **FIGURE 33A** (average tumor volume throughout the course of the experiment) and **FIGURE 33B** (tumor volume of individual mice on day 21), mice treated with M259-Fc-N297A exhibited reduced tumor volume compared to mice treated with the isotype control antibody.

Example 13

[00388] This Example describes the construction and expression of anti-HER2 antibody-sialidase genetic fusion proteins, and anti-HER2 antibody sialidase conjugates (ASCs) containing the fusion proteins, with mutated human sialidases.

[00389] A Janus Antibody Sialidase Conjugate (ASC) was made using Neu2 with M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, A242F, Q270T, and C332A substitutions and trastuzumab. This ASC, referred to as "Janus Trastuzumab 2," included a first polypeptide chain with amino acid sequence SEQ ID NO: 66, encoded by nucleotide sequence SEQ ID NO: 86, a second polypeptide chain with amino acid sequence SEQ ID NO: 189, encoded by nucleotide sequence SEQ ID NO: 245, and a third polypeptide chain with amino acid sequence SEQ ID NO: 205, encoded by nucleotide sequence SEQ ID NO: 246.

[00390] Janus Trastuzumab 2 was expressed in a 1,000 mL transfection of Expi293 human cells using the pCEP4 mammalian expression vector. The ASC was purified using protein A, cation exchange and ceramic hydroxyapatite (CHT) chromatography, quantified with a UV-

Vis spectrophotometer (NanoDrop), and examined by SDS-PAGE. Janus Trastuzumab 2 expressed well with 95% monomer purity as determined by SEC-HPLC (FIGURE 35).

[00391] The enzymatic activity of the recombinantly expressed Janus Trastuzumab 2 was assayed by measuring the release of sialic acid from the fluorogenic substrate 4-methylumbelliferyl-N-acetylneuraminic acid (4MU-NeuAc), as described above. Janus Trastuzumab 2 was enzymatically active, with a Vmax of 2.2x108.

[00392] Janus Trastuzumab 2 was tested for antigen (HER2) binding by using ForteBio Octet with the ASC captured on anti-Fc sensors with dipping into serial dilutions of HER2 (titrated from 100 nM in a 2x series dilution). The buffer reference was subtracted from the signal and aligned to the baseline. KD, Kon and Koff values were generated using 1:1 fitting model. Janus Trastuzumab 2 bound to HER2 with a KD of 5.5E-10, Kon of 1.24E06 (1/Ms), and a Koff of 6.91E-04 (1/s) as shown in FIGURE 36.

[00393] Example 14

[00394] This Example describes the in vivo administration of anti-HER2 antibody sialidase conjugates (ASCs) containing human sialidases.

[00395] Janus Trastuzumab 2, as described above in Example 13, and including a first polypeptide chain with amino acid sequence SEQ ID NO: 66, encoded by nucleotide sequence SEQ ID NO: 86, a second polypeptide chain with amino acid sequence SEQ ID NO: 189, encoded by nucleotide sequence SEQ ID NO: 245, and a third polypeptide chain with amino acid sequence SEQ ID NO: 205, encoded by nucleotide sequence SEQ ID NO: 246, was made and tested in this Example.

[00396] Janus Trastuzumab 2 was compared to isotype control antibody and trastuzumab in a mouse syngeneic tumor model injected with a murine breast cancer cell line stably expressing human HER2 (EMT6-HER2). Mice, 6-8 weeks of age, were inoculated subcutaneously in the right lower flank region with HER2-expressing cells for tumor development. Mice were randomly allocated to 5 groups of 8 animals each when tumors reached a mean ~ 75-100 mm3 and treated as shown in TABLE 38.

TABLE 38

Group	Treatment	Dose	Route	Schedule
1	Isotype Control	10 mg/kg	IP	Every other day; 8 doses
2	Trastuzumab	1 mg/kg		
3	Trastuzumab	10 mg/kg		
4	Janus Trastuzumab 2	1 mg/kg		
5	Janus Trastuzumab 2	10 mg/kg		

[00397] Mice were treated with intraperitoneal (IP) injections of 10 mg/kg of trastuzumab, Janus Trastuzumab 2, or isotype control every other day, and tumor volume (mm3) was recorded. Complete Responses (CR) were defined as regression below the limit of palpitation at any point during the study and Partial Responses (PR) were defined as palpable tumors which were not.

[00398] Tumor volumes for individual mice are shown in FIGURE 37A-37E. As depicted, Janus Trastuzumab 2 exhibited increased anti-tumor activity based on CRs and PRs as compared to equivalent doses of trastuzumab. Mean tumor volumes are shown in FIGURE 37F. Collectively, these results show that the Janus Trastuzumab 2 construct showed comparable or greater activity than trastuzumab.

INCORPORATION BY REFERENCE

[00399] The entire disclosure of each of the patent and scientific documents referred to herein is incorporated by reference for all purposes. Additionally, the entire disclosure of each of U.S. Provisional Patent Application No. 62/870,354, filed July 3, 2019, U.S. Provisional Patent Application No. 62/956,957, filed January 3, 2020, International (PCT) Patent Application No. PCT/US20/40815, filed July 3, 2020, U.S. Provisional Patent Application No. 62/870,348, filed July 3, 2019, U.S. Provisional Patent Application No. 62/956,977, filed January 3, 2020, International (PCT) Patent Application No. PCT/US20/40814, filed July 3, 2020, U.S. Provisional Patent Application No. 62/870,341,

filed July 3, 2019, U.S. Provisional Patent Application No. 62/957,041, filed January 3, 2020, and International (PCT) Patent Application No. PCT/US20/40816, filed July 3, 2020, are incorporated by reference for all purposes.

EQUIVALENTS

[00400] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

SEQUENCE LISTING

[00401] SEQ ID NO: 1:

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EDLRP

[00404] SEQ ID NO: 4:

MEDLRP

[00405] SEQ ID NO: 5:

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[00413] SEQ ID NO: 13:

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[00414] SEQ ID NO: 14:

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[00415] SEQ ID NO: 15:

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[00416] SEQ ID NO: 16:

SMDQGSTW

[00417] SEQ ID NO: 17:

STDGGKTW

[00418] SEQ ID NO: 18:

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GCCCACCGCCTGGTGCTGAGGAGGGGCACGCTGGCCGGGGGCTCCGTGCGGTGGGGTGCCCT
GCACGTGCTGGGGACAGCAGCCCTGGCGGAGCACCGGTCCATGAACCCCTGCCCTGTGCACG
ATGCTGGCACGGGCACCGTCTTCCTCTTCTTCATCGCGGTGCTGGGCCACACGCCTGAGGCC
GTGCAGATCGCCACGGGAAGGAACGCCGCGCGCCTCTGCTGTGTGGCCAGCCGTGACGCCGG
CCTCTCGTGGGGCAGCGCCCGGGACCTCACCGAGGAGGCCATCGGTGGTGCCGTGCAGGACT
GGGCCACATTCGCTGTGGGTCCCGGCCACGGTGTGCAGCTGCCCTCAGGCCGCCTGCTGGTA
CCCGCCTACACCTACCGCGTGGACCGCCGAGAGTGTTTTGGCAAGATCTGCCGGACCAGCCC
TCACTCCTTCGCCTTCTACAGCGATGACCACGGCCGCACCTGGCGCTGTGGAGGCCTCGTGC
CCAACCTGCGCTCAGGCGAGTGCCAGCTGGCAGCGGTGGACGGTGGGCAGGCCGGCAGCTTC
CTCTACTGCAATGCCCGGAGCCCACTGGGCAGCCGTGTGCAGGCGCTCAGCACTGACGAGGG
CACCTCCTTCCTGCCCGCAGAGCGCGTGGCTTCCCTGCCCGAGACTGCCTGGGGCTGCCAGG
GCAGCATCGTGGGCTTCCCAGCCCCCGCCCCCAACAGGCCACGGGATGACAGTTGGTCAGTG
GGCCCCGGGAGTCCCCTCCAGCCTCCACTCCTCGGTCCTGGAGTCCACGAACCCCCAGAGGA
GGCTGCTGTAGACCCCCGTGGAGGCCAGGTGCCTGGTGGGCCCTTCAGCCGTCTGCAGCCTC
GGGGGGATGGCCCCAGGCAGCCTGGCCCCAGGCCTGGGGTCAGTGGGGATGTGGGGTCCTGG
ACCCTGGCACTCCCCATGCCCTTTGCTGCCCCGCCCCAGAGCCCCACGTGGCTGCTGTACTC
CCACCCAGTGGGGCGCAGGGCTCGGCTACACATGGGTATCCGCCTGAGCCAGTCCCCGCTGG
ACCCGCGCAGCTGGACAGAGCCCTGGGTGATCTACGAGGGCCCCAGCGGCTACTCCGACCTG
GCGTCCATCGGGCCGGCCCCTGAGGGGGGCCTGGTTTTTGCCTGCCTGTACGAGAGCGGGGC
CAGGACCTCCTATGATGAGATTTCCTTTTGTACATTCTCCCTGCGTGAGGTCCTGGAGAACG
TGCCCGCCAGCCCCAAACCGCCCAACCTTGGGGACAAGCCTCGGGGGTGCTGCTGGCCCTCC

[00436] SEQ ID NO: 36:

MRFKNVKKTALMLAMFGMATSSNAALFDYNATGDTEFDSPAKQGWMQDNTNNGSGVLTNADG
MPAWLVQGIGGRAQWTYSLSTNQHAQASSFGWRMTTEMKVLSGGMITNYYANGTQRVLPIIS
LDSSGNLVVEFEGQTGRTVLATGTAATEYHKFELVFLPGSNPSASFYFDGKLIRDNIQPTAS
KQNMIVWGNGSSNTDGVAAYRDIKFEIQGDVIFRGPDRIPSIVASSVTPGVVTAFAEKRVGG
GDPGALSNTNDIITRTSRDGGITWDTELNLTEQINVSDEFDFSDPRPIYDPSSNTVLVSYAR
WPTDAAQNGDRIKPWMPNGIFYSVYDVASGNWQAPIDVTDQVKERSFQIAGWGGSELYRRNT
SLNSQQDWQSNAKIRIVDGAANQIQVADGSRKYVVTLSIDESGGLVANLNGVSAPIILQSEH
AKVHSFHDYELQYSALNHTTTLFVDGQQITTWAGEVSQENNIQFGNADAQIDGRLHVQKIVL
TQQGHNLVEFDAFYLAQQTPEVEKDLEKLGWTKIKTGNTMSLYGNASVNPGPGHGITLTRQQ
NISGSQNGRLIYPAIVLDRFFLNVMSIYSDDGGSNWQTGSTLPIPFRWKSSSILETLEPSEA
DMVELQNGDLLLTARLDFNQIVNGVNYSPRQQFLSKDGGITWSLLEANNANVFSNISTGTVD
ASITRFEQSDGSHFLLFTNPQGNPAGTNGRQNLGLWFSFDEGVTWKGPIQLVNGASAYSDIY
QLDSENAIVIVETDNSNMRILRMPITLLKQKLTLSQN

[00437] SEQ ID NO: 37:

TTGTCAATCAAGATGACTTCACAACGAAGAAGAGCATCGATTCACAAGGAAACAGATTCTAA
TATAAAGGGAGTAGATATGCGTTTCAAAAACGTAAAGAAAACCGCTTTAATGCTTGCAATGT
TCGGTATGGCGACAAGCTCAAACGCCGCACTTTTTGACTATAACGCAACGGGTGACACTGAG
TTTGACAGTCCAGCCAAACAGGGATGGATGCAAGACAACACGAATAATGGCAGCGGCGTTTT
AACCAATGCAGATGGAATGCCCGCTTGGTTGGTGCAAGGTATTGGAGGGAGAGCTCAATGGA
CATATTCTCTCTCTACTAATCAACATGCCCAAGCATCAAGTTTCGGTTGGCGAATGACGACA
GAAATGAAAGTGCTCAGTGGTGGAATGATCACAAACTACTACGCCAACGGCACTCAGCGTGT
CTTACCCATCATTTCATTAGATAGCAGTGGTAACTTAGTTGTTGAGTTTGAAGGGCAAACTG
GACGCACCGTTTTGGCAACCGGCACAGCAGCAACGGAATATCATAAATTTGAATTGGTATTC
CTTCCTGGAAGTAACCCATCCGCTAGCTTTTACTTCGATGGCAAACTCATTCGTGACAACAT
CCAGCCGACTGCATCAAAACAAAATATGATCGTATGGGGGAATGGCTCATCAAATACGGATG
GTGTCGCCGCTTATCGTGATATTAAGTTTGAAATTCAAGGCGACGTCATCTTCAGAGGCCCA
GACCGTATACCGTCCATTGTAGCAAGTAGCGTAACACCAGGGGTGGTAACCGCATTTGCAGA
GAAACGTGTGGGGGGAGGAGATCCCGGTGCTCTGAGTAATACCAATGACATAATCACTCGTA
CCTCACGAGATGGCGGTATAACTTGGGATACCGAGCTCAACCTCACTGAGCAAATCAATGTC
AGTGATGAGTTTGATTTCTCCGATCCTCGGCCTATCTATGATCCTTCCTCCAATACGGTTCT
TGTCTCTTATGCTCGATGGCCGACCGATGCCGCTCAAAACGGAGATCGAATAAAACCATGGA
TGCCAAACGGTATTTTTTACAGCGTCTATGATGTTGCATCAGGGAACTGGCAAGCGCCTATC
GATGTTACCGATCAGGTGAAAGAACGCAGTTTCCAAATCGCTGGTTGGGGTGGTTCAGAGCT
GTATCGCCGAAATACCAGCCTAAATAGCCAGCAAGACTGGCAATCAAACGCTAAGATCCGAA
TTGTTGATGGTGCAGCGAACCAGATACAAGTTGCCGATGGTAGCCGAAAATATGTTGTCACA
CTGAGTATTGATGAATCAGGTGGTCTAGTCGCTAATCTAAACGGTGTTAGTGCTCCGATTAT
CCTGCAATCTGAACACGCAAAGGTACACTCTTTCCATGACTACGAACTTCAATATTCGGCGT
TAAACCACACCACAACGTTATTCGTGGATGGTCAGCAAATCACAACTTGGGCTGGCGAAGTA
TCGCAGGAGAACAACATTCAGTTTGGTAATGCGGATGCCCAAATTGACGGCAGACTGCATGT
GCAAAAAATTGTTCTCACACAGCAAGGCCATAACCTCGTGGAGTTTGATGCTTTCTATTTAG
CACAGCAAACCCCTGAAGTAGAGAAAGACCTTGAAAAGCTTGGTTGGACAAAAATTAAAACG
GGCAACACCATGAGTTTGTATGGAAATGCCAGTGTCAACCCAGGACCGGGTCATGGCATCAC
CCTTACTCGACAACAAAATATCAGTGGCAGCCAAAACGGCCGCTTGATCTACCCAGCGATTG
TGCTTGATCGTTTCTTCTTGAACGTCATGTCTATTTACAGTGATGATGGCGGTTCAAACTGG
CAAACCGGTTCAACACTCCCTATCCCCTTTCGCTGGAAGAGTTCGAGTATCCTAGAAACTCT
CGAACCTAGTGAAGCTGATATGGTTGAACTCCAAAACGGTGATCTACTCCTTACTGCACGCC
TTGATTTTAACCAAATCGTTAATGGTGTGAACTATAGCCCACGCCAGCAATTTTTGAGTAAA

GATGGTGGAATCACGTGGAGCCTACTTGAGGCTAACAACGCTAACGTCTTTAGCAATATCAG
TACTGGTACCGTTGATGCTTCTATTACTCGGTTCGAGCAAAGTGACGGTAGCCATTTCTTAC
TCTTTACTAACCCACAAGGAAACCCTGCGGGGACAAATGGCAGGCAAAATCTAGGCTTATGG
TTTAGCTTCGATGAAGGGGTGACATGGAAAGGACCAATTCAACTTGTTAATGGTGCATCGGC
ATATTCTGATATTTATCAATTGGATTCGGAAAATGCGATTGTCATTGTTGAAACGGATAATT
CAAATATGCGAATTCTTCGTATGCCTATCACATTGCTAAAACAGAAGCTGACCTTATCGCAA
AACTAA

[00438] SEQ ID NO: 38:

MVGADPTRPRGPLSYWAGRRGQGLAAIFLLLVSAAESEARAEDDFSLVQPLVTMEQLLWVSG
KQIGSVDTFRIPLITATPRGTLLAFAEARKKSASDEGAKFIAMRRSTDQGSTWSSTAFIVDD
GEASDGLNLGAVVNDVDTGIVFLIYTLCAHKVNCQVASTMLVWSKDDGISWSPPRNLSVDIG
TEMFAPGPGSGIQKQREPGKGRLIVCGHGTLERDGVFCLLSDDHGASWHYGTGVSGIPFGQP
KHDHDFNPDECQPYELPDGSVIINARNQNNYHCRCRIVLRSYDACDTLRPRDVTFDPELVDP
VVAAGALATSSGIVFFSNPAHPEFRVNLTLRWSFSNGTSWLKERVQVWPGPSGYSSLTALEN
STDGKKQPPQLFVLYEKGLNRYTESISMVKISVYGTL

[00439] SEQ ID NO: 39:

MTVQPSPWFSDLRPMATCPVLQKETLFRTGVHAYRIPALLYLKKQKTLLAFAEKRASKTDEH
AELIVLRRGSYNEATNRVKWQPEEVVTQAQLEGHRSMNPCPLYDKQTKTLFLFFIAVPGRVS
EHHQLHTKVNVTRLCCVSSTDHGRTWSPIQDLTETTIGSTHQEWATFAVGPGHCLQLRNPAG
SLLVPAYAYRKLHPAQKPTPFAFCFISLDHGHTWKLGNFVAENSLECQVAEVGTGAQRMVYL
NARSFLGARVQAQSPNDGLDFQDNRVVSKLVEPPHGCHGSVVAFHNPISKPHALDTWLLYTH
PTDSRNRTNLGVYLNQMPLDPTAWSEPTLLAMGICAYSDLQNMGQGPDGSPQFGCLYESGNY
EEIIFLIFTLKQAFPTVFDAQ

[00440] SEQ ID NO: 40:

MEEVPPYSLSSTLFQQEEQSGVTYRIPALLYLPPTHTFLAFAEKRTSVRDEDAACLVLRRGL
MKGRSVQWGPQRLLMEATLPGHRTMNPCPVWEKNTGRVYLFFICVRGHVTERCQIVWGKNAA
RLCFLCSEDAGCSWGEVKDLTEEVIGSEVKRWATFAVGPGHGIQLHSGRLIIPAYAYYVSRW
FLCFACSVKPHSLMIYSDDFGVTWHHGKFIEPQVTGECQVAEVAGTAGNPVLYCSARTPSRF
RAEAFSTDSGGCFQKPTLNPQLHEPRTGCQGSVVSFRPLKMPNTYQDSIGKGAPATQKCPLL
DSPLEVEKGAETPSATWLLYSHPTSKRKRINLGIYYNRNPLEVNCWSRPWILNRGPSGYSDL
AVVEEQDLVACLFECGEKNEYERIDFCLFSDHEVLSCEDCTSPSSD

[00441] SEQ ID NO: 41:

METAGAPFCFHVDSLVPCSYWKVMGPTRVPRRTVLFQRERTGLTYRVPALLCVPPRPTLLAF
AEQRLSPDDSHAHRLVLRRGTLTRGSVRWGTLSVLETAVLEEHRSMNPCPVLDEHSGTIFLF
FIAVLGHTPEAVQIATGKNAARLCCVTSCDAGLTWGSVRDLTEEAIGAALQDWATFAVGPGH
GVQLRSGRLLVPAYTYHVDRRECFGKICWTSPHSLAFYSDDHGISWHCGGLVPNLRSGECQL
AAVDGDFLYCNARSPLGNRVQALSADEGTSFLPGELVPTLAETARGCQGSIVGFLAPPSIEP
QDDRWTGSPRNTPHSPCFNLRVQESSGEGARGLLERWMPRLPLCYPQSRSPENHGLEPGSDG
DKTSWTPECPMSSDSMLQSPTWLLYSHPAGRRARLHMGIYLSRSPLDPHSWTEPWVIYEGPS
GYSDLAFLGPMPGASLVFACLFESGTRTSYEDISFCLFSLADVLENVPTGLEMLSLRDKAQG
HCWPS

[00442] SEQ ID NO: 42:

GGGTCACATGCTGATGGACTAATTGGAGTCGCGGCAGCGCGGGCTGCGGCCCCCAAGGGGAG
GGGTCGGAGTGACGTGCGCGCTTTTAAAGGGCCGAGGTCAGCTGACGGCTTGCCACCGGTGA
CCAGTTCCTGGACAGGGATCGCCGGGAGCTATGGTGGGGGCAGACCCGACCAGACCCCGGGG
ACCGCTGAGCTATTGGGCGGGCCGTCGGGGTCAGGGGCTCGCAGCGATCTTCCTGCTCCTGG
TGTCCGCGGCGGAATCCGAGGCCAGGGCAGAGGATGACTTCAGCCTGGTGCAGCCGCTGGTG
ACCATGGAGCAGCTGCTGTGGGTGAGCGGGAAGCAGATCGGCTCTGTAGACACTTTCCGCAT
CCCGCTCATCACAGCCACCCCTCGGGGCACGCTCCTGGCCTTCGCTGAGGCCAGGAAAAAAT
CTGCATCCGATGAGGGGGCCAAGTTCATCGCCATGAGGAGGTCCACGGACCAGGGTAGCACG
TGGTCCTCTACAGCCTTCATCGTAGACGATGGGGAGGCCTCCGATGGCCTGAACCTGGGCGC
TGTGGTGAACGATGTAGACACAGGGATAGTGTTCCTTATCTATACCCTCTGTGCTCACAAGG
TCAACTGCCAGGTGGCCTCTACCATGTTGGTTTGGAGTAAGGACGACGGCATTTCCTGGAGC
CCACCCCGGAATCTCTCTGTGGATATTGGCACAGAGATGTTTGCCCCTGGACCTGGCTCAGG
CATTCAGAAACAGCGGGAGCCTGGGAAGGGCCGGCTCATTGTGTGTGGACACGGGACGCTGG
AGCGAGATGGGGTCTTCTGTCTCCTCAGTGATGACCACGGTGCCTCCTGGCACTACGGCACT
GGAGTGAGCGGCATTCCCTTTGGCCAGCCCAAACACGATCACGATTTCAACCCCGACGAGTG
CCAGCCCTACGAGCTTCCAGATGGCTCGGTCATCATCAACGCCCGGAACCAGAATAACTACC
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GTGACCTTCGACCCTGAGCTCGTGGACCCTGTGGTAGCTGCAGGAGCACTAGCCACCAGCTC
CGGCATTGTCTTCTTCTCCAATCCAGCCCACCCTGAGTTCCGAGTGAACCTGACCCTGCGCT
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GTTCGTTCTGTACGAGAAAGGCCTGAACCGGTACACCGAGAGCATCTCCATGGTCAAAATCA
GCGTCTACGGCACGCTCTGAGCCCCGTGCCCAAAGGACACCAAGTCCTGGTCGCTGACTTCA
CAGCTCTCTGGACCATCTGCAGAGGGTGCCTGAAACACAGCTCTTCCTCTGAACTCTGACCT
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CCATTCTCTTCCAGGACAACGGAGCTGTGCCTTTCTGGGACAGGATGGGGGAGGGGCTCCCC
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TCCTGGAGAGACAGGAAGGCAGCTGGAAGAGGAGCCGATGTACTTACTGGGAAGCAGAAACC
CCTAGATTCCATCCTGGCTGCTGCTGTTTGCAAGTGTCAAAGATGGGGGGGCGTGTTTATAT
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CACGTGGAAAGAGCCCAGATGGACGCTAAGCATGTTGGGCACCTGTAACCCCGCACTCGCTG
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CACACTGGCCCACATGTACACATCGACTCACAGGTACACAGACCCACTTTGACACACATATA
CACAGACACAAACGCACTGGCACACACATATACACAGGCACACATGGATAGATGGACACACG
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GAGACGTGTTGACTTCATTTTTAGCAAAAATCCTGTCATGTATCTTAAAGTGGATTGAACCC

ACTATGTAGCCCAGGCTGGCCTCCAAATGGGCATCCTTCTGCCTCAGTCTCCCGAGGGCTAG
GATAACAGGAGTATGCCATCACACCTGGCTAATAGAAATTTTCAAAATTGTTTGTTTGAAGG
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GACTGTCAATATAACCCACCAAGACAGGCCAACATTCACAATTGATTGTTAGTTTGTGGTCT
GAATCAAGGTCTTATACTGTAGCCCAGGCTAGCCCGGAATACACGATATCTCCAGTGCTTCA
GATCCTCAGTTCTAACTAAGCATGGCCACATCCATGTTTAACTGCAAATTTGATGTTACCAT
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AACCCCAGTTCCAGGGGACCTGACACCCTCTGGCCTCCACAAGTATTAGGCACATCTGTGGT
GCACAGACATACAATCAGGCAAAATATTCATACACATAAAATAAAATAATTTAAAACAAAAG
CAAAAATCAGGACCTAAGAAAAAAATCTATTCCTGATTCTTTTATGTTTTGTTTGTATTTTA
TCAAGACAGGGTTGTTTCTCTGTATAGCCCTGGCTGTCTTGGAATTCACTCTGTAGACCAGG
CTGGCCTCAAACTCAGAAATCCTCCTGCCTTTGCCTTCCAAGTGCTGGAATTAAAGGCATGC
GCCACC

[00443] SEQ ID NO: 43:

GACATGACCCAAACGGCCCCTGGCTGCAAGGTAATATCGGAAGTTGACTAAGAATGGACGCC
CCACCACTGACTGACCCGCCCCCTGAGTCTGAGATTGGACTTGTCTCTGGATACAGTCATAC
TTTGAGGTACTACAAGTTAGAAACTGTTAGGTTACTCAGTTCAGTCCATGACAGTCCAACCT
TCTCCATGGTTTTCCGATCTCAGGCCCATGGCGACCTGCCCTGTCCTGCAGAAGGAGACACT
GTTCCGCACAGGCGTCCATGCTTACAGAATCCCTGCTCTGCTCTACCTGAAGAAGCAGAAGA
CCCTGCTGGCCTTTGCGGAAAAGCGAGCCAGCAAGACGGATGAGCACGCAGAGTTGATTGTC
CTGAGAAGAGGAAGCTACAACGAAGCCACCAACCGTGTCAAGTGGCAGCCTGAGGAAGTGGT
GACCCAAGCCCAGCTGGAAGGCCACCGCTCCATGAATCCATGTCCCTTGTATGACAAGCAAA
CAAAGACCCTCTTCCTTTTCTTCATCGCTGTCCCTGGGCGTGTATCAGAACATCATCAGCTC
CACACTAAGGTTAATGTCACACGGCTGTGCTGTGTCAGCAGCACTGACCATGGGAGGACCTG
GAGCCCCATCCAGGACCTCACAGAGACCACCATTGGCAGCACTCATCAGGAATGGGCCACAT
TTGCTGTGGGTCCTGGGCATTGTCTGCAGCTGCGGAACCCAGCTGGGAGCCTGCTGGTACCT
GCTTATGCCTACCGGAAACTGCACCCTGCTCAGAAGCCTACCCCCTTTGCCTTCTGCTTCAT
CAGCCTTGACCATGGGCACACATGGAAACTAGGCAACTTTGTGGCTGAAAACTCACTGGAGT
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CTGGGAGCCAGGGTCCAGGCACAAAGTCCTAATGATGGTCTGGATTTCCAGGACAACCGGGT
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GCCCACCCTGCTGGCCATGGGCATCTGTGCCTACTCAGACTTACAGAACATGGGGCAAGGCC
CTGATGGCTCCCCACAGTTTGGGTGTCTGTATGAATCAGGTAACTATGAAGAGATCATTTTC
CTCATATTCACCCTGAAGCAAGCTTTCCCCACTGTATTTGATGCCCAGTGATCTCAGTGCAC
GTGGCCCAAAGGGCTTCCTTGTGCTTCAAAACACCCATCTCTCTTTGCTTCCAGCATCCTCT
GGACTCTTGAGTCCAGCTCTTGGGTAACTTCCTCAGGAGGATGCAGAGAATTTGGTCTCTTG
ACTCTCTGCAGGCCTTATTGTTTCAGCCTCTGGTTCTCTTTTCAGCCCAGAAATCAAAGGAG
CCTGGCTTTCCTCAGCCTGTTGGCAGGGCAGGTGGGGACAGTATATATAGAGGCTGCCATTC
TGCATGTCGGTTGTCACTATGCTAGTTTAACCTGCCTGTTTCCCCATGCCTAGTGTTTGAAT
GAGTATTAATAAAATATCCAACCCAGCCCATTTCTTCCTGGAAAAAAA

[00444] SEQ ID NO: 44:

ACTGCGCGGTGAAGGGGCGTGGCCTGGCCGGGGAGGTTGACACCCAGACGCTGCTCTCAGTC
CTCTGGCGCCTGCTCCCCAGCGCATTCCTTCTGCTCCTGGGATATTTGTCTCATTACTGCCA
GTTCTTGCGCAGCGGTCACTGGGTTCGTTTCAGCGTCTGTGGTTTCTGTCGCTGTTATCCAG

TCTCCATCGCCCCAGCTCAGCTTCAGGCCTTCTTCCGAGACTCCACGGGAGAGCCCAGAGAG
CCTCCGGAGCCGAAGCCATGGAGGAAGTCCCACCCTACTCCCTCAGCAGCACCCTGTTCCAG
CAGGAAGAACAGAGTGGGGTGACCTACCGGATCCCAGCCCTGCTGTACCTTCCTCCCACCCA
CACCTTCCTGGCCTTTGCAGAGAAGCGGACCTCAGTCAGAGATGAGGATGCTGCCTGCCTGG
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GAGGCCACATTACCTGGGCATCGCACCATGAACCCCTGCCCTGTGTGGGAGAAAAATACTGG
CCGTGTGTACCTGTTTTTCATCTGTGTGCGGGGCCATGTTACTGAGAGGTGCCAGATTGTGT
GGGGCAAAAATGCCGCCCGTCTCTGCTTCCTTTGCAGTGAAGATGCCGGCTGCTCTTGGGGT
GAAGTGAAAGACTTGACCGAGGAGGTCATTGGCTCAGAGGTGAAGCGCTGGGCCACATTTGC
TGTGGGCCCAGGTCATGGCATCCAGCTACACTCGGGAAGGCTGATCATCCCCGCCTATGCCT
ACTATGTCTCACGTTGGTTTCTCTGCTTTGCGTGTTCAGTCAAGCCCCATTCCCTGATGATC
TACAGTGATGACTTTGGAGTCACATGGCACCATGGCAAGTTCATTGAGCCCCAGGTGACAGG
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AACACCAAGCCGATTTCGAGCAGAGGCTTTTAGTACTGATAGTGGTGGCTGCTTTCAGAAGC
CAACCCTGAACCCACAACTCCATGAGCCTCGAACCGGCTGCCAAGGTAGTGTAGTGAGCTTC
CGGCCTTTGAAGATGCCAAATACCTATCAAGACTCAATTGGCAAAGGTGCTCCCGCTACTCA
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CATGGCTCTTGTACTCACATCCAACTAGCAAGAGGAAGAGGATTAACCTAGGCATCTACTAC
AACCGGAACCCCTTGGAGGTGAACTGCTGGTCCCGCCCGTGGATCTTGAACCGTGGGCCCAG
TGGCTACTCTGATCTGGCTGTTGTGGAAGAACAGGACTTGGTGGCGTGTTTGTTTGAGTGTG
GGGAGAAGAATGAGTATGAGCGGATTGACTTCTGTCTGTTTTCAGACCATGAGGTCCTGAGC
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CAGAGGTCCTTAGCTGCATCCACCCATTTCCAGGGGGACATTCTAACACTGCTGAACAGTCA
GCTAAAATGAGAGCTGTGTGTCCTAGCCTGATTCCAGGTTAGTCATGATGCTTCCTGGAGCT
GGGCTTTTATCTAATCCCAGGAGCCATCTAGGGGAGGCTCAGAGCTAGCAGGTGATCTTCCT
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TATAGGAAAGATTTCTAGTATTAATATGCCTTTTCTCTGTGTGTGTACTGTCTTGTAGTGAT
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CCTGCCTCTGCCTCCCGAGTGCTGGGATTAAAGGTGTGCACCACCACACCTTAATGATGATC
CTATAAGTATTCCTAAAATTATACTAGTAATTATTAACTCCTTTATAATAGGACTGCTATTA
AAGCCCTCGCTGATATGAAAACTACAGTGAGAACTCTGCCAGTCTTCACATGTCATAATTAC
TTCTGAGATAGAAAGCAGGCATTTACAACTTAGAACACATTTCTTAGAGCTGTAAAACAATT
AACTAGAGGTCATAAAAGGGAATGAAAGATTTATTGTAGGTGCTAGGACAGAACATAAAATA
TTGACTGGGCTTATCTATATGAAACTTCATTGTTAACTTTTACACAAGAATTATGGTTTTTA
ACTTTCAGTGAACCTGCGGAGCTAGTGACAGAAGAGAAATGTCTAGTTAGATAACTACTCTT
AATGGAAATTCACATAAACATCTGTTGCCATCTTCTTTTTGAATTTATGTTTAAACTTGTGA
ATGTTTGAATTAGACACTACGCGAGCACATAGAAAATAAAGAACTAAGCGTGAA

[00445] SEQ ID NO: 45:

GGACAGTGTGCATCACGGAGCTTGTGGCCCAGACTGTGCCTGGCAGACCCAGAGGACCTAAG
GCTTGGCTCTAGTGGTGGTCAGCACAGCCCTCGGTGGTCTGCGGAGCCTGATATTGCTTTAC
GTAAGGGCTGTTCTGCTGTGCATCTCCTGTGTCTGAAGCTATTCGCCATGGAGACTGCTGGA
GCTCCCTTCTGCTTCCATGTGGACTCCCTGGTACCTTGCTCCTACTGGAAGGTTATGGGGCC
CACGCGTGTTCCCAGGAGAACGGTGCTCTTCCAGAGGGAAAGGACGGGCCTGACCTACCGTG
TGCCTGCGTTACTCTGTGTGCCTCCCAGGCCTACTCTGCTGGCCTTCGCGGAACAGCGACTT
AGCCCTGATGACTCCCATGCCCACCGCCTGGTGCTACGGAGGGGCACGCTGACCAGGGGCTC
AGTGCGGTGGGGCACTCTGAGTGTACTGGAGACTGCAGTACTGGAGGAGCACAGGTCTATGA
ACCCTTGCCCGGTGCTGGATGAGCACTCTGGTACCATCTTCCTCTTCTTCATTGCCGTGCTG
GGCCACACACCGGAGGCCGTGCAAATCGCCACTGGCAAGAACGCTGCTCGCCTCTGCTGTGT
GACCAGCTGTGACGCTGGCCTCACCTGGGGCAGTGTTCGAGATCTCACTGAGGAAGCCATTG
GTGCTGCATTGCAGGACTGGGCCACCTTTGCTGTGGGTCCGGGCCATGGAGTTCAGCTGCGC
TCGGGTCGCCTGCTTGTTCCTGCTTACACCTATCATGTGGACCGACGGGAATGTTTTGGCAA
GATCTGCTGGACCAGTCCCCACTCCTTGGCATTCTACAGTGATGATCATGGGATCTCCTGGC
ATTGTGGAGGCCTTGTGCCCAACCTACGCTCTGGAGAGTGCCAACTGGCTGCGGTAGATGGA
GACTTTCTCTACTGTAATGCTCGAAGCCCTCTGGGTAACCGTGTGCAGGCACTGAGTGCTGA
TGAAGGCACGTCCTTCCTACCAGGGGAGCTGGTGCCTACATTGGCAGAGACGGCTCGTGGTT
GCCAGGGTAGCATTGTGGGCTTCCTAGCTCCACCCTCAATCGAGCCTCAGGATGACCGGTGG
ACAGGGAGTCCTAGGAACACCCCACATTCCCCATGCTTCAATCTCAGAGTACAGGAGTCTTC
GGGGGAAGGTGCCAGAGGTCTTCTTGAACGTTGGATGCCCAGGTTGCCTCTCTGCTACCCAC
AGTCCCGGAGCCCAGAGAATCATGGCCTAGAGCCTGGGTCAGATGGAGATAAGACATCCTGG
ACTCCGGAATGTCCTATGTCCTCTGATTCCATGCTTCAGAGCCCCACATGGCTACTATATTC
CCACCCAGCAGGGCGTAGAGCTCGGCTCCACATGGGAATCTACCTGAGCCGATCCCCCTTGG
ATCCCCACAGCTGGACAGAGCCCTGGGTGATCTATGAGGGCCCCAGTGGCTACTCTGACCTT
GCCTTTCTTGGGCCTATGCCTGGGGCATCCCTGGTTTTTGCCTGTCTGTTTGAGAGCGGGAC
CAGGACTTCCTATGAAGACATTTCTTTTTGCTTGTTCTCACTGGCGGATGTCCTGGAGAATG
TGCCCACTGGCTTAGAGATGCTAAGTCTCAGGGATAAGGCTCAGGGGCATTGCTGGCCCTCT
TGATGGCCTCACCCTCTCGTAGCCGCCTGGAGAGGAAGGGTAGACTATATAGAGGAGGTTAG
GGGTAGGTCAGCATGATGCTAGGATGGAGAGAGCTCTGTCCCCTCGTGGATGGTGGTGGTGA
CTCACCCGGGGGGCCAGCTGCTTTCTGAGTGCAAATGAGAAAAATAAAGAGCTGCGCTGTGA
CTTTTCTTTCCACATCAAAGCTTGGGTGTCAGTGCTTTAGCTTGATGCTCTGATCACCATGC
AAATCTTCCACCGGCGCCTTGCTCAGCTTTCATATCCCAAGGGTGCCTGGGAGGAAGGCAAC
AGGGACAGTGGACATCACTGCACCACTTTCCACGACCCTGTGTGCCAACCTCAGCCACTTTG
AAACATGCTGATGACTGAGGTCTGTTCACTTTCTTAATTTCAAGCAGGAGAAGCAGGTTGGG
GAGCCAGCCTCCCCAGCTAGAGGGGACAGAACTTGACTTGAGCAGGGGGGTACCTCCTAGGA
CCTGCTCCATGTGCCTACTTCTTTACCCTTCTCTAGAGAGGGCTCTTGTCCTGTCAGAGCTG
TTTTCTCCCTTCTCTTGTTTTTTCTTTTTCAAGACTGTTTCTCTGTGTTAGCCCTGGCTGTC
CTGGATCTCACTCTGTAGATCAGGCTGACCTTGAGTTCAAAGCTCCATCTGCCTCTACTTCT
CACATTACTGTGATTAAAGGCATATACTACCACTGCCTGGTGCCCTTTTGTATTTCTTATTA
AAGTCCTAATGTCTGATTATAAAAACAGTCTGTGTGGGCTGGAGTGATGGCTTACTCAGTAA
AGCACTTGCCATGGAATCTGGGCAATCTGAGTTTCATTTTTAGCATCCTGTAAAAATCCCAA
TTTGATGGTGTACTTGTAATGTCAGCATGGAGAGGCAGAGATAGGTAAGTTCCCCAAGACTC
TTTGAACCGACAGCTTGGCCTCACTGGCACATTCCAGGTCTCAGTGAGAGACCCTGCCTCAA
AATACAAAGAAAGAGCTGCTGAAGAGTGGGTCAGAGTTGACCTCTGATCTCCGGAAGTATAT
GATACACACCCGTGCATGCACTCTTCCTTACAAAATAAAAAGCAAAACAAAACCCCAACAGG
TATATGGCCATTTTAGAAAAATTAGAAGATTTAGAAAGCTATACATAAAAAAAAATGACCTA
AAGAAAAATCTTTACTGTTCTGGGCACTATCCCTATCAAACCACTGTGTTCTTTGGCCAAGC
CTTGGGGTGGACACTGTTTTGAGGTGGGTCCTGTTATCTCCACTAGGTAGTGGAGTTTTGTG
TCAGACTAACTGGGTCTTAAAGCTGTCTTTAAGGCCATCAGGAGCTACTGACTTGCCTGCCT

CAGCAGAGCATATCCTGAAGGTCGGGGTTAAGTCTCCTTCCCGAGCGAGTTGCCTTCCAGTG
GGCCCCTGGACTCCTAGGTCCTCAGCGCTCATCAGCTGCCAAGGACTCTGAGGGAATGTCCT
CTGACTGTGGCCCCGAAAGGTAGGGGAGGGGGATGTGCTTAGGCTTAGGACAGGGTCCTGTT
TCAGTCTGCCTTCACTGTTAGTAGCACTGTGCCACATGGCACAGACTGGGCGAGCTTTAAAG
GAAGGAGGTTGATATTGGTTCCCACTTCTGGGGATCATGGTTGAGCAGCCTTGTCTGATGAT
GGTTGTCTTGATGGTAGATCGTGAGGTAGTTGATGAAGGTATGACATGGTGAGAAACTCTGT
GTGTGTGTGTTATTTTCTCTGTGTTCTACCTATACATCTATCTATGTATATATGTATCTATC
TATCTACCTGGAGGCTGGAGAGATAGCTTAGTGGTTAAGAACATTTGTTGTTCTTGCATAGT
CCTGGATTTAAATTTTCAGCACCCACATGGCAGCTCACAACAACCCATAAATCCAGTTTCAG
AGGATCCAACCTCTGATATACCATGTCAGCCAGAGCAGACACGGCTGAAGGTGGTTTGATCC
CCGTATGGAGAGGTGACAATTGGGAAGAGAGAAAGATCAACTTAACCATGCAAGGAACAGGA
AGTTAAATACTGAACAGGGAAGGTAAAGGCAGGAAGTAGATGTAGAGGGCAAATCAATGAAA
CCCAAACATACCCAAATTACGCTAAACACACACTGACATGCCAATTAAAAGGACAAATTGGC
TCCACTGGCAAAACCAAAACAGACACTGAAGATCCAAACAGTCACATGCCAACTACCGCGGA
GGGAGACAGACACAGAGAAGACCGTGACAGACACTTGGACACTCTTGAGAGTGGATGTGCAG
GAAGAGAGCTCTGCCAGTGGAGAAGAAAGCACTCAGAAGAAAGTGACAGCAGCTGTAAATTT
GTATTCTGCTAATGTTATGTTCCAAAGTTGAAAGCAAAATTGTACCAATTCATAAGAACAAA
CAGGCTGACTCTCAGTTGTGACTGAACGTCTCTCAGTAACTGACGGGGCGAGCAGGCCAAAG
GAGAGTCGGCTCAGAAGGGTGCATAGCCACGCCAAATCAAATAAGCAAGTACAACCGGCAGG
CTCTATTTCTAGCACAAAGGGGTCTGTGCCTCATTCTGTGCTTGGGTCAGAGCTTGGGTCTC
TCATTTGGATGTAAGTGGTGTAGTGGAGAAGCAGGAAATAATCCGGAGCGCATATTTTGATT
TTAACATAAGTGCTGATTTGGGAGGGAGTTTTGTCAAATTGTGTTTTTACAATGTTTTTTTT
TTTTTAAATGATGCTTTTTTGTAAAGTGTACAAATGTGATATAAGATTGGTTCTGCTACATT
CAGTTTCTATAAAAGTGGTTCTAAAATATTGTACTGTCAATCATCTCATGATTATTCTACTG
TACACATTACTGACTTTGTATGTAATAATTAATATTAGAAGAAAATATAATTTATTTGAATA
TAAAAAAAAAAAAAAAAAAA

[00446] SEQ ID NO: 46:

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX_6QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQ
AQSTNDGLDFQESQLVKKLVEPPPX_7GCQGSVISFPSPRSGPGSPAQWLLYTHPTH$X_8$$X_9$QRA
DLGAYLNPRPPAPEAWSEPVLLAKGSX$_{10}$AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX_{11}FX
$_{12}$MFTLKQAFPAEYLPQ

[00447] SEQ ID NO: 47:

X_1X_2S$X_3X_4X_5$LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX$_7$X$_8$DEHAELIVX$_9$RR
GDYDAX$_{10}$THQVQWX$_{11}$AQEVVAQAX$_{12}$LDGHRSMNPCPLYDX$_{13}$QTGTLFLFFIAIPX$_{14}$X$_{15}$VT
EX$_{16}$QQLQTRANVTRLX$_{17}$X$_{18}$VTSTDHGRTWSSPRDLTDAAIGPX$_{19}$YREWSTFAVGPGHX$_{20}$LQ
LHDRX$_{21}$RSLVVPAYAYRKLHPX$_{22}$QRPIPSAFX$_{23}$FLSHDHGRTWARGHFVAQDTX$_{24}$ECQVAE
VETGEQRVVTLNARSHLRARVQAQSX$_{25}$NX$_{26}$GLDFQX$_{27}$SQLVKKLVEPPPX$_{28}$GX$_{29}$QGSVISF
PSPRSGPGSPAQX$_{30}$LLYTHPTHX$_{31}$X$_{32}$QRADLGAYLNPRPPAPEAWSEPX$_{33}$LLAKGSX$_{34}$AYS
DLQSMGTGPDGSPLFGX$_{35}$LYEANDYEEIX$_{36}$FX$_{37}$MFTLKQAFPAEYLPQ

[00448] SEQ ID NO: 48:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00449] SEQ ID NO: 49:

DASLPYLQDESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA
FPAEYLPQ

[00450] SEQ ID NO: 50:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00451] SEQ ID NO: 51:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00452] SEQ ID NO: 52:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00453] SEQ ID NO: 53:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00454] SEQ ID NO: 54:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00455] SEQ ID NO: 55:

ASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQST
NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAYL
NPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
PAEYLPQ

[00456] SEQ ID NO: 56:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00457] SEQ ID NO: 57:

ASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQST
NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAYL
NPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
PAEYLPQ

[00458] SEQ ID NO: 58:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00459] SEQ ID NO: 59:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00460] SEQ ID NO: 60:

AASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00461] SEQ ID NO: 61:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00462] SEQ ID NO: 62:

AASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00463] SEQ ID NO: 63:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYAD
SVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK

[00464] SEQ ID NO: 64:

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRF
SGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY
EKHKVYACEVTHQGLSSPVTKSFNRGEC

[00465] SEQ ID NO: 65:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYAD
SVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSGGGG
SGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSA
SFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

[00466] SEQ ID NO: 66:

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRF
SGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY
EKHKVYACEVTHQGLSSPVTKSFNRGEC

[00467] SEQ ID NO: 67:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYAD
SVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK

[00468] SEQ ID NO: 68:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA

FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00469] SEQ ID NO: 69:

DASLPYLQDESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00470] SEQ ID NO: 70:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00471] SEQ ID NO: 71:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00472] SEQ ID NO: 72:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY

LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00473] SEQ ID NO: 73:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00474] SEQ ID NO: 74:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00475] SEQ ID NO: 75:

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX_6QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQ
AQSTNDGLDFQESQLVKKLVEPPPX_7GCQGSVISFPSPRSGPGSPAQWLLYTHPTH$X_8$$X_9$QRA
DLGAYLNPRPPAPEAWSEPVLLAKGSX_{10}AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX_{11}FX
$_{12}$MFTLKQAFPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPGK

[00476] SEQ ID NO: 76:

X_1X_2S$X_3X_4X_5$LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX$_7$X$_8$DEHAELIVX$_9$RR
GDYDAX$_{10}$THQVQWX$_{11}$AQEVVAQAX$_{12}$LDGHRSMNPCPLYDX$_{13}$QTGTLFLFFIAIPX$_{14}$X$_{15}$VT
EX$_{16}$QQLQTRANVTRLX$_{17}$X$_{18}$VTSTDHGRTWSSPRDLTDAAIGPX$_{19}$YREWSTFAVGPGHX$_{20}$LQ

LHDRX$_{21}$RSLVVPAYAYRKLHPX$_{22}$QRPIPSAFX$_{23}$FLSHDHGRTWARGHFVAQDTX$_{24}$ECQVAE
VETGEQRVVTLNARSHLRARVQAQSX$_{25}$NX$_{26}$GLDFQX$_{27}$SQLVKKLVEPPPX$_{28}$GX$_{29}$QGSVISF
PSPRSGPGSPAQX$_{30}$LLYTHPTHX$_{31}$X$_{32}$QRADLGAYLNPRPPAPEAWSEPX$_{33}$LLAKGSX$_{34}$AYS
DLQSMGTGPDGSPLFGX$_{35}$LYEANDYEEIX$_{36}$FX$_{37}$MFTLKQAFPAEYLPQGGGGSGGGGSDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00477] SEQ ID NO: 77:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00478] SEQ ID NO: 78:

DASLPYLQDESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00479] SEQ ID NO: 79:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP

KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00480] SEQ ID NO: 80:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00481] SEQ ID NO: 81:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00482] SEQ ID NO: 82:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00483] SEQ ID NO: 83:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00484] SEQ ID NO: 84:

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX_6QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQ
AQSTNDGLDFQESQLVKKLVEPPPX_7GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX_8X$_9$QRA
DLGAYLNPRPPAPEAWSEPVLLAKGSX_{10}AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX_{11}FX
$_{12}$MFTLKQAFPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPGKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPG
KGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNT

AVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYT
TPPTFGQGTKVEIK

[00485] SEQ ID NO: 85:

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX_7X_8DEHAELIVX_9RR$
$GDYDAX_{10}THQVQWX_{11}AQEVVAQAX_{12}LDGHRSMNPCPLYDX_{13}QTGTLFLFFIAIPX_{14}X_{15}VT$
$EX_{16}QQLQTRANVTRLX_{17}X_{18}VTSTDHGRTWSSPRDLTDAAIGPX_{19}YREWSTFAVGPGHX_{20}LQ$
$LHDRX_{21}RSLVVPAYAYRKLHPX_{22}QRPIPSAFX_{23}FLSHDHGRTWARGHFVAQDTX_{24}ECQVAE$
$VETGEQRVVTLNARSHLRARVQAQSX_{25}NX_{26}GLDFQX_{27}SQLVKKLVEPPPX_{28}GX_{29}QGSVISF$
$PSPRSGPGSPAQX_{30}LLYTHPTHX_{31}X_{32}QRADLGAYLNPRPPAPEAWSEPX_{33}LLAKGSX_{34}AYS$
$DLQSMGTGPDGSPLFGX_{35}LYEANDYEEIX_{36}FX_{37}MFTLKQAFPAEYLPQGGGGSGGGGSDKT$
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEVQLVESGG
GLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTIS
ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPS
RFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

[00486] SEQ ID NO: 86:

GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCAGCGTGGGAGACAGAGTGACCAT
CACCTGTAGAGCCAGCCAGGACGTGAACACAGCCGTGGCTTGGTATCAGCAGAAGCCTGGCA
AGGCCCCTAAGCTGCTGATCTACAGCGCCAGCTTTCTGTACTCCGGCGTGCCCAGCAGATTC
AGCGGCTCTAGAAGCGGCACCGACTTCACCCTGACCATAAGCAGTCTGCAGCCCGAGGACTT
CGCCACCTACTACTGTCAGCAGCACTACACCACACCTCCAACCTTTGGCCAGGGCACCAAGG
TGGAAATCAAGCGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAG
TTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAA
AGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGC
AGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTAC
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[00487] SEQ ID NO: 87:

GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGCCTGGCGGATCTCTGAGACTGTC
TTGTGCCGCCAGCGGCTTCAACATCAAGGACACCTACATCCACTGGGTCCGACAGGCCCCTG
GCAAAGGACTTGAATGGGTCGCCAGAATCTACCCCACCAACGGCTACACCAGATACGCCGAC
TCTGTGAAGGGCAGATTCACCATCAGCGCCGACACCAGCAAGAACACCGCCTACCTGCAGAT
GAACAGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTTCTAGATGGGGAGGCGACGGCT
TCTACGCCATGGATTATTGGGGCCAGGGCACCCTGGTCACCGTTTCTTCTGCtagcACCAAG
GGCCCATCcGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCT
GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCcTGGAACTCAGGCGCtC
TGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGC
AGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA
CAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACA
CATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCA
AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGT

GAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG
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CCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcT
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AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAA
CTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCA
CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00488] SEQ ID NO: 88:

GATGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
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CCAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCGGC
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATGAACAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTCAAGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
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AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
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ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
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CGCTGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
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TCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGGACCGTCAGTCTTCCTCTTCC
CCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTG
GACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA
TAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCC
TCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA
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GCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATG
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[00489] SEQ ID NO: 89:

GATGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
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ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATGAACAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG

TGTCAAGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
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AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGAGCCAGAGTGCAGGCCCAGAGC
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CGCTGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
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[00490] SEQ ID NO: 90:

TVEKSVVFKAEGEHFTDQKGNTIVGSGSGGTTKYFRIPAMCTTSKGTIVVFADARHNTASDQ
SFIDTAAARSTDGGKTWNKKIAIYNDRVNSKLSRVMDPTCIVANIQGRETILVMVGKWNNND
KTWGAYRDKAPDTDWDLVLYKSTDDGVTFSKVETNIHDIVTKNGTISAMLGGVGSGLQLNDG
KLVFPVQMVRTKNITTVLNTSFIYSTDGITWSLPSGYCEGFGSENNIIEFNASLVNNIRNSG
LRRSFETKDFGKTWTEFPPMDKKVDNRNHGVQGSTITIPSGNKLVAAHSSAQNKNNDYTRSD
ISLYAHNLYSGEVKLIDDFYPKVGNASGAGYSCLSYRKNVDKETLYVVYEANGSIEFQDLSR
HLPVIKSYNGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
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[00491] SEQ ID NO: 91:

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AGCTTCATCGATACCGCTGCCGCCAGATCTACCGATGGCGGCAAGACCTGGAACAAGAAGAT
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TGGCCAACATCCAGGGCAGAGAAACCATCCTGGTCATGGTCGGAAAGTGGAACAACAACGAT
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GAGCACCGATGACGGCGTGACCTTCAGCAAGGTGGAAACAAACATCCACGACATCGTGACCA
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CATCTGCCCGTGATCAAGAGCTACAACggcggaggtggaagtggcggaggcggatccgacaa
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[00492] SEQ ID NO: 92:

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SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSTVEKSVVFKAEGEHFTDQKGNTIVGSGSGGT
TKYFRIPAMCTTSKGTIVVFADARHNTASDQSFIDTAAARSTDGGKTWNKKIAIYNDRVNSK
LSRVMDPTCIVANIQGRETILVMVGKWNNNDKTWGAYRDKAPDTDWDLVLYKSTDDGVTFSK
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SLPSGYCEGFGSENNIIEFNASLVNNIRNSGLRRSFETKDFGKTWTEFPPMDKKVDNRNHGV
QGSTITIPSGNKLVAAHSSAQNKNNDYTRSDISLYAHNLYSGEVKLIDDFYPKVGNASGAGY
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[00493] SEQ ID NO: 93:

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cggcagcatcgagtttcaggacctgagcagacatctgcccgtgatcaagagctacaat

[00494] SEQ ID NO: 94:

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SFIDTAAARSTDGGKTWNKKIAIYNDRVNSKLSRVMDPTCIVANIQGRETILVMVGKWNNND
KTWGAYRDKAPDTDWDLVLYKSTDDGVTFSKVETNIHDIVTKNGTISAMLGGVGSGLQLNDG
KLVFPVQMVRTKNITTVLNTSFIYSTDGITWSLPSGYCEGFGSENNIIEFNASLVNNIRNSG
LRRSFETKDFGKTWTEFPPMDKKVDNRNHGVQGSTITIPSGNKLVAAHSSAQNKNNDYTRSD
ISLYAHNLYSGEVKLIDDFYPKVGNASGAGYSCLSYRKNVDKETLYVVYEANGSIEFQDLSR
HLPVIKSYNGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
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GGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVA
RIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWG
QGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQ
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GTKVEIK

[00495] SEQ ID NO: 95:

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[00496] SEQ ID NO: 96:

TVEKSVVFKAEGEHFTDQKGNTIVGSGSGGTTKYFRIPAMCTTSKGTIVVFADARHNTASDQ
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KTWGAYRDKAPDTDWDLVLYKSTDDGVTFSKVETNIHDIVTKNGTISAMLGGVGSGLQLNDG
KLVFPVQMVRTKNITTVLNTSFIYSTDGITWSLPSGYCEGFGSVNNIIEFNASLVNNIRNSG
LRRSFETKDFGKTWTEFPPMDKKVDNRNHGVQGSTITIPSGNKLVAAHSSAQNKNNDYTRSD
ISLYAHNLYSGEVKLIDDFYPKVGNASGAGYSCLSYRKNVDKETLYVVYEANGSIEFQDLSR
HLPVIKSYNGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
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[00497] SEQ ID NO: 97:

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gagcaccgacgacggcgtgaccttcagcaaggtggaaacaaacatccacgacatcgtgacca
agaacggcaccatctctgccatgctcggcggcgttggatctggcctgcaactgaatgatggc
aagctggtgttccccgtgcagatggtccgaacaaagaacatcaccaccgtgctgaataccag
cttcatctactccaccgacggcatcacatggtccctgcctagcggctactgtgaaggctttg
gcagcgtgaacaacatcatcgagttcaacgccagcctggtcaacaacatccggaacagcggc
ctgcggagaagcttcgagacaaaggacttcggaaagacgtggaccgagtttcctccaatgga
caagaaggtggacaaccggaaccacggcgtgcagggcagcacaatcacaatccctagcggca
acaaactggtggccgctcactctagcgcccagaacaagaacaacgattacaccagaagcgac
atcagcctgtacgcccacaacctgtactccggcgaagtgaagctgatcgacgacttctaccc
caaagtgggcaatgccagcggagccggctacagctgtctgagctaccggaaaaatgtggaca
aagaaaccctgtacgtggtgtacgaggccaacggcagcatcgagtttcaggacctgagcaga
catctgcccgtgatcaagagctacaatggcggaggtggaagtggcggaggcggatccgacaa
aactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctct
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gtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggt
gcataatgccaagacaaagccgcgggaggagcagtacaacagcacgtaccgtgtggtcagcg
tcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaac
aaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaacc
acaggtctacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacct
gcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccg
gagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctcactag
caagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgc
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[00498] SEQ ID NO: 98:

ASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQST
NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAYL
NPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
PAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00499] SEQ ID NO: 99:

ASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQST
NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAYL
NPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
PAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI

EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00500] SEQ ID NO: 100:

AASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00501] SEQ ID NO: 101:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00502] SEQ ID NO: 102:

AASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00503] SEQ ID NO: 103:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE

DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00504] SEQ ID NO: 104:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00505] SEQ ID NO: 105:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00506] SEQ ID NO: 106:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00507] SEQ ID NO: 107:

DASLPYLQDESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA

FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00508] SEQ ID NO: 108:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00509] SEQ ID NO: 109:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00510] SEQ ID NO: 110:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00511] SEQ ID NO: 111:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY

LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00512] SEQ ID NO: 112:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00513] SEQ ID NO: 113:

ASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQST
NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAYL
NPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
PAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00514] SEQ ID NO: 114:

ASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQST
NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAYL
NPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
PAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00515] SEQ ID NO: 115:

AASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS

TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00516] SEQ ID NO: 116:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00517] SEQ ID NO: 117:

AASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00518] SEQ ID NO: 118:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00519] SEQ ID NO: 119:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP

KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00520] SEQ ID NO: 120:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00521] SEQ ID NO: 121:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00522] SEQ ID NO: 122:

DASLPYLQDESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00523] SEQ ID NO: 123:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP

KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00524] SEQ ID NO: 124:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00525] SEQ ID NO: 125:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00526] SEQ ID NO: 126:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00527] SEQ ID NO: 127:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL

CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00528] SEQ ID NO: 128:

ASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQST
NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAYL
NPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
PAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00529] SEQ ID NO: 129:

ASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQST
NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAYL
NPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
PAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00530] SEQ ID NO: 130:

AASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00531] SEQ ID NO: 131:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00532] SEQ ID NO: 132:

AASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00533] SEQ ID NO: 133:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00534] SEQ ID NO: 134:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00535] SEQ ID NO: 135:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00536] SEQ ID NO: 136:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00537] SEQ ID NO: 137:

DASLPYLQDESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00538] SEQ ID NO: 138:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00539] SEQ ID NO: 139:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00540] SEQ ID NO: 140:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00541] SEQ ID NO: 141:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00542] SEQ ID NO: 142:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00543] SEQ ID NO: 143

:

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX_7X_8DEHAELIVX_9RR$
$GDYDAX_{10}THQVQWX_{11}AQEVVAQAX_{12}LDGHRSMNPCPLYDX_{13}QTGTLFLFFIAIPX_{14}X_{15}VT$
$EX_{16}QQLQTRANVTRLX_{17}X_{18}VTSTDHGRTWSSPRDLTDAAIGPX_{19}YREWSTFAVGPGHX_{20}LQ$
$LHDRX_{21}RSLVVPAYAYRKLHPX_{22}QRPIPSAFX_{23}FLSHDHGRTWARGHFVAQDTX_{24}ECQVAE$
VETGEQRVVTLNARSHLRARVQAQSX$_{25}$NX$_{26}$GLDFQX$_{27}$SQLVKKLVEPPPX$_{28}$GX$_{29}$QGSVISF
PSPRSGPGSPAQX$_{30}$LLYTHPTHX$_{31}$X$_{32}$QRADLGAYLNPRPPAPEAWSEPX$_{33}$LLAKGSX$_{34}$AYS
DLQSMGTGPDGSPLFGX$_{35}$LYEANDYEEIX$_{36}$FX$_{37}$MFTLKQAFPAEYLPQX$_{38}$DKTHTCPPCPA
PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00544] SEQ ID NO: 144:

X$_1$ASLPX$_2$LQX$_3$ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
AX$_4$THQVQWQAQEVVAQARLDGHRSMNPCPLYDX$_5$QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX$_6$QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQ
AQSTNDGLDFQESQLVKKLVEPPPX$_7$GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX$_8$X$_9$QRA
DLGAYLNPRPPAPEAWSEPVLLAKGSX$_{10}$AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX$_{11}$FX
$_{12}$MFTLKQAFPAEYLPQX$_{13}$DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00545] SEQ ID NO: 145:

GGGGSGGGGS

[00546] SEQ ID NO: 146:

EPKSS

[00547] SEQ ID NO: 147:

EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00548] SEQ ID NO: 148:

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00549] SEQ ID NO: 149:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHARQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00550] SEQ ID NO: 150:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHARQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00551] SEQ ID NO: 151:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHARQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00552] SEQ ID NO: 152:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHARQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00553] SEQ ID NO: 153:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHARQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00554] SEQ ID NO: 154:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00555] SEQ ID NO: 155:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00556] SEQ ID NO: 156:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00557] SEQ ID NO: 157:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00558] SEQ ID NO: 158:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00559] SEQ ID NO: 159:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00560] SEQ ID NO: 160:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00561] SEQ ID NO: 161:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00562] SEQ ID NO: 162:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00563] SEQ ID NO: 163:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00564] SEQ ID NO: 164:

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCX_6VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX_7QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX_8RV
QAQSTNDGLDFQESQLVKKLVEPPPX_9GCQGSVISFPSPRSGPGSPAQWLLYTHPTH$X_{10}X_{11}$Q
RADLGAYLNPRPPAPEAWSEPVLLAKGSX_{12}AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX_{13}
FX_{14}MFTLKQAFPAEYLPQX_{15}DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00565] SEQ ID NO: 165:

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX_7X_8DEHAELIVX_9RR$
$GDYDAX_{10}THQVQWX_{11}AQEVVAQAX_{12}LX_{13}GHRSMNPCPLYDX_{14}QTGTLFLFFIAIPX_{15}X_{16}V$
$TEX_{17}QQLQTRANVTRLX_{18}X_{19}VTSTDHGRTWSSPRDLTDAAIGPX_{20}YREWSTFAVGPGHX_{21}L$
$QLHDX_{22}X_{23}RSLVVPAYAYRKLHPX_{24}X_{25}X_{26}PIPSAFX_{27}FLSHDHGRTWARGHFVX_{28}QDTX_{29}$
$ECQVAEVX_{30}TGEQRVVTLNARSX_{31}X_{32}X_{33}X_{34}RX_{35}QAQSX_{36}NX_{37}GLDFQX_{38}X_{39}QX_{40}VKKL$
$X_{41}EPPPX_{42}GX_{43}QGSVISFPSPRSGPGSPAQX_{44}LLYTHPTHX_{45}X_{46}QRADLGAYLNPRPPAP$
$EAWSEPX_{47}LLAKGSX_{48}AYSDLQSMGTGPDGSPLFGX_{49}LYEANDYEEIX_{50}FX_{51}MFTLKQAFP$
$AEYLPQX_{52}DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK$
$FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI$
$SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL$
$DSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK$

[00566] SEQ ID NO: 166:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHARQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00567] SEQ ID NO: 167:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00568] SEQ ID NO: 168:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00569] SEQ ID NO: 169:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

[00570] SEQ ID NO: 170:

DASLPYLQDESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP

KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

[00571] SEQ ID NO: 171:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

[00572] SEQ ID NO: 172:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

[00573] SEQ ID NO: 173:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG

GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

[00574] SEQ ID NO: 174:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

[00575] SEQ ID NO: 175:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSPRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

[00576] SEQ ID NO: 176:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHARQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE

DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

[00577] SEQ ID NO: 177:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

[00578] SEQ ID NO: 178:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

[00579] SEQ ID NO: 179:

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLCX_6VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
LHPX_7QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX_8RV

QAQSTNDGLDFQESQLVKKLVEPPPX$_9$GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX$_{10}$X$_{11}$Q
RADLGAYLNPRPPAPEAWSEPVLLAKGSX$_{12}$AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX$_{13}$
FX$_{14}$MFTLKQAFPAEYLPQX$_{15}$DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKG
GGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWV
ARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW
GQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQ
QKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFG
QGTKVEIK

[00580] SEQ ID NO: 180:

X$_1$X$_2$SX$_3$X$_4$X$_5$LQX$_6$ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX$_7$X$_8$DEHAELIVX$_9$RR
GDYDAX$_{10}$THQVQWX$_{11}$AQEVVAQAX$_{12}$LX$_{13}$GHRSMNPCPLYDX$_{14}$QTGTLFLFFIAIPX$_{15}$X$_{16}$V
TEX$_{17}$QQLQTRANVTRLX$_{18}$X$_{19}$VTSTDHGRTWSSPRDLTDAAIGPX$_{20}$YREWSTFAVGPGHX$_{21}$L
QLHDX$_{22}$X$_{23}$RSLVVPAYAYRKLHPX$_{24}$X$_{25}$X$_{26}$PIPSAFX$_{27}$FLSHDHGRTWARGHFVX$_{28}$QDTX$_{29}$
ECQVAEVX$_{30}$TGEQRVVTLNARSX$_{31}$X$_{32}$X$_{33}$X$_{34}$RX$_{35}$QAQSX$_{36}$NX$_{37}$GLDFQX$_{38}$X$_{39}$QX$_{40}$VKKL
X$_{41}$EPPPX$_{42}$GX$_{43}$QGSVISFPSPRSGPGSPAQX$_{44}$LLYTHPTHX$_{45}$X$_{46}$QRADLGAYLNPRPPAP
EAWSEPX$_{47}$LLAKGSX$_{48}$AYSDLQSMGTGPDGSPLFGX$_{49}$LYEANDYEEIX$_{50}$FX$_{51}$MFTLKQAFP
AEYLPQX$_{52}$DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGG
GSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRY
ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSGG
GGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIY
SASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

[00581] SEQ ID NO: 181:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGG
CCAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAA

[00582] SEQ ID NO: 182:

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX_7X_8DEHAELIVX_9RR$
$GDYDAX_{10}THQVQWX_{11}AQEVVAQAX_{12}LX_{13}GHRSMNPCPLYDX_{14}QTGTLFLFFIAIPX_{15}X_{16}V$
$TEX_{17}QQLQTRANVTRLX_{18}X_{19}VTSTDHGRTWSSPRDLTDAAIGPX_{20}YREWSTFAVGPGHX_{21}L$
$QLHDX_{22}X_{23}RSLVVPAYAYRKLHPX_{24}X_{25}X_{26}PIPSAFX_{27}FLSHDHGRTWARGHFVX_{28}QDTX_{29}$
$ECQVAEVX_{30}TGEQRVVTLNARSX_{31}X_{32}X_{33}X_{34}RX_{35}QAQSX_{36}NX_{37}GLDFQX_{38}X_{39}QX_{40}VKKL$
$X_{41}EPPPX_{42}GX_{43}QGSVISFPSPRSGPGSPAQX_{44}LLYTHPTHX_{45}X_{46}QRADLGAYLNPRPPAP$
$EAWSEPX_{47}LLAKGSX_{48}AYSDLQSMGTGPDGSPLFGX_{49}LYEANDYEEIX_{50}FX_{51}MFTLKQAFP$
AEYLPQ

[00583] SEQ ID NO: 183:

$X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD$
$AX_4THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_5QTGTLFLFFIAIPGQVTEQQQLQTRANV$
$TRLCX_6VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK$
$LHPX_7QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX_8RV$
$QAQSTNDGLDFQESQLVKKLVEPPPX_9GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX_{10}X_{11}Q$
$RADLGAYLNPRPPAPEAWSEPVLLAKGSX_{12}AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX_{13}$
$FX_{14}MFTLKQAFPAEYLPQ$

[00584] SEQ ID NO: 184:

GGGGS

[00585] SEQ ID NO: 185:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00586] SEQ ID NO: 186:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGG
CCAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC

CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGAGCCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGtaCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00587] SEQ ID NO: 187:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00588] SEQ ID NO: 188:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGG
CCAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGAttCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC

CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGtaCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00589] SEQ ID NO: 189:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYAD
SVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK

[00590] SEQ ID NO: 190:

GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGCCTGGCGGATCTCTGAGACTGTC
TTGTGCCGCCAGCGGCTTCAACATCAAGGACACCTACATCCACTGGGTCCGACAGGCCCCTG
GCAAAGGACTTGAATGGGTCGCCAGAATCTACCCCACCAACGGCTACACCAGATACGCCGAC
TCTGTGAAGGGCAGATTCACCATCAGCGCCGACACCAGCAAGAACACCGCCTACCTGCAGAT
GAACAGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTTCTAGATGGGGAGGCGACGGCT
TCTACGCCATGGATTATTGGGGCCAGGGCACCCTGGTCACCGTTTCTTCTGCtagcACCAAG
GGCCCATCcGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCT
GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCcTGGAACTCAGGCGCtC
TGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGC
AGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA
CAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACA
CATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCA
AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGT
GAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG
CCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACC
GTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
CCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcT
ACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTC
AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAA
CTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCacTAGCAAGCTCA
CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00591] SEQ ID NO: 191:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00592] SEQ ID NO: 192:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00593] SEQ ID NO: 193:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00594] SEQ ID NO: 194:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT

VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

[00595] SEQ ID NO: 195:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00596] SEQ ID NO: 196:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00597] SEQ ID NO: 197:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00598] SEQ ID NO: 198:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00599] SEQ ID NO: 199:

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_7SX_8X_9DEHAELIVX_{10}R$
$RGDYDAX_{11}THQVQWX_{12}AQEVVAQAX_{13}LX_{14}GHRSMNPCPLYDX_{15}QTGTLFLFFIAIPX_{16}X_{17}$
$VTEX_{18}QQLQTRANVTRLX_{19}X_{20}VTSTDHGRTWSSPRDLTDAAIGPX_{21}YREWSTFAVGPGHX_{22}$
$LQLHDX_{23}X_{24}RSLVVPAYAYRKLHPX_{25}X_{26}X_{27}PIPSAFX_{28}FLSHDHGRTWARGHFVX_{29}QDTX$
$_{30}ECQVAEVX_{31}TGEQRVVTLNARSX_{32}X_{33}X_{34}X_{35}RX_{36}QAQSX_{37}NX_{38}GLDFQX_{39}X_{40}QX_{41}VKK$
$LX_{42}EPPPX_{43}GX_{44}QGSVISFPSPRSGPGSPAQX_{45}LLYTHPTHX_{46}X_{47}QRADLGAYLNPRPPA$
$PEAWSEPX_{48}LLAKGSX_{49}AYSDLQSMGTGPDGSPLFGX_{50}LYEANDYEEIX_{51}FX_{52}MFTLKQAF$
PAEYLPQ

[00600] SEQ ID NO: 200:

$X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_4SKKDEHAELIVLRRGDYD$
$AX_5THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_6QTGTLFLFFIAIPGQVTEQQQLQTRANV$
$TRLCX_7VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK$
$LHPX_8QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX_9RV$
$QAQSTNDGLDFQESQLVKKLVEPPPX_{10}GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX_{11}X_{12}$
$QRADLGAYLNPRPPAPEAWSEPVLLAKGSX_{13}AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX$
$_{14}FX_{15}MFTLKQAFPAEYLPQ$

[00601] SEQ ID NO: 201:

$X_1X_2SX_3X_4X_5LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_7SX_8X_9DEHAELIVX_{10}R$
$RGDYDAX_{11}THQVQWX_{12}AQEVVAQAX_{13}LX_{14}GHRSMNPCPLYDX_{15}QTGTLFLFFIAIPX_{16}X_{17}$
$VTEX_{18}QQLQTRANVTRLX_{19}X_{20}VTSTDHGRTWSSPRDLTDAAIGPX_{21}YREWSTFAVGPGHX_{22}$
$LQLHDX_{23}X_{24}RSLVVPAYAYRKLHPX_{25}X_{26}X_{27}PIPSAFX_{28}FLSHDHGRTWARGHFVX_{29}QDTX$
$_{30}ECQVAEVX_{31}TGEQRVVTLNARSX_{32}X_{33}X_{34}X_{35}RX_{36}QAQSX_{37}NX_{38}GLDFQX_{39}X_{40}QX_{41}VKK$
$LX_{42}EPPPX_{43}GX_{44}QGSVISFPSPRSGPGSPAQX_{45}LLYTHPTHX_{46}X_{47}QRADLGAYLNPRPPA$
$PEAWSEPX_{48}LLAKGSX_{49}AYSDLQSMGTGPDGSPLFGX_{50}LYEANDYEEIX_{51}FX_{52}MFTLKQAF$
$PAEYLPQX_{53}DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV$
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
LDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00602] SEQ ID NO: 202:

$X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_4SKKDEHAELIVLRRGDYD$
$AX_5THQVQWQAQEVVAQARLDGHRSMNPCPLYDX_6QTGTLFLFFIAIPGQVTEQQQLQTRANV$
$TRLCX_7VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK$
$LHPX_8QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX_9RV$

QAQSTNDGLDFQESQLVKKLVEPPPX$_{10}$GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX$_{11}$X$_{12}$
QRADLGAYLNPRPPAPEAWSEPVLLAKGSX$_{13}$AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX
$_{14}$FX$_{15}$MFTLKQAFPAEYLPQX$_{16}$DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
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[00603] SEQ ID NO: 203:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00604] SEQ ID NO: 204:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00605] SEQ ID NO: 205:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00606] SEQ ID NO: 206:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL

CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00607] SEQ ID NO: 207:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00608] SEQ ID NO: 208:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00609] SEQ ID NO: 209:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00610] SEQ ID NO: 210:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00611] SEQ ID NO: 211:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK

[00612] SEQ ID NO: 212:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK

[00613] SEQ ID NO: 213:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK

[00614] SEQ ID NO: 214:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
YCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK

[00615] SEQ ID NO: 215:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK

[00616] SEQ ID NO: 216:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
YCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK

[00617] SEQ ID NO: 217:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00618] SEQ ID NO: 218:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00619] SEQ ID NO: 219:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTcTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACgccAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTAAGcTTGTCTCCGGGTAAA

[00620] SEQ ID NO: 220:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEEQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP

KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00621] SEQ ID NO: 221:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGgaaCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00622] SEQ ID NO: 222:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVCTGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPCQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP

IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00623] SEQ ID NO: 223:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGtgtACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTt
gtCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00624] SEQ ID NO: 224:

ASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAGT
HQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
YVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQST
NDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAYL
NPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
PAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00625] SEQ ID NO: 225:

GCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAGAAT
TCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGcggA
GCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggcACA
CATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAGATC
TATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCGCTA
TCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTGTGT
tacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGCCGC
CATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCCAGC
TGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCCAAA
CAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGCCAG
AGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCGAGC
AGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGCACA
AACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCCAac
cGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTGCTC
AGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTACCTG
AATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAGCgc
tGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCTGTC
TGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCCTTT
CCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTG
CCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACA
CCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGAC
CCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCC
GCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGG
ACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATC
GAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCCCCC
ATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATC
CCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACG
CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAAGAG
CAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT
ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00626] SEQ ID NO: 226:

DASLPVLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00627] SEQ ID NO: 227:

gatGCATCTCTGCCTgtgCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc

ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00628] SEQ ID NO: 228:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00629] SEQ ID NO: 229:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGG
CCAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC

AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00630] SEQ ID NO: 230:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00631] SEQ ID NO: 231:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCcct
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC

AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00632] SEQ ID NO: 232:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00633] SEQ ID NO: 233:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgccCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC

TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00634] SEQ ID NO: 234:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00635] SEQ ID NO: 235:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTcagGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC

AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00636] SEQ ID NO: 236:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
IQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00637] SEQ ID NO: 237:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
atcCAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA

GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00638] SEQ ID NO: 238:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00639] SEQ ID NO: 239:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGAgccAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00640] SEQ ID NO: 240:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00641] SEQ ID NO: 241:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAACTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AcagGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00642] SEQ ID NO: 242:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP

KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
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[00643] SEQ ID NO: 243:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCCACGCCTACAG
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ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
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CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCGTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CtgtGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAA
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ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00644] SEQ ID NO: 244:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
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CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK

ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQK
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TKVEIK

[00645] SEQ ID NO: 245:

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TCTGTGAAGGGCAGATTCACCATCAGCGCCGACACCAGCAAGAACACCGCCTACCTGCAGAT
GAACAGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTTCTAGATGGGGAGGCGACGGCT
TCTACGCCATGGATTATTGGGGCCAGGGCACCCTGGTCACCGTTTCTTCTGCtagcACCAAG
GGCCCATCcGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCT
GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCcTGGAACTCAGGCGCtC
TGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGC
AGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA
CAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACA
CATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCA
AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGT
GAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG
CCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACC
GTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
CCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcT
ACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTC
AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAA
CTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCaccAGCAAGCTCA
CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
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[00646] SEQ ID NO: 246:

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ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
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AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
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CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG

CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTCACCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
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GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
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CCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGtaCTGCCTGGTCAAAGGCTTCT
ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
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ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00647] SEQ ID NO: 247:

X_1ASLPX_2LQX_3ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_4SKKDEHAELIVLRRGDY
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VTRLCX_7VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAY
RKLHPX_8QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX$_9$
RVQAQSTNDGLDFQESQLVKKLVEPPPX$_{10}$GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX$_{11}$
X$_{12}$QRADLGAYLNPRPPAPEAWSEPVLLAKGSX$_{13}$AYSDLQSMGTGPDGSPLFGCLYEANDYE
EIX$_{14}$FX$_{15}$MFTLKQAFPAEYLPQX$_{16}$DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGK
GLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFY
AMDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTA
VAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTT
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[00648] SEQ ID NO: 248:

$X_1X_2SX_3X_4X_5$LQX_6ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX_7SX_8X_9DEHAELIVX_{10}R
RGDYDAX_{11}THQVQWX_{12}AQEVVAQAX_{13}LX_{14}GHRSMNPCPLYDX_{15}QTGTLFLFFIAIP$X_{16}X_{17}$
VTEX_{18}QQLQTRANVTRL$X_{19}X_{20}$VTSTDHGRTWSSPRDLTDAAIGPX_{21}YREWSTFAVGPGHX_{22}
LQLHD$X_{23}X_{24}$RSLVVPAYAYRKLHP$X_{25}X_{26}X_{27}$PIPSAFX_{28}FLSHDHGRTWARGHFVX_{29}QDTX
$_{30}$ECQVAEVX_{31}TGEQRVVTLNARS$X_{32}X_{33}X_{34}X_{35}$RX_{36}QAQSX_{37}NX_{38}GLDFQ$X_{39}X_{40}$QX_{41}VKK
LX_{42}EPPPX$_{43}$GX_{44}QGSVISFPSPRSGPGSPAQX_{45}LLYTHPTHX$_{46}X_{47}$QRADLGAYLNPRPPA
PEAWSEPX$_{48}$LLAKGSX$_{49}$AYSDLQSMGTGPDGSPLFGX$_{50}$LYEANDYEEIX$_{51}$FX$_{52}$MFTLKQAF
PAEYLPQX$_{53}$DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGG
GGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTR
YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSG
GGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLI
YSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

[00649] SEQ ID NO: 249:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
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CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
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GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVT
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEI
K

WHAT IS CLAIMED IS:

1. A recombinant mutant human Neu2 sialidase, wherein the sialidase comprises

(i) a substitution of an alanine residue at a position corresponding to position 42 of wild-type human Neu2 (SEQ ID NO: 1) with an arginine residue (A42R), and (ii) an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 198.

2. The sialidase of claim 1, wherein, in the sialidase:

(a) a methionine residue at a position corresponding to position 1 of wild-type human Neu2 is substituted by aspartic acid (M1D);

(b) a valine residue at a position corresponding to position 6 of wild-type human Neu2 is substituted by tyrosine (V6Y);

(c) a proline residue at a position corresponding to position 62 of wild-type human Neu2 is substituted by glycine (P62G);

(d) an alanine residue at a position corresponding to position 93 of wild-type human Neu2 is substituted by glutamic acid (A93E);

(e) a glutamine residue at a position corresponding to position 126 of wild-type human Neu2 is substituted by tyrosine (Q126Y);

(f) an alanine residue at a position corresponding to position 242 of wild-type human Neu2 is substituted by phenylalanine (A242F);

(g) a glutamine residue at a position corresponding to position 270 of wild-type human Neu2 is substituted by threonine (Q270T); or

(h) a cysteine residue at a position corresponding to position 332 of wild-type human Neu2 is substituted by alanine (C332A);

or the sialidase comprises a combination of any of the foregoing substitutions.

3. The sialidase of claim 2, wherein the sialidase comprises the M1D, V6Y, A42R, P62G, A93E, Q126Y, A242F, Q270T, and C332A substitutions.

4. A fusion protein comprising:

(a) the recombinant enzyme of any one of claims 1-3; and

(b) an immunoglobulin Fc domain and/or an immunoglobulin antigen-binding domain;

wherein the enzyme and the immunoglobulin Fc domain and/or the immunoglobulin antigen-binding domain are linked by a peptide bond or an amino acid linker.

5. The fusion protein of claim 4, wherein the fusion protein comprises an immunoglobulin Fc domain.

6. The fusion protein of claim 5, wherein the immunoglobulin Fc domain is derived from a human IgG1, IgG2, IgG3, or IgG4 Fc domain.

7. The fusion protein of claim 6, wherein the immunoglobulin Fc domain is derived from a human IgG1 Fc domain.

8. The fusion protein of any one of claims 4-7, wherein the fusion protein comprises an immunoglobulin antigen-binding domain.

9. The fusion protein of claim 8, wherein the immunoglobulin antigen-binding domain is associated with a second immunoglobulin antigen-binding domain to produce an antigen-binding site.

10. The fusion protein of claim 8 or 9, wherein the immunoglobulin antigen-binding domain is derived from an antibody selected from trastuzumab, daratumumab, girentuximab, ofatumumab, avelumab, and rituximab.

11. The fusion protein of any one of claims 4-10, wherein the fusion protein comprises SEQ ID NO: 210.

12. An antibody conjugate comprising the fusion protein of any one of claims 4-11.

13. The antibody conjugate of claim 12, wherein the antibody conjugate comprises:

(a) a first polypeptide comprising an immunoglobulin light chain;
(b) a second polypeptide comprising an immunoglobulin heavy chain; and
(c) a third polypeptide comprising an immunoglobulin Fc domain and a sialidase;

wherein the first and second polypeptides are covalently linked together and the second and third polypeptides are covalently linked together, and wherein the first polypeptide and the second polypeptide together define an antigen-binding site.

14. The antibody conjugate of claim 13, wherein the third polypeptide comprises the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation.

15. An isolated nucleic acid comprising a nucleotide sequence encoding the recombinant enzyme of any one of claims 1-3, the fusion protein of any one of claims 4-11, or at least a portion of the antibody conjugate of any one of claims 12-14.

16. An expression vector comprising the nucleic acid of claim 15.

17. A host cell comprising the expression vector of claim 16.

18. A pharmaceutical composition comprising the recombinant enzyme of any one of claims 1-3, the fusion protein of any one of claims 4-11, or the antibody conjugate of any one of claims 12-14.

19. Use of the recombinant enzyme of any one of claims 1-3, the fusion protein of any one of claims 4-11, or at least a portion of the antibody conjugate of any one of claims 12-14, or the pharmaceutical composition of claim 18 in the preparation of a medicament for the treatment of cancer in a subject.