

SIALIDASE-HER2-ANTIBODY FUSION PROTEINS AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent
5 Application No. 63/134,411, filed January 6, 2021, and U.S. Provisional Patent Application
No. 63/217,998, filed July 2, 2021, the entire disclosures of which are incorporated herein by
reference in their entirety for all purposes.

FIELD OF THE INVENTION

[0002] The invention relates generally to recombinant sialidase fusion proteins and antibody
10 conjugates, 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)
15 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.,
20 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
25 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.
30 ACAD. SCI. USA 113(37): 10304-9).

- [0005] The gene encoding HER2 is located on chromosome 17 and is a member of the EGF/erbB growth factor receptor gene family, which also includes epidermal growth factor receptor (EGFR, or HER1), HER3/erbB3 and HER4/erbB4. All of these genes encode transmembrane growth factor receptors, which are tyrosine kinase type 1 receptors with growth stimulating potential. Activation of HER family members generally occurs when the ligand and a dimer of the same monomer or other member of the HER family are bound together. HER2 has no known ligand. Once activation has occurred, tyrosine autophosphorylation of cytoplasmic signal proteins transmit signals to the nucleus, thus regulating aspects of cell growth, division, differentiation and migration.
- [0006] Overexpression of HER2 receptors results in receptors transmitting excessive signals for cell proliferation to the nucleus (Gutierrez *et al.* (2011) ARCH. PATHOL. LAB. MED. 135(1): 55–62). Data supports the hypothesis that, for certain cancers, overexpression of HER2 directly contributes to the pathogenesis and clinical aggressiveness of tumor cells, and is associated with poor prognosis, including reduced relapse-free and overall survival (Iqbal *et al.* (2014) MOL. BIOL. INT. 2014: 852748). Anti-HER2 antibodies include trastuzumab, which has been approved in the United States for use in the treatment of, for example, breast cancer and gastric or gastroesophageal junction adenocarcinomas, and pertuzumab, which has been approved in the United States for use in the treatment of, for example, breast cancer.
- [0007] Cancer immunotherapies have improved the outcome of many cancer patients. However, despite advances that have been made to date, many patients do not respond or only partially respond to currently available therapies. Accordingly, there is still a need for effective interventions for treating cancers associated with hypersialylated cancer cells.

SUMMARY OF THE INVENTION

- [0008] The invention is based, in part, upon the discovery that it is possible to produce fusion proteins containing a sialidase enzyme and an anti-HER2 immunoglobulin or a portion thereof, *e.g.*, an antigen-binding domain and/or an immunoglobulin Fc domain, and/or antibody conjugates including a sialidase enzyme and an anti-HER2 antibody or a portion thereof, *e.g.*, an antigen-binding domain and/or an immunoglobulin Fc domain. The sialidase enzyme portion of the fusion protein and/or antibody conjugate may comprise at least one mutation relative to a wild-type sialidase. The mutations, or combination of mutations, can improve the expression, activity or both the expression and activity of the sialidase to improve its use in cancer diagnosis and/or treatment.

[0009] The fusion proteins and/or antibody conjugates have suitable substrate specificities and activities to be useful in removing sialic acid and/or sialic acid containing molecules from the surface of cancer cells, *e.g.*, HER2-expressing cancer cells, and/or removing sialic acid and/or sialic acid containing molecules from the tumor microenvironment, and/or
5 reducing the concentration of sialic acid and/or sialic acid containing molecules in the tumor microenvironment.

[0010] Accordingly, in one aspect, the invention provides a fusion protein comprising (or consisting essentially of): (a) sialidase enzyme; and (b) an anti-HER2 immunoglobulin antigen-binding domain.

10 [0011] In certain embodiments, the sialidase is a human sialidase, *e.g.*, a recombinant mutant human sialidase. In certain embodiments, 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
15 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
20 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
25 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
30 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
5 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
10 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
15 (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
20 251 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
25 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
30 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 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 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),
 5 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
 10 (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
 15 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.
- 20 **[0013]** In certain embodiments, the sialidase 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
 25 position corresponding to position 332 of wild-type human Neu2 (C332); or a combination of any of the foregoing substitutions.
- [0014]** In certain embodiments, in the sialidase: (a) the methionine residue at a position corresponding to position 1 of wild-type human Neu2 is deleted (Δ M1), is substituted by alanine (M1A), or is substituted by aspartic acid (M1D); (b) the valine residue at a position
 30 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 embodiments, 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 embodiments, the sialidase is selected from Neu1, Neu2, Neu3, and Neu4, *e.g.*, the sialidase is Neu2.

[0017] In certain embodiments, the sialidase has a different substrate specificity than the corresponding wild-type sialidase. For example, in certain embodiments the sialidase can cleave α 2,3, α 2,6, and/or α 2,8 linkages. In certain embodiments the sialidase can cleave α 2,3 and α 2,8 linkages.

[0018] In certain embodiments, 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.

[0019] In certain embodiments, the sialidase comprises mutation or combination of mutations set forth in any one of TABLES 1-11, hereinbelow.

[0020] In certain embodiments, the fusion protein further comprises an immunoglobulin Fc domain. In certain embodiments, 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 embodiments, the anti-HER2 immunoglobulin antigen-binding domain is associated (for example, covalently or non-covalently associated) with a second anti-HER2 immunoglobulin antigen-binding domain to produce an anti-HER2 antigen-binding site.
- [0022] In certain embodiments, the anti-HER2 immunoglobulin antigen-binding domain is
5 derived from an antibody selected from trastuzumab, pertuzumab, CT-P6, trastuzumab-dkst, MGAH22 (margetuximab), PF-05280014, ertumaxomab, gancotamab, timigutuzumab, Ontruzant, ABP-980, SB3, DS-8201, MYL-1410, BCD-022, and HD201, *e.g.*, the anti-HER2 immunoglobulin antigen-binding domain is derived from trastuzumab.
- [0023] In certain embodiments, the sialidase and the immunoglobulin Fc domain and/or the
10 anti-HER2 immunoglobulin antigen-binding domain are linked by a peptide bond or an amino acid linker.
- [0024] In certain embodiments, the fusion protein comprises 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.
- [0025] In another aspect, the invention provides an antibody conjugate comprising any of the
15 foregoing fusion proteins. In certain embodiments, the antibody conjugate comprises a single sialidase. In other embodiments, the antibody conjugate comprises two sialidases, which can be the same or different. In certain embodiments the antibody conjugate comprises two identical sialidases. In certain embodiments, the antibody conjugate comprises a single anti-
20 HER2 antigen-binding site. In other embodiments, the antibody conjugate comprises two anti-HER2 antigen-binding sites, which can be the same or different. In certain embodiments, the antibody conjugate comprises two identical anti-HER2 antigen-binding sites.
- [0026] In certain embodiments, the antibody conjugate has a molecular weight from about
25 135 kDa to about 165 kDa, or the antibody conjugate has a molecular weight from about 215 kDa to about 245 kDa.
- [0027] In certain embodiments, 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
30 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 anti-HER2 antigen-

binding site. The third polypeptide may, for example, comprise the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation. The first polypeptide may, for example, comprise SEQ ID NO: 66, the second polypeptide may, for example, comprise any one of SEQ ID NOs: 67 or 189, and/or the third polypeptide may, for example, comprise
5 any one of SEQ ID NOs: 68-74, 98-112, 150, 151, 155, 156, 160, 161, 185, 187, 192, 195, 203-208. 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.

[0028] In certain embodiments, the antibody conjugate comprises: (a) a first polypeptide
10 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,
15 and the second and third polypeptides are covalently linked together, and wherein the first polypeptide and the second polypeptide together define a first anti-HER2 antigen-binding site, and the third polypeptide and the fourth polypeptide together define a second anti-HER2 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
20 an N- to C-terminal orientation.

[0029] In certain embodiments, 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
25 (scFv); wherein the first and second polypeptides are covalently linked together, and wherein the first scFv defines a first anti-HER2 antigen-binding site, and the second scFv, when present, defines a second anti-HER2 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
30 second sialidase, the second immunoglobulin Fc domain, and the optional second scFv in an N- to C-terminal orientation. The first polypeptide may, for example, comprise any one of SEQ ID NOs: 77-83, 166-178, 194, 197, 244, or 249, and/or the second polypeptide may, for example, comprise any one of SEQ ID NOs: 77-83, 166-178, 194, 197, 244, or 249.

[0030] In certain embodiments, 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 anti-HER2 antigen-binding site and the scFv defines a second anti-HER2 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.

[0031] In another aspect, the invention provides an isolated nucleic acid comprising a nucleotide sequence encoding any of the foregoing fusion proteins or at least a portion of any of the foregoing antibody conjugates. In another aspect, the invention provides an expression vector comprising any of the foregoing nucleic acids. In another aspect, the invention provides a host cell comprising any of the foregoing expression vectors.

[0032] In another aspect, the invention provides a pharmaceutical composition comprising any of the foregoing fusion proteins or any of the foregoing antibody conjugates.

[0033] In another aspect, the invention 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 fusion proteins, any of the foregoing antibody conjugates, or any of the foregoing pharmaceutical compositions.

[0034] In certain embodiments, the cancer is selected from lung bronchioloalveolar carcinoma (BAC), bladder cancer, a female genital tract malignancy (*e.g.*, uterine serous carcinoma, endometrial carcinoma, vulvar squamous cell carcinoma, and uterine sarcoma), an ovarian surface epithelial carcinoma (*e.g.*, clear cell carcinoma of the ovary, epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer), breast carcinoma, non-small cell lung cancer (NSCLC), a male genital tract malignancy (*e.g.*, testicular cancer), retroperitoneal or peritoneal carcinoma, gastroesophageal adenocarcinoma, esophagogastric junction carcinoma, liver hepatocellular carcinoma, esophageal and esophagogastric junction carcinoma, cervical cancer, cholangiocarcinoma, pancreatic adenocarcinoma, extrahepatic bile duct adenocarcinoma, a small intestinal malignancy, gastric adenocarcinoma, cancer of

unknown primary (CUP), colorectal adenocarcinoma, esophageal carcinoma, prostatic adenocarcinoma, kidney cancer, head and neck squamous carcinoma, thymic carcinoma, non-melanoma skin cancer, thyroid carcinoma (*e.g.*, papillary carcinoma), a head and neck cancer, anal carcinoma, non-epithelial ovarian cancer (non-EOC), uveal melanoma, malignant pleural
5 mesothelioma, small cell lung cancer (SCLC), a central nervous system cancer, a neuroendocrine tumor, and a soft tissue tumor. For example, in certain embodiments, the cancer is breast cancer, non-small cell lung cancer, bladder cancer, kidney cancer, colon cancer, and melanoma.

[0035] In another aspect, the invention provides a method of promoting infiltration of
10 immune cells into a tumor in a subject in need thereof. The method comprises administering to the subject an effective amount of any of the foregoing fusion proteins, any of the foregoing antibody conjugates, or any of the foregoing pharmaceutical compositions. 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
15 natural killer (NK) cells.

[0036] In another aspect, the invention provides a method of increasing the number of circulating natural killer (NK) cells in a subject in need thereof. The method comprises administering to the subject an effective amount of any of the foregoing fusion proteins, any of the foregoing antibody conjugates, or any of the foregoing pharmaceutical compositions,
20 so as to increase the number of circulating NK cells relative to prior to administration of the fusion protein, antibody conjugate or pharmaceutical composition.

[0037] In another aspect, the invention provides a method of increasing the number of T-cells in the draining lymph node in subject in need thereof. The method comprises administering to the subject an effective amount of any of the foregoing fusion proteins, any of the
25 foregoing antibody conjugates, or any of the foregoing pharmaceutical compositions, so as to increase the number of T-cells in the draining lymph node relative to prior to administration of the fusion protein, antibody conjugate or pharmaceutical composition. In certain embodiments, the immune cells are T-cells, *e.g.*, CD4⁺ and/or CD8⁺ T-cells.

[0038] In another aspect, the invention 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,
30 tissue, or subject with an effective amount of any of the foregoing fusion proteins, any of the

foregoing antibody conjugates, or any of the foregoing pharmaceutical compositions, 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 fusion protein, antibody conjugate or pharmaceutical composition.

- 5 [0039] These and other aspects and features of the invention are described in the following detailed description and claims.

DESCRIPTION OF THE DRAWINGS

[0040] The invention can be more completely understood with reference to the following drawings.

- 10 [0041] FIGURES 1A-II depict schematic representations of certain antibody conjugate constructs containing a sialidase enzyme, *e.g.*, a human sialidase enzyme, and an anti-HER2 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) anti-HER2 antigen binding site, each anti-HER2 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.

- 25 [0042] FIGURE 2 depicts schematic representations of certain antibody conjugate constructs containing a sialidase enzyme, *e.g.*, a human sialidase enzyme, and an anti-HER2 antigen binding site. For each antibody conjugate construct that contains more than one (*e.g.*, two) anti-HER2 antigen binding site, each anti-HER2 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.

[0043] FIGURES 3A-3E are schematic representations of exemplary fusion protein conjugates referred to as a Raptor antibody sialidase conjugate (FIGURE 3A), a Janus antibody sialidase conjugate (FIGURE 3B), a Lobster antibody sialidase conjugate (FIGURE 3C), a Bunk antibody sialidase conjugate (FIGURE 3D), and a Lobster-Fab antibody sialidase conjugate (FIGURE 3E).

[0044] FIGURE 4A depicts an SDS-PAGE gel showing recombinant Neu2-M259-Fc under non-reducing and reducing conditions. FIGURE 4B is an SEC-HPLC trace of Neu2-M259-Fc.

[0045] FIGURE 5A is a line graph showing enzymatic activity of the indicated Neu2-Fc variants as a function of substrate (4-MU-Neu5Ac) concentration. FIGURE 5B is a line graph showing enzymatic activity of the indicated Neu2-Fc variants as a function of enzyme concentration.

[0046] FIGURE 6 is a line graph depicting thermal stability of the indicated Neu2-Fc variants.

[0047] FIGURE 7 is a bar graph depicting enzymatic activity of the indicated Neu2-Fc variants following incubation at 37 °C for the indicated length of time.

[0048] FIGURE 8 is an SEC-HPLC trace of Janus Trastuzumab 2.

[0049] FIGURE 9 depicts binding to HER2 antigen as determined by ForteBio Octet for Janus Trastuzumab 2.

[0050] FIGURE 10 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 10A), 1 mg/kg trastuzumab (FIGURE 10B), 10 mg/kg trastuzumab (FIGURE 10C), 1 mg/kg Janus Trastuzumab 2 (FIGURE 10D), or 10 mg/kg Janus Trastuzumab 2 (FIGURE 10E), where each line represents an individual mouse, and in FIGURE 10F, each line represents the mean tumor volume for the indicated treatment group. Triangles indicate dosing frequency. In FIGURES 10A-E, Complete Responses (CR) and Partial Responses (PR) are indicated.

[0051] FIGURE 11 is a line graph showing enzymatic activity of Janus Trastuzumab 2 as a function of substrate (4-MU-Neu5Ac) concentration. Enzyme kinetics (V_{max} , K_m , and K_{cat}) are indicated.

[0052] **FIGURE 12** is a line graph depicting the thermal enzymatic stability of Janus Trastuzumab 2.

5 [0053] **FIGURES 13A-13B** are line graphs depicting desialylation of SKBR-3 cells, human cells with high levels of HER2 expression, by Janus Trastuzumab 2 (“Janus”) or Janus LOF, an enzymatically inactive variant. **FIGURE 13A** depicts staining by Hydra 9 following treatment with either Janus Trastuzumab 2 or Janus LOF at the indicated concentrations for 17 hours, where decreased staining is indicative of desialylation. **FIGURE 13B** depicts staining by PNA following treatment with either Janus Trastuzumab 2 or Janus LOF at the indicated concentrations for 17 hours, where increased staining is indicative of desialylation.

10 [0054] **FIGURES 14A-14B** are line graphs depicting desialylation of HT-29 cells, human cells with low but detectable levels of HER2 expression, by Janus Trastuzumab 2 (“Janus”) or Janus LOF, an enzymatically inactive variant. **FIGURE 14A** depicts staining by Hydra 9 following treatment with either Janus Trastuzumab 2 or Janus LOF at the indicated concentrations for 17 hours, where decreased staining is indicative of desialylation.
15 **FIGURE 14B** depicts staining by PNA following treatment with either Janus Trastuzumab 2 or Janus LOF at the indicated concentrations for 17 hours, where increased staining is indicative of desialylation.

[0055] **FIGURES 15A-15C** are line graphs depicting ADCC activity mediated by Janus Trastuzumab 2 (“Janus”), Janus LOF, or trastuzumab, at the indicated Effector to Target (E:T) ratios, towards BT-20 cells (**FIGURE 15A**), HT-29 cells (**FIGURE 15B**), or SKBR3 cells (**FIGURE 15C**).

[0056] **FIGURES 16A-16C** are bar graphs depicting ADCP activity mediated by Janus Trastuzumab 2 (“Janus”), Janus LOF, or trastuzumab, at either 10 µg/mL or 30 µg/mL, as measured by percent killing by phagocytosis of BT-20 cells (**FIGURE 16A**), percent killing
25 by phagocytosis of HT-29 cells (**FIGURE 16B**), or percent killing by phagocytosis of SKBR3 cells (**FIGURE 16C**).

[0057] **FIGURE 17** depicts testing of Janus Trastuzumab 2 (“Janus”) 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 10 mg/kg isotype control (**FIGURE**
30 **17A**), 5 mg/kg trastuzumab (**FIGURE 17B**), 10 mg/kg Janus LOF (**FIGURE 17C**), 1 mg/kg Janus Trastuzumab 2 (**FIGURE 17D**), 3 mg/kg Janus Trastuzumab 2 (**FIGURE 17E**), or 10

mg/kg Janus Trastuzumab 2 (**FIGURE 17F**). Each line represents an individual mouse, and triangles represent dosing.

[0058] **FIGURE 18A** depicts the average of the tumor volumes from **FIGURE 17** for the Janus Trastuzumab 2 and Janus LOF treatment groups (both dosed at 10 mg/kg). Triangles represent dosing. **, $p < 0.05$, as determined by One-way ANOVA. **FIGURE 18B** depicts survival curves for the Janus Trastuzumab 2, Janus LOF, and trastuzumab treatment groups. ns, not significant.

[0059] Various features and aspects of the invention are discussed in more detail below.

DETAILED DESCRIPTION

10 [0060] The invention is based, in part, upon the discovery that it is possible to produce fusion proteins containing a sialidase enzyme and an anti-HER2 immunoglobulin or a portion thereof, *e.g.*, an antigen-binding domain and/or an immunoglobulin Fc domain, and/or antibody conjugates including a sialidase enzyme and an anti-HER2 antibody or a portion thereof, *e.g.*, an antigen-binding domain and/or an immunoglobulin Fc domain. The sialidase
15 enzyme portion of the fusion protein and/or antibody conjugate may comprise at least one mutation relative to a wild-type sialidase. The mutations, or combination of mutations, can improve the expression, activity or both the expression and activity of the sialidase to improve its use in cancer diagnosis and/or treatment.

[0061] The fusion proteins and/or antibody conjugates have suitable substrate specificities
20 and activities to be useful in removing sialic acid and/or sialic acid containing molecules from the surface of cancer cells, *e.g.*, HER2-expressing 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.

25 [0062] The invention further relates to pharmaceutical compositions and methods of using fusion proteins and/or antibody conjugates to treat cancer.

I. Sialidase anti-HER2 Fusion Proteins

[0063] To promote the selective removal of sialic acids on hypersialylated cancer cells, *e.g.*, HER2 expressing cancer cells, and/or in the tumor microenvironment, it may be helpful to
30 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).

5 [0064] Accordingly, the invention further provides fusion proteins comprising a sialidase enzyme, or a functional fragment thereof, and a portion or fragment of an anti-HER2 antibody, such as an immunoglobulin antigen-binding domain (also referred to herein as an antigen-binding domain or an immunoglobulin Fc domain (also referred to herein as an Fc domain). In certain embodiments, the sialidase and anti-HER2 antibody or portion thereof (*e.g.*, antigen-binding domain or immunoglobulin Fc domain) are linked by a peptide bond or
10 an amino acid linker.

[0065] 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
15 linker. A nucleotide sequence encoding such a fusion protein can, for example, be created using conventional recombinant DNA technologies.

[0066] In certain embodiments, a 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.

20 **a. Sialidase Portion**

[0067] 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
25 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
30 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.

5 [0068] In certain embodiments, a sialidase portion of a sialidase-anti-HER2 fusion protein is derived from a eukaryotic sialidase, *e.g.*, a mammalian sialidase, *e.g.*, a human or mouse sialidase.

[0069] Four sialidases are encoded in the human genome: Neu1, Neu2, Neu3 and Neu4. 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
10 ID NO: 7, and a nucleotide sequence encoding human Neu1 is depicted in SEQ ID NO: 23.

[0070] 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.

15 [0071] 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
20 human Neu3, isoform 2 is depicted in SEQ ID NO: 34.

[0072] 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
25 2 is depicted in SEQ ID NO: 11, and a nucleotide sequence encoding human Neu4, isoform 2 is depicted in SEQ ID NO: 35.

[0073] 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.
30 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.

[0074] In certain embodiments, a sialidase portion of a sialidase-anti-HER2 fusion protein is derived from a prokaryotic sialidase. Exemplary prokaryotic sialidases include sialidases
 5 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.

10 [0075] In certain embodiments, the sialidase portion of a sialidase-anti-HER2 fusion protein is a mutant sialidase, *e.g.*, a recombinant mutant human sialidase. In certain embodiments, the recombinant mutant 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
 15 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 human sialidase.

[0076] In certain embodiments, the recombinant mutant human sialidase has about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%,
 20 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 human sialidase.

[0077] In certain embodiments, the recombinant mutant human sialidase has the same substrate specificity as the corresponding wild-type human sialidase. In other embodiments,
 25 the recombinant mutant human sialidase has a different substrate specificity than the corresponding wild-type human sialidase. For example, in certain embodiments the recombinant mutant human sialidase can cleave α 2,3, α 2,6, and/or α 2,8 linkages. In certain embodiments the sialidase can cleave α 2,3 and α 2,8 linkages.

[0078] In certain embodiments, the expression yield of the recombinant mutant human
 30 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 human sialidase.

[0079] In certain embodiments, the recombinant mutant human sialidase has about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%,
 5 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 human sialidase, and the expression yield of the recombinant mutant 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
 10 300%, about 400%, about 500%, about 600%, about 700%, about 800%, about 900%, or about 1,000% of the expression yield of a corresponding wild-type human sialidase.

[0080] In certain embodiments, the amino acid sequence of the recombinant mutant 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
 15 human sialidase.

1. Substitution of Cysteine Residues

[0081] In certain embodiments, the recombinant mutant human sialidase 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
 20 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
 25 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),
 30 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).

- 5 **[0082]** 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.

- 10 **[0083]** In certain embodiments, the recombinant mutant human sialidase is a Neu2 sialidase and comprises the substitutions C322A and C352L.

[0084] 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.

- [0085]** In certain embodiments, the recombinant mutant human sialidase comprises a
15 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

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

Substitution(s)
C125S + C196L
C196L + C352L
C196L + C332A
C196L + C332A + C352L

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

- [0086] 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).
- [0087] 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.

- [0088] 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
- 5 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).
- 10 [0089] 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
- 15 V325K, A2K and E257K, and E257K and A2K and V325K.

[0090] 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 2** (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)).

20

TABLE 2

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

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

[0091] 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.

- 5 [0092] 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
- 10 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.*,
- 15 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.

- [0093] 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
- 20 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.

- [0094] In certain embodiments, 1-5 amino acids of the 12 amino acid N-terminal region of
- 25 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).

- 30 [0095] 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.

- 5 [0096] 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),
 10 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),
 15 tyrosine (V6Y), or phenylalanine (V6F). In certain embodiments, the sialidase comprises the V6Y substitution.

- [0097] 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
 20 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
 25 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.

- [0098] In certain embodiments, the recombinant mutant human sialidase comprises a mutation or combination of mutations corresponding to a mutation or combination of
 30 mutations listed in **TABLE 3** (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)).

TABLE 3

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

- [0099] 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 (Δ M1) of wild-type human Neu2 (SEQ ID NO: 1).
- [00100] 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

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

4. Substitutions of Residues to Decrease Proteolytic Cleavage

[00101] 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.

[00102] 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.

[00103] 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.

[00104] 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 5 (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)).

TABLE 5

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

[00105] 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.

[00106] 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 6 (amino acid positions corresponding to wild-type human Neu2 (SEQ ID NO: 1)).

TABLE 6

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
A242F, L260F
A242F, V265F
L240Y
L240Y, L260F
L240D, L260T
L240N, L260T
L240N, L260D
L240N, L260Q
L240Y, A242F
R241A, A242F
R241Y, A242F

5. Other Substitutions

- [00107] In certain embodiments, the recombinant mutant human sialidase comprises 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 (I187K). 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).

- [00108] In certain embodiments, the recombinant mutant human sialidase comprises 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.
- [00109] In certain embodiments, the recombinant mutant human sialidase comprises 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

Wild Type Human Neu2 (SEQ ID NO: 1) Amino Acid	Exemplary Substitution(s) at Specified Position(s)
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
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

Wild Type Human Neu2 (SEQ ID NO: 1) Amino Acid	Exemplary Substitution(s) at Specified Position(s)
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
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

Wild Type Human Neu2 (SEQ ID NO: 1) Amino Acid	Exemplary Substitution(s) at Specified Position(s)
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

- [00110] 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);
 5 (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
 10 of K9, A42, P62, A93, Q216, A242, Q270, S301, W302, V363, or L365, or a combination of any of the foregoing substitutions.

[00111] 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
 15 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
 20 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
 25 (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
 30 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.

[00112] 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 (Δ L184), a deletion of a histidine residue at a position corresponding to position 185 of wild-type human Neu2 (Δ H185), a deletion of a proline residue at a position corresponding to position 186 of wild-type human Neu2 (Δ P186), a deletion of an isoleucine residue at a position corresponding to position 187 of wild-type human Neu2 (Δ I187), and a deletion of a glutamine residue at a position corresponding to position 184 of wild-type human Neu2 (Δ Q188), or a combination of any of the foregoing deletions.

[00113] 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.

[00114] 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, filed July 3, 2020, including in the Detailed Description in the section entitled "I. Recombinant Human Sialidases," and in the Examples in Examples 2, 3, 4, and 5, and in International (PCT) Patent Application No. PCT/US2021/040240, filed July 2, 2021, including in the Detailed Description in the section entitled "I. Recombinant Human Sialidases," and in the Examples in Examples 2, 3, 4, 5, and 11.

6. Combinations of Substitutions

[00115] In certain embodiments, the recombinant mutant human sialidase comprises 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.

[00116] For example, the recombinant mutant sialidase enzyme may comprise an M1 deletion (Δ M1), 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.

- 5 [00117] In certain embodiments, the recombinant mutant sialidase enzyme comprises a M1 deletion (Δ M1), 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; Δ M1 and V6Y; Δ M1 and I187K; Δ M1 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; Δ M1, V6Y, and I187K; Δ M1, V6Y, and C332A; Δ M1, I187K, and C332A; V6Y, I187K, and C332A; M1A, V6Y, I187K, and C332A; M1D, V6Y, I187K, and C332A; and Δ M1, V6Y, I187K, and C332A.

- [00118] In certain embodiments, the recombinant mutant sialidase enzyme 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 (Δ M1), 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; Δ M1 and V6Y; Δ M1 and I187K; Δ M1 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; Δ M1, V6Y, and I187K; Δ M1, V6Y, and C332A; Δ M1, I187K, and C332A; V6Y, I187K, and C332A; M1A, V6Y, I187K, and C332A; M1D, V6Y, I187K, and C332A; and Δ M1, V6Y, I187K, and C332A.

- 30 [00119] 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.

[00120] 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
S301A, W302S
S301A, W302T
S301K, W302S
S301N, W302S
S301T, W302S
S301T, W302T
S301T, W302R
S301A, W302A
S301K, W302R

Substitutions
S301K, W302T
S301N, W302T
S301K, W302K
S301P, W302R
S301P, W302S
S301P, W302T

[00121] 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
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

Substitutions
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
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

Substitutions
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
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

Substitutions
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
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

Substitutions
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

[00122] 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 1). 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.

[00123] 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 1). 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.

[00124] 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 1). 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.

[00125] In certain embodiments, the recombinant mutant sialidase enzyme comprises: (a) the V6Y, A42R, P62G, A93E, Q126Y, I187K, Q270T, A242F, and C332A substitutions; (b) the Δ M1 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.

[00126] In certain embodiments, the sialidase comprises a substitution of M1, V6, A42, P62, A93, Q126, I187, A242, Q270, or 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.

[00127] 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.

- 5 [00128] In certain embodiments, the recombinant mutant human sialidase comprises the amino acid sequence of

- 10 X₁X₂SX₃X₄X₅LQX₆ESVFQSGAHAYRIPALLYLPQGQSLLAFAEQRX₇SX₈X₉DEHAELIVX₁₀R
RGDYDAX₁₁THQVQWX₁₂AQEVVAQAX₁₃LX₁₄GHRSMNPCPLYDX₁₅QTGTLFLFFIAIPX₁₆X₁₇
VTEX₁₈QQLQTRANVTRLX₁₉X₂₀VTSTDHGRTWSSPRDLTDAAIGPX₂₁YREWSTFAVGPGHX₂₂
10 LQLHDX₂₃X₂₄RSLVVPAYAYRKLHPX₂₅X₂₆X₂₇PIPSAFX₂₈FLSHDHGRTWARGHFVX₂₉QDTX₃₀
ECQVAEVX₃₁TGEQRVVTLNARSX₃₂X₃₃X₃₄X₃₅RX₃₆QAQSX₃₇NX₃₈GLDFQX₃₉X₄₀QX₄₁VKK
LX₄₂EPPFX₄₃GX₄₄QGSVISFSPRSGPGSPAQX₄₅LLYTHPTHX₄₆X₄₇QRADLGAYLNPRPPA
PEAWSEFX₄₈LLAKGSX₄₉AYSDLQSMGTGPDGSPFLFGX₅₀LYEANDYEEIX₅₁FX₅₂MFTLKQAF
PAEYLPQ (SEQ ID NO: 199),
15 wherein X₁ is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not
present, X₂ is Ala or Lys, X₃ is Asn or Leu, X₄ is Pro or His, X₅ is Phe, Trp, Tyr or Val, X₆ is
Lys or Asp, X₇ is Ala or Arg, X₈ is Lys, Arg, or Glu, X₉ is Lys, Ala, Arg, or Glu, X₁₀ is Leu or
Met, X₁₁ is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X₁₂ is Gln or His, X₁₃ is Arg or Lys, X₁₄
is Asp or Pro, X₁₅ is Ala, Glu or Lys, X₁₆ is Gly or Asp, X₁₇ is Gln or His, X₁₈ is Gln, Arg, or
20 Lys, X₁₉ is Ala, Cys, Ile, Ser, Val, or Leu, X₂₀ is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X₂₁
is Ala or Val, X₂₂ is Cys or Gly, X₂₃ is Arg or Pro, X₂₄ is Ala or Gly, X₂₅ is Arg, Ile, or Lys,
X₂₆ is Gln or Pro, X₂₇ is Arg or Pro, X₂₈ is Ala, Cys, Leu, or Val, X₂₉ is Ala, Cys, Asn, Ser, or
Thr, X₃₀ is Leu, Ala, or Val, X₃₁ is Glu or Pro, X₃₂ is His or Pro, X₃₃ is Leu, Asp, Asn, or Tyr,
X₃₄ is Arg, Ala, Asp, Leu, Gln, or Tyr, X₃₅ is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met,
25 Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X₃₆ is Val, Ile, or Lys, X₃₇ is Thr or Ala, X₃₈ is Asp or
Gly, X₃₉ is Glu, Lys, or Pro, X₄₀ is Ser or Cys, X₄₁ is Leu, Asp, Phe, Gln, or Thr, X₄₂ is Val or
Phe, X₄₃ is Gln, Ala, His, Phe, Pro, Ser, or Thr, X₄₄ is Cys or Val, X₄₅ is Trp or Arg, X₄₆ is
Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or
Tyr, X₄₇ is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg,
30 Ser, Thr, Val, or Tyr, X₄₈ is Lys or Val, X₄₉ is Ala, Cys, Ser, or Val, X₅₀ is Cys, Leu, or Val,
X₅₁ is Val or Arg, and X₅₂ 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).

[00129] In certain embodiments, the recombinant mutant human sialidase comprises the amino acid sequence of

X₁ASLPX₂LQX₃ESVFQSGAHAYRIPALLYLPGQQSLLAF₄AEQRX₄SKKDEHAELIVLRRGDYD
 AX₅THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₆QTGTFLFLFFIAIPGQVTEQQQLQTRANV
 TRLCX₇VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRK
 LHPX₈QRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQVAEVETGEQRVVTLNARSHLRX₉RV
 5 QAQSTNDGLDFQESQLVKKLVEPPPX₁₀GCQGSVISFPSPRSGPGSPAQWLLYTHPTHX₁₁X₁₂
 QRADLGAYLNPRPPAPEAWSEPVLAKGSX₁₃AYS₁₄DLQSMGTGPDGSP₁₅LF₁₆GCLYEANDYEEIX
 14FX₁₅MFTLKQAFPAEYLPQ (SEQ ID NO: 200),

[00130] wherein X₁ is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr,
 Val, or not present, X₂ is Phe, Trp, Tyr or Val, X₃ is Lys or Asp, X₄ is Arg or Ala, X₅ is Pro,
 10 Asn, Asp, His, Glu, Gly, Ser or Thr, X₆ is Ala, Glu, or Lys, X₇ is Gln, Leu, Glu, Phe, His, Ile,
 Leu, or Tyr, X₈ is Arg, Ile, or Lys, X₉ is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln,
 Arg, Ser, Val, Trp, or Tyr, X₁₀ is Gln, Ala, His, Phe, Pro, Ser, or Thr, X₁₁ is Ser, Arg, Ala,
 Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X₁₂ is Trp,
 Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or
 15 Tyr, X₁₃ is Ala, Cys, Ser, or Val, X₁₄ is Val or Arg, and X₁₅ 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, X₁ is Ala, Asp, Met, or not present, X₂ is Tyr or Val, X₃ is
 Lys or Asp, X₄ is Arg or Ala, X₅ is Pro, Asn, Gly, Ser or Thr, X₆ is Ala or Glu, X₇ is Gln or
 Tyr, X₈ is Ile or Lys, X₉ is Ala or Thr, X₁₀ is Gln, Ala, or Thr, X₁₁ is Ser, Arg, or Ala, X₁₂ is
 20 Trp, Lys, or Arg, X₁₃ is Ala or Cys, X₁₄ is Val or Arg, and X₁₅ is Leu or Ile.

[00131] 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
 25 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 matrix
 (e.g., the PAM 250 matrix).

30 [00132] 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,
 35 (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

5 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

10 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

15 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 =

20 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

25 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.

30 **b. Antibody Portion**

[00133] 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 an antigen-binding fragment of an antibody (e.g., an antigen-binding fragment of a

monoclonal antibody) or a Fc fragment of an antibody (*e.g.*, an Fc 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.

[00134] 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).

[00135] 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.

[00136] 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).

[00137] 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.

[00138] 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).
- 10 [00139] 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 or N297G mutation (residue numbers according to EU numbering, Kabat, E.A., *et al.*, *supra*). For example, in certain embodiments, the fusion
- 15 protein comprises SEQ ID NO: 212, SEQ ID NO: 215, or SEQ ID NO: 216.
- [00140] 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, e.g., a HER2 expressing cancer cell, and/or to the tumor microenvironment. As used herein, unless otherwise indicated, the term “immunoglobulin
- 20 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, e.g., an anti-HER2 antigen binding site.
- 25 [00141] In certain embodiments, the immunoglobulin antigen-binding domain is derived from an anti-HER2 antibody. Exemplary anti-HER2 antibodies include trastuzumab (Herceptin[®]), pertuzumab (Perjeta[®]), CT-P6 (Herzuma[®]), trastuzumab-dkst (Ogivri[™]), MGAH22 (margetuximab), PF-05280014, ertumaxomab, gancotamab, timigutuzumab, Ontruzant, ABP-980, SB3, DS-8201, MYL-1410, BCD-022, and HD201.
- 30 [00142] 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.

c. Linker

[00143] In certain embodiments, the sialidase portion of the fusion protein can be linked or
5 fused directly to the anti-HER2 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 anti-HER2 antibody portion by a linker.

[00144] 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
10 (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.

15 [00145] 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.

[00146] 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
20 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*.

[00147] The linker may be from about 1 angstroms (Å) to about 150 Å in length, or from
25 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,
30 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, and 120 Å in length.

[00148] In certain embodiments, the linker comprises a polypeptide linker that connects or fuses the sialidase portion of the fusion protein to the anti-HER2 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.

- 5 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.
- 10 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
- 15 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
- 20 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.

- [00149] 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
- 25 249, 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

- 30 [00150] 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 (*e.g.*, anti-HER2 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. 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, *e.g.*, an anti-HER2 antigen-binding site.

[00151] 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 anti-HER2 antigen-binding site. In other embodiments, the antibody conjugate can include more than one (*e.g.*, two) anti-HER2 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.

[00152] 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.

[00153] **FIGURE 1** depicts exemplary antibody conjugate constructs containing one or more sialidase enzymes. For example, in **FIGURE 1A**, a first anti-HER2 antigen-binding site (*e.g.*, defined by a V_H and V_L domains) is depicted as 10, a second anti-HER2 antigen-binding site is depicted as 20, a sialidase is depicted as 30, and a Fc is depicted as 40. In each of the constructs depicted in **FIGURES 1A-1I** 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 1B**. Throughout **FIGURE 1** similar structures are depicted by similar schematic representations.

[00154] **FIGURE 1A** 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 anti-HER2 antigen-binding site as depicted as 10, and the third polypeptide and the fourth polypeptide together define a second anti-HER2 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.

[00155] **FIGURE 1B** 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 anti-HER2 antigen-binding site, and the third polypeptide and the fourth polypeptide together define a second anti-HER2 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.

[00156] **FIGURE 1C** 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 anti-HER2 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.

[00157] **FIGURE 1D** 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
5 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 anti-HER2 antigen-binding site. An optional second sialidase enzyme can be conjugated to the N- or C-terminus
10 of the first immunoglobulin light chain or the first immunoglobulin heavy chain.

[00158] **FIGURE 1E** 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
15 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 anti-HER2 antigen-binding site. An optional second sialidase enzyme can be conjugated to the N- or C-
20 terminus of the first immunoglobulin light chain or the first immunoglobulin heavy chain.

[00159] **FIGURE 1F** 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
25 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.

[00160] **FIGURE 1G** depicts antibody conjugate constructs comprising a first polypeptide
30 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 anti-HER2

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.

- [00161]** **FIGURE 1H** 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.
- [00162]** **FIGURE 1I** depicts antibody conjugate constructs similar to those depicted in **FIGURE 1H** except that each scFv is replaced with an immunoglobulin antigen binding fragment, *e.g.*, an Fab. For example, **FIGURE 1I** 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 anti-HER2 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, *e.g.*, HER2. 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, *e.g.*, HER2.

5 [00163] **FIGURE 2** depicts additional antibody conjugate constructs. For example, **FIGURE 2** 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
10 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
15 polypeptide together define a first antigen-binding site. In certain embodiments, the scFv defines a second antigen-binding site. **FIGURE 2** 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
20 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
25 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 2** 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 2**, it is understood that the Fc may optionally be modified in
30 some manner.

[00164] 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 3A**. 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 anti-HER2 antigen-binding site, and the third polypeptide and the fourth polypeptide together define a second anti-HER2 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.
- [00165] 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 3B**. 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 anti-HER2 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.
- [00166] 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 any one of SEQ ID NOs: 67 or 189, 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: 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, 203-208.

[00167] In certain embodiments, the third polypeptide comprises the amino acid sequence of

5 X₁X₂SX₃X₄X₅LQX₆ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX₇SX₈X₉DEHAELIVX₁₀R
RGDYDAX₁₁THQVQWX₁₂AQEVVAQAX₁₃LX₁₄GHRSMNPCPLYDX₁₅QTGTLFLFFIAIPX₁₆X₁₇
VTEX₁₈QQLQTRANVTRLX₁₉X₂₀VTSTDHGRTWSSPRDLTDAAIGPX₂₁YREWSTFAVGPGHX₂₂
LQLHDX₂₃X₂₄RSLVVPAYAYRKLHPX₂₅X₂₆X₂₇PIPSAFX₂₈FLSHDHGRTWARGHFVX₂₉QDTX₃₀
ECQVAEVX₃₁TGEQRVVTLNARSX₃₂X₃₃X₃₄X₃₅RX₃₆QAQX₃₇NX₃₈GLDFQX₃₉X₄₀QX₄₁VKK
10 LX₄₂EPPPX₄₃GX₄₄QGSVISFSPSPRSGPGSPAQX₄₅LLYTHPTHX₄₆X₄₇QRADLGAYLNPRPPA
PEAWSEPX₄₈LLAKGSX₄₉AYSDLQSMGTGPDGSPFGX₅₀LYEANDYEEIX₅₁FX₅₂MFTLKQAF
PAEYLPQX₅₃DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
KENWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPV
15 LDSDGSFFLTSLKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:
201),

wherein X₁ is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X₂ is Ala or Lys, X₃ is Asn or Leu, X₄ is Pro or His, X₅ is Phe, Trp, Tyr or Val, X₆ is Lys or Asp, X₇ is Ala or Arg, X₈ is Lys, Arg, or Glu, X₉ is Lys, Ala, Arg, or Glu, X₁₀ is Leu or
20 Met, X₁₁ is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X₁₂ is Gln or His, X₁₃ is Arg or Lys, X₁₄ is Asp or Pro, X₁₅ is Ala, Glu or Lys, X₁₆ is Gly or Asp, X₁₇ is Gln or His, X₁₈ is Gln, Arg, or Lys, X₁₉ is Ala, Cys, Ile, Ser, Val, or Leu, X₂₀ is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X₂₁ is Ala or Val, X₂₂ is Cys or Gly, X₂₃ is Arg or Pro, X₂₄ is Ala or Gly, X₂₅ is Arg, Ile, or Lys, X₂₆ is Gln or Pro, X₂₇ is Arg or Pro, X₂₈ is Ala, Cys, Leu, or Val, X₂₉ is Ala, Cys, Asn, Ser, or
25 Thr, X₃₀ is Leu, Ala, or Val, X₃₁ is Glu or Pro, X₃₂ is His or Pro, X₃₃ is Leu, Asp, Asn, or Tyr, X₃₄ is Arg, Ala, Asp, Leu, Gln, or Tyr, X₃₅ is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X₃₆ is Val, Ile, or Lys, X₃₇ is Thr or Ala, X₃₈ is Asp or Gly, X₃₉ is Glu, Lys, or Pro, X₄₀ is Ser or Cys, X₄₁ is Leu, Asp, Phe, Gln, or Thr, X₄₂ is Val or Phe, X₄₃ is Gln, Ala, His, Phe, Pro, Ser, or Thr, X₄₄ is Cys or Val, X₄₅ is Trp or Arg, X₄₆ is
30 Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X₄₇ is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X₄₈ is Lys or Val, X₄₉ is Ala, Cys, Ser, or Val, X₅₀ is Cys, Leu, or Val, X₅₁ is Val or Arg, X₅₂ is Leu, Gln, His, Ile, Lys, or Ser, and X₅₃ is GGGGS (SEQ ID NO: 184), GGGGSGGGGS (SEQ ID NO: 145), or EPKSS (SEQ ID NO: 146), and the sialidase
35 comprises at least one mutation relative to wild-type human Neu2 (SEQ ID NO: 1).

[00168] In certain embodiments, the third polypeptide comprises the amino acid sequence of

X₁ASLPX₂LQX₃ESVFQSGAHAYRIPALLYLPQQSLLAFAEQRX₄SKKDEHAELIVLRRGDYD
 AX₅THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₆QTGTLLFLFFIAIPGQVTEQQQLQTRANV
 TRLCX₇VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
 LHPX₈QRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQVAEVETGEQRVVTLNARSHLRX₉RV
 5 QAQSTNDGLDFQESQLVKKLVPPX₁₀GCQGSVISFSPSPRSGPGSPAQWLLYTHPTHX₁₁X₁₂
 QRADLGAYLNPRPPAPEAWSEPVLLAKGSX₁₃AYSDLQSMGTGPDGSPFGCLYEANDYEEIX
 14FX₁₅MFTLKQAFPAEYLPQX₁₆DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
 CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
 VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
 10 GQPENNYKTTPVLDSDGSFFLTSTKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPG
 K (SEQ ID NO: 202),

wherein X₁ is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not
 present, X₂ is Phe, Trp, Tyr or Val, X₃ is Lys or Asp, X₄ is Arg or Ala, X₅ is Pro, Asn, Asp,
 His, Glu, Gly, Ser or Thr, X₆ is Ala, Glu, or Lys, X₇ is Gln, Leu, Glu, Phe, His, Ile, Leu, or
 15 Tyr, X₈ is Arg, Ile, or Lys, X₉ is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg,
 Ser, Val, Trp, or Tyr, X₁₀ is Gln, Ala, His, Phe, Pro, Ser, or Thr, X₁₁ is Ser, Arg, Ala, Asp,
 Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X₁₂ is Trp, Lys,
 Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr,
 X₁₃ is Ala, Cys, Ser, or Val, X₁₄ is Val or Arg, X₁₅ is Leu, Gln, His, Ile, Lys, or Ser, and X₁₆ is
 20 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, X₁ is Ala, Asp, Met, or not present, X₂ is Tyr or
 Val, X₃ is Lys or Asp, X₄ is Arg or Ala, X₅ is Pro, Asn, Gly, Ser or Thr, X₆ is Ala or Glu, X₇ is
 Gln or Tyr, X₈ is Ile or Lys, X₉ is Ala or Thr, X₁₀ is Gln, Ala, or Thr, X₁₁ is Ser, Arg, or Ala,
 25 X₁₂ is Trp, Lys, or Arg, X₁₃ is Ala or Cys, X₁₄ is Val or Arg, and X₁₅ is Leu or Ile.

[00169] 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.
 30 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
 35 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.

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.

[00170] 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 3C** (in the construct depicted in **FIGURE 3C** 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 anti-HER2 antigen-

- binding site, and the second scFv defines a second anti-HER2 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.
- 10 **[00171]** 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.

[00172] In certain embodiments, the first and/or second polypeptide comprises the amino acid sequence of

- 20 X₁X₂SX₃X₄X₅LQX₆ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX₇SX₈X₉DEHAELIVX₁₀R
RGDYDAX₁₁THQVQWX₁₂AQEVVAQAX₁₃LX₁₄GHRSMNPCPLYDX₁₅QTGTLFLFFIAIPX₁₆X₁₇
VTEX₁₈QQLQTRANVTRLX₁₉X₂₀VTSTDHGRTWSSPRDLTDAAIGPX₂₁YREWSTFAVGPGHX₂₂
LQLHDX₂₃X₂₄RSLVVPAYAYRKLHPX₂₅X₂₆X₂₇PIPSAFX₂₈FLSHDHGRTWARGHFVX₂₉QDTX₃₀
ECQVAEVX₃₁TGEQRVVTLNARSX₃₂X₃₃X₃₄X₃₅RX₃₆QAQSX₃₇NX₃₈GLDFQX₃₉X₄₀QX₄₁VKK
25 LX₄₂EPXPX₄₃GX₄₄QGSVISFSPSPRSGPGSPAQX₄₅LLYTHPTHX₄₆X₄₇QRADLGAYLNPRPPA
PEAWSEPX₄₈LLAKGSX₄₉AYS DLQSMGTGPDGSP LFGX₅₀LYEANDYEEIX₅₁FX₅₂MFTLKQAF
PAEYLPQX₅₃DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEV
KENWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPV
30 LDDSGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGKGGGGSGGGSGG
GGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTR
YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGT LVTVSSG
GGGSGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAPKLLI
YSASFYSGVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKEIK
- 35 (SEQ ID NO: 248), wherein X₁ is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X₂ is Ala or Lys, X₃ is Asn or Leu, X₄ is Pro or His, X₅ is Phe, Trp, Tyr or Val, X₆ is Lys or Asp, X₇ is Ala or Arg, X₈ is Lys, Arg, or Glu, X₉ is Lys, Ala, Arg, or Glu, X₁₀ is Leu or Met, X₁₁ is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X₁₂ is Gln or

His, X₁₃ is Arg or Lys, X₁₄ is Asp or Pro, X₁₅ is Ala, Glu or Lys, X₁₆ is Gly or Asp, X₁₇ is Gln or His, X₁₈ is Gln, Arg, or Lys, X₁₉ is Ala, Cys, Ile, Ser, Val, or Leu, X₂₀ is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X₂₁ is Ala or Val, X₂₂ is Cys or Gly, X₂₃ is Arg or Pro, X₂₄ is Ala or Gly, X₂₅ is Arg, Ile, or Lys, X₂₆ is Gln or Pro, X₂₇ is Arg or Pro, X₂₈ is Ala, Cys, Leu, or Val, X₂₉ is Ala, Cys, Asn, Ser, or Thr, X₃₀ is Leu, Ala, or Val, X₃₁ is Glu or Pro, X₃₂ is His or Pro, X₃₃ is Leu, Asp, Asn, or Tyr, X₃₄ is Arg, Ala, Asp, Leu, Gln, or Tyr, X₃₅ is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X₃₆ is Val, Ile, or Lys, X₃₇ is Thr or Ala, X₃₈ is Asp or Gly, X₃₉ is Glu, Lys, or Pro, X₄₀ is Ser or Cys, X₄₁ is Leu, Asp, Phe, Gln, or Thr, X₄₂ is Val or Phe, X₄₃ is Gln, Ala, His, Phe, Pro, Ser, or Thr, X₄₄ is Cys or Val, X₄₅ is Trp or Arg, X₄₆ is Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X₄₇ is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X₄₈ is Lys or Val, X₄₉ is Ala, Cys, Ser, or Val, X₅₀ is Cys, Leu, or Val, X₅₁ is Val or Arg, X₅₂ is Leu, Gln, His, Ile, Lys, or Ser, and X₅₃ 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).

[00173] In certain embodiments, the first and/or second polypeptide comprises the amino acid sequence of

X₁ASLPX₂LQX₃ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX₄SKKDEHAELIVLRRGDYD
 AX₅THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₆QTGTLFLFFIAIPGQVTEQQQLQTRANV
 TRLCX₇VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRK
 LHPX₈QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECCQVAEVETGEQRVVTLNARSHLRX₉RV
 QAQSTNDGLDFQESQLVKKLVEPPX₁₀GCQGSVISFSPSPRSGPGSPAQWLLYTHPTHX₁₁X₁₂
 QRADLGAYLNP RPAPAEAWSEPVLLAKGSX₁₃AYS DLQSMGTGPDGSP LFGCLYEANDYEEIX
₁₄FX₁₅MFTLKQAFPAEYLPQX₁₆DKTHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
 CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
 VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
 GQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPG
 KGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLE
 WVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMD
 YWGQGTLLVTVSSGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAW
 YQKPKGAPKLLIYSASFLYSGVPSRFSRSGTDFTLTISSLQPEDFATYYCQGHYTPPT
 FGQGTKVEIK

(SEQ ID NO: 247), wherein X₁ is Ala, Arg, Asn, Asp, Gln, Glu, Gly, His, Leu, Lys, Met, Phe, Thr, Val, or not present, X₂ is Phe, Trp, Tyr or Val, X₃ is Lys or Asp, X₄ is Arg or Ala, X₅ is Pro, Asn, Asp, His, Glu, Gly, Ser or Thr, X₆ is Ala, Glu, or Lys, X₇ is Gln, Leu, Glu, Phe, His, Ile, Leu, or Tyr, X₈ is Arg, Ile, or Lys, X₉ is Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Val, Trp, or Tyr, X₁₀ is Gln, Ala, His, Phe, Pro, Ser, or Thr, X₁₁ is

Ser, Arg, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Thr, Val, Trp, or Tyr, X₁₂ is Trp, Lys, Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, or Tyr, X₁₃ is Ala, Cys, Ser, or Val, X₁₄ is Val or Arg, X₁₅ is Leu, Gln, His, Ile, Lys, or Ser, and X₁₆ 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, X₁ is Ala, Asp, Met, or not present, X₂ is Tyr or Val, X₃ is Lys or Asp, X₄ is Arg or Ala, X₅ is Pro, Asn, Gly, Ser or Thr, X₆ is Ala or Glu, X₇ is Gln or Tyr, X₈ is Ile or Lys, X₉ is Ala or Thr, X₁₀ is Gln, Ala, or Thr, X₁₁ is Ser, Arg, or Ala, X₁₂ is Trp, Lys, or Arg, X₁₃ is Ala or Cys, X₁₄ is Val or Arg, and X₁₅ is Leu or Ile.

[00174] 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.

- [00175] 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 3D**. 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 anti-HER2 antigen-binding site (*i.e.*, the immunoglobulin light chain and immunoglobulin heavy chain together define a first anti-HER2 antigen-binding site). In certain embodiments, the scFv defines a second anti-HER2 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.
- [00176] 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 3E**. 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 anti-HER2 antigen-binding site, and the third and fourth polypeptides define a second anti-HER2 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.

10 [00177] 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.

[00178] 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
15
20 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 or 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).

25 [00179] 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
30 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).

[00180] 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*.

5 [00181] 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
10 to increase its circulating half-life.

[00182] 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.

15 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 (Pluronic); polymethacrylates; carbomers; and branched or unbranched polysaccharides which comprise the saccharide monomers such as D-mannose, D- and L-
20 galactose, fucose, fructose, D-xylose, L-arabinose, and D-glucuronic acid.

[00183] 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
25 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
30 poly(N-isopropylacrylamide). The modifier prior to conjugation need not be, but preferably is, water soluble, but the final conjugate should be water soluble.

[00184] 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.

[00185] 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.

- 5 [00186] 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
- 10 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-
- 15 SS). Such PEGS are commercially available from Nektar Therapeutics or SunBiowest.

- [00187] 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
- 20 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.).

25 **II. Methods of Making a Fusion Protein or Antibody Conjugate**

- [00188] Methods for producing 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
- 30 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.

- 5 [00189] Nucleic acids encoding desired 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
10 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.

- [00190] Specific expression and purification conditions will vary depending upon the
15 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
20 sonication. The refractile bodies then are solubilized, and the protein may be refolded and/or cleaved by methods known in the art.

- [00191] 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
25 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.

- 30 [00192] The host cells express 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).

[00193] A polypeptide comprising 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.

[00194] 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.

- [00195] In certain embodiments, in order to express a protein, *e.g.*, a fusion protein, 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 fusion protein, 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 fusion protein, as a secreted protein, a C terminal lysosomal signal motif, *e.g.*, YGTL (SEQ ID NO: 29) is removed.
- 10 [00196] 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.
- 15 [00197] 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).
- 20 [00198] 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.
- 25 30 [00199] 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.

- [00200] 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).
- 10 [00201] 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).
- 15 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,
- 20 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).

[00202] Any suitable approach, including any of the above approaches, can be used to reduce or eliminate human immunogenicity of an antibody.

- 25 [00203] 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
- 30 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).

[00204] 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.

5 [00205] 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
10 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
15 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.

20 [00206] 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
25 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.

[00207] Examples of heterodimeric or asymmetric IgG-like molecules include but are not
30 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.

[00208] 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.

- 5 [00209] 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
10 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,
15 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.
- 20 [00210] 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 CH₃ domain of the first
25 heavy chain and the CH₃ domain of the second heavy chain are both engineered in a complementary manner so that the heavy chain comprising one engineered CH₃ domain can no longer homodimerize with another heavy chain of the same structure (*e.g.*, a CH₃-engineered first heavy chain can no longer homodimerize with another CH₃-engineered first heavy chain; and a CH₃-engineered second heavy chain can no longer homodimerize with
30 another CH₃-engineered second heavy chain). Thereby the heavy chain comprising one engineered CH₃ domain is forced to heterodimerize with another heavy chain comprising the CH₃ domain, which is engineered in a complementary manner. As a result, the CH₃ domain of the first heavy chain and the CH₃ 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).

III. Pharmaceutical Compositions

5 [00211] For therapeutic use, a fusion protein and/or antibody conjugate 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
10 response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00212] 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
15 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,
20 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.

25 [00213] 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,
30 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 dextrans); 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)).

[00214] 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).

[00215] 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.

[00216] Pharmaceutical compositions containing a 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 sialidase fusion protein or an antibody conjugate disclosed herein is administered by IV infusion. In certain embodiments, a sialidase fusion protein or an antibody conjugate disclosed herein is administered by intratumoral injection.

- 5 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
- 10 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.

- [00217] For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline
- 15 (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.

- [00218] In certain embodiments, a pharmaceutical composition may contain a stabilizing
- 20 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).

- [00219] 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
- 25 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, or from about 1 mM to about 2 mM.

- 30 [00220] 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.

[00221] 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.

[00222] Generally, a therapeutically effective amount of active component, for example, a fusion protein and/or antibody conjugate, 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 fusion protein and/or antibody conjugate, 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 fusion protein and/or antibody conjugate is lyophilized, and then reconstituted in buffered saline, at the time of administration.

IV. Therapeutic Uses

[00223] 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 sialidase anti-HER2 fusion protein and/or antibody conjugate, *e.g.*, a 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.*, fusion protein 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.

- [00224]** 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.
- [00225]** 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, myelodysplastic 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).
- [00226]** 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 adenomatousum, 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, cerebriiform 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, epierrmoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniformi 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, scirrhus 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, tuberos carcinoma, verrucous carcinoma, and carcinoma villosum.
- 25 **[00227]** In certain embodiments the cancer is selected from lung bronchioloalveolar carcinoma (BAC), bladder cancer, a female genital tract malignancy (*e.g.*, uterine serous carcinoma, endometrial carcinoma, vulvar squamous cell carcinoma, and uterine sarcoma), an ovarian surface epithelial carcinoma (*e.g.*, clear cell carcinoma of the ovary, epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer), breast carcinoma, non-
- 30 small cell lung cancer (NSCLC), a male genital tract malignancy (*e.g.*, testicular cancer), retroperitoneal or peritoneal carcinoma, gastroesophageal adenocarcinoma, esophagogastric junction carcinoma, liver hepatocellular carcinoma, esophageal and esophagogastric junction carcinoma, cervical cancer, cholangiocarcinoma, pancreatic adenocarcinoma, extrahepatic

bile duct adenocarcinoma, a small intestinal malignancy, gastric adenocarcinoma, cancer of unknown primary (CUP), colorectal adenocarcinoma, esophageal carcinoma, prostatic adenocarcinoma, kidney cancer, head and neck squamous carcinoma, thymic carcinoma, non-melanoma skin cancer, thyroid carcinoma (*e.g.*, papillary carcinoma), a head and neck cancer, 5 anal carcinoma, non-epithelial ovarian cancer (non-EOC), uveal melanoma, malignant pleural mesothelioma, small cell lung cancer (SCLC), a central nervous system cancer, a neuroendocrine tumor, and a soft tissue tumor.

[00228] In certain embodiments, the cancer is melanoma, non-small cell lung cancer, colon cancer, breast cancer, bladder cancer, or kidney cancer.

10 [00229] 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.

[00230] 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.

[00231] The methods and compositions described herein can be used alone or in 15 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 20 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 25 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 30 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.

[00232] 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.

[00233] 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.

[00234] 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.).

[00235] In certain embodiments, a method or composition described herein is administered
 5 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.
 10 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.

15 [00236] 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.

[00237] In certain embodiments, a method or composition described herein is administered in combination with an IDO inhibitor. Exemplary IDO inhibitors include 1-methyl-D-
 20 tryptophan (known as indoximod), epacadostat (INCB24360), navoximod (GDC-0919), and BMS-986205.

[00238] 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,
 25 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
 30 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, teniposide, 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.

[00239] The invention also provides a method of increasing the expression of HLA-DR, CD86, CD83, IFN γ , IL-1b, IL-6, TNF α , 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 fusion protein and/or antibody conjugate, *e.g.*, a 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).

[00240] In certain embodiments, expression of HLA-DR, CD86, CD83, IFN γ , IL-1b, IL-6, TNF α , 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 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.

[00241] 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 fusion protein and/or antibody conjugate, *e.g.*, a 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.

[00242] 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 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.

[00243] The invention also provides a method of increasing the number of circulating natural killer (NK) cells in a subject in need thereof. The method comprises administering to the subject an effective amount of a fusion protein and/or antibody conjugate, *e.g.*, a fusion protein or antibody conjugate disclosed herein, so as to increase the number of circulating NK cells relative to prior to administration of the fusion protein, antibody conjugate or pharmaceutical composition.

[00244] In certain embodiments, the number 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 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.

[00245] The invention also provides a method of increasing the number 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 fusion protein, antibody conjugate, and/or pharmaceutical composition, *e.g.*, a 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 fusion protein, antibody conjugate or pharmaceutical composition. In certain embodiments, the immune cells are T-cells, *e.g.*, CD4+ and/or CD8+ T-cells.

[00246] In certain embodiments, the number 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 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.

[00247] The invention also provides a method of increasing expression of Cd3, Cd4, Cd8, Cd274, Ctla4, Icos, Pcdcl1, 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 fusion protein, antibody conjugate, and/or pharmaceutical composition, *e.g.*, a fusion protein, antibody conjugate, and/or pharmaceutical composition disclosed herein, so as to increase the expression of Cd3, Cd4, Cd8, Cd274, Ctla4, Icos, Pcdcl1, 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 fusion protein, antibody conjugate or pharmaceutical composition.

[00248] In certain embodiments, expression of Cd3, Cd4, Cd8, Cd274, Ctla4, Icos, Pcdcl1, 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 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.

[00249] 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 fusion protein and/or antibody conjugate, *e.g.*, a 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 fusion protein and/or antibody conjugate, *e.g.*, a fusion protein or antibody conjugate disclosed herein, thereby to remove sialic acid from the cell.

[00250] 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 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.

[00251] The invention also provides a method of enhancing phagocytosis of a tumor cell. The method comprises contacting the tumor cell with a fusion protein and/or antibody conjugate, *e.g.*, a 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 fusion protein and/or antibody conjugate, *e.g.*, a 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.

[00252] 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 fusion protein and/or antibody conjugate. Phagocytosis may be measured by any suitable method known in the art.

[00253] 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 fusion protein and/or antibody conjugate, *e.g.*, a 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 fusion protein and/or antibody conjugate, *e.g.*, a 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
5 population of DCs in the subject.

[00254] 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
10 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 fusion protein and/or antibody conjugate. Activation may be measured by any suitable method known in the art.

[00255] 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
15 contacting a T cell with a fusion protein and/or antibody conjugate, *e.g.*, a 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
20 effective amount of a pharmaceutical composition comprising a fusion protein and/or antibody conjugate, *e.g.*, a fusion protein or antibody conjugate disclosed herein, thereby to increase anti-tumor activity (*e.g.*, T cell activity) in the subject.

[00256] 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
25 Siglec-15 that has not or have not been contacted with the fusion protein and/or antibody conjugate. Binding may be measured by any suitable method known in the art.

[00257] 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
30 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.

[00258] 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.

[00259] 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.

[00260] 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.

[00261] 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.

[00262] 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 $\pm 10\%$ variation from the nominal value unless otherwise indicated or inferred.

[00263] 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.

- 5 [00264] 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

- 10 [00265] The following Examples are merely illustrative and are not intended to limit the scope or content of the invention in any way.

Example 1

[00266] This Example describes the construction of recombinant human sialidases with mutations that increase expression and/or activity of the sialidase.

- 15 [00267] 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.

- [00268] 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.
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- [00269] 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 (with amino acid sequence SEQ ID NO: 48, encoded by nucleotide sequence SEQ ID NO:
- 30

89, and including mutations M1D, V6Y, P62G, A93E, I187K, and C332A), and Neu2-173-Fc (with amino acid sequence SEQ ID NO: 159, encoded by nucleotide sequence SEQ ID NO: 181, and including mutations M1D, V6Y, P62G, A93E, Q126Y, I187K, A242F, Q270T, and C332A).

- 5 [00270] **FIGURE 4A** is an image of an SDS-PAGE gel showing Neu2-M259-Fc under non-reducing and reducing conditions. **FIGURE 4B** 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%.

- [00271] 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). A Michaelis-Menton kinetics characterization (measured at a variable substrate concentration) of Neu2-M259-Fc, Neu2-M106-Fc, and Neu2-173-Fc is depicted in **FIGURE 5A**. Estimated K_M values were 0.27 mM (Neu2-M106-Fc), 0.46 mM (Neu2-M173-Fc), and 0.20 mM
10 (Neu2-M259-Fc). Enzyme potency (measured at variable enzyme concentration) of Neu2-M259-Fc, Neu2-M106-Fc, and Neu2-173-Fc is depicted in **FIGURE 5B**. Approximate EC_{50} values were 20.7 $\mu\text{g/mL}$ (Neu2-M106-Fc), 38.3 $\mu\text{g/mL}$ (Neu2-M173-Fc), and 15.18 $\mu\text{g/mL}$ (Neu2-M259-Fc).

- [00272] 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
20 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. T_m was determined by fitting enzyme activity curves versus temperature curves. **FIGURE 6** depicts a thermal stability characterization of Neu2-M259-Fc, Neu2-M106-Fc,
25 and Neu2-173-Fc.

- [00273] 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 10**. In **TABLE 10**, 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
30 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 10

Name	Mutations	Yield (mg/L)	T _m (°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	++

[00274] 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

5 **FIGURE 7**, and show increased thermal stability for Neu2-M259-Fc.

[00275] 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 backmutated to the corresponding residue in wildtype Neu2, resulting in ten variants (M262-Fc through M271-Fc) each having nine mutations. The resulting variants are

10 described in **TABLE 11**.

TABLE 11

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

- [00276] 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). 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. T_m was determined by fitting enzyme activity curves versus temperature curves. Results are depicted in **TABLE 12**. In **TABLE 12**, 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 12

Name	SEC-HPLC Monomer %	Yield (mg/L)	T _m (°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	+++

[00277] 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 2

[00278] 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.

[00279] The architecture for five types of exemplary ASCs is depicted in **FIGURE 3**. 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 3A**). 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 3B**). 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 3C**). 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 3D**). The fifth type of ASC, referred to as “Lobster-Fab,” contains two Fc domain polypeptides each with a sialidase fused at the N-terminus of the Fc and a Fab fused at the C-terminus of the Fc (**FIGURE 3E**).

[00280] 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.

[00281] 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 8**).

[00282] 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 V_{max} of 2.2×10^8 .

[00283] 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. K_D , K_{on} and K_{off} values were generated using 1:1 fitting model. Janus Trastuzumab 2 bound to HER2 with a K_D of $5.5E-10$, K_{on} of $1.24E06$ (1/Ms), and a K_{off} of $6.91E-04$ (1/s) as shown in **FIGURE 9**.

[00284] An additional Janus Antibody Sialidase Conjugate (ASC) was made using Neu2 with M1D, V6Y, A42R, P62G, A93E, Q126Y, I187K, E218A, A242F, Q270T, and C332A substitutions and trastuzumab. This ASC, which included an E218A mutation resulting in a loss of sialidase activity, was referred to as “Janus Trastuzumab LOF” or “Janus LOF,” and 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: 250, encoded by nucleotide sequence SEQ ID NO: 251.

- 5 [00285] Janus LOF was expressed and purified generally as described above, yielding a protein of 89% monomeric purity at 100 mg/mL, and no measurable enzymatic activity.

[00286] Example 3

[00287] This Example describes the in vivo administration of anti-HER2 antibody sialidase conjugates (ASCs) containing human sialidases.

- 10 [00288] Janus Trastuzumab 2, as described above in Example 2, 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.
- 15

- [00289] 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 13.
- 20

TABLE 13

Group	Treatment	Dose	Route	Schedule
1	Isotype Control	10 mg/kg	IP	Twice per week; 6 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		
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[00290] Mice were treated with intraperitoneal 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.

[00291] Tumor volumes for individual mice are shown in FIGURES 10A-10E. 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 10F. Collectively, these results show that the Janus Trastuzumab 2 construct showed comparable or greater activity than trastuzumab.

Example 4

[00292] This Example describes characterization of anti-HER2 antibody sialidase conjugates (ASCs).

[00293] Janus Trastuzumab 2, as described above in Example 2, 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, and Janus LOF, as described above in Example 2, 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: 250, encoded by nucleotide sequence SEQ ID NO: 251, were made and tested in this Example.

[00294] The enzymatic activity of 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. Results are shown in FIGURE 11. Janus Trastuzumab 2 had a V_{max} of 0.002354 mM/min, a K_m of 1.464 mM, and a K_{cat} of 8260 per second.

[00295] The thermal stability of Janus Trastuzumab 2 was assayed by incubating samples including 2 µg of Janus Trastuzumab 2 and 0.5 mM substrate for 15 minutes across a temperature gradient from 37 °C to 80 °C. Enzymatic activity was then measured, and T_m was determined by fitting enzyme activity curves versus temperature curves. Results are shown in **FIGURE 12**. Janus Trastuzumab 2 had a thermal stability (T_m) of 58.7 ± 0.2 °C.

[00296] The ability of Janus Trastuzumab 2 to desialylate human tumor cells with either a low or high level of HER2 expression was also evaluated. Cells were incubated for 17 hours at 37 °C with varying concentrations of either Janus Trastuzumab 2 or enzymatically inactive Janus LOF. Cells were washed and then stained with Hydra9, a hexameric version of the extracellular domain of human Siglec 9 (as described in International (PCT) Application Publication No. WO2019/237070). Hydra9 binds to sialic acid-based glycostructures on the cell surface, and therefore a decrease in Hydra9 staining is indicative of desialylation. Cells were also stained with biotinylated peanut agglutinin (PNA, Vector Laboratories, B-1075-5). PNA binds to galactosyl structures exposed by removal of sialic acid, and therefore an increase in PNA staining is indicative of desialylation.

[00297] Results using SKBR-3 cells, a human cell line with high levels of HER2 expression, are shown in **FIGURE 13**. **FIGURE 13A** depicts Hydra9 staining following treatment with either Janus Trastuzumab 2 or Janus LOF. Janus Trastuzumab 2 demonstrated an IC₅₀ of .0002992 µg/mL while Janus LOF demonstrated no appreciable activity. **FIGURE 13B** depicts PNA staining following treatment with Janus Trastuzumab 2 or Janus LOF. Janus Trastuzumab 2 demonstrated a EC₅₀ of 0.1298 µg/mL while Janus LOF demonstrated no appreciable activity.

[00298] Results using HT-29 cells, a human cell line with low but detectable levels of HER2 expression, are shown in **FIGURE 14**. **FIGURE 14A** depicts Hydra9 staining following treatment with either Janus Trastuzumab 2 or Janus LOF. Janus Trastuzumab 2 demonstrated an IC₅₀ of 0.1129 µg/mL while Janus LOF demonstrated no appreciable activity. **FIGURE 14B** depicts PNA staining following treatment with Janus Trastuzumab 2 or Janus LOF. Janus Trastuzumab 2 demonstrated a EC₅₀ of 14.48 µg/ml while Janus LOF demonstrated no appreciable activity.

[00299] The IC₅₀ and EC₅₀ values for Janus Trastuzumab 2 for the higher HER2-expressing SKBR-3 cells were both lower than the corresponding IC₅₀ and EC₅₀ values for the lower

HER2-expressing HT-29 cells, suggesting that HER2 antibody mediated cell binding increased cell surface desialylation efficiency.

Example 5

5 **[00300]** This Example describes Antibody-Dependent Cellular Cytotoxicity (ADCC) and Antibody-Dependent Cellular Phagocytosis Assay (ADCP) assays using anti-HER2 antibody sialidase conjugates (ASCs).

10 **[00301]** For ADCC assays, natural killer cells (1024-5133JN21, Cellero/Hemacare) were cultured overnight in RPMI-1640 medium containing 10% heat-inactivated fetal bovine serum, antibiotics, and recombinant human interleukin-2 at a concentration of 10 ng/mL. On the day of the ADCC assay, NK cells were harvested, washed, and counted.

15 **[00302]** Target tumor cell lines were cultured in appropriate media supplemented with 10% heat-inactivated fetal bovine serum, antibiotics, non-essential amino acids, pyruvic acid and grown to logarithmic growth phase by passaging 2-3 times. Target tumor cells were prepared by washing with PBS, lifted from culture dishes by treating with Accutase, washed with PBS, spun down, and resuspended in appropriate media at a concentration of 25 cells/mL.

[00303] Target tumor cells were treated with trastuzumab, Janus Trastuzumab 2, Janus LOF, or isotype control (IgG) overnight (~15 hours) at a concentration of 10 µg/mL. For a direct killing control, target tumor cells were treated with PBS.

20 **[00304]** ADCC assays were carried out at multiple effector:target (E:T) ratios and each ratio was set up in triplicate. 50 µL of NK cells were aliquoted into wells of a 96-well V-bottom assay plate, and 50 µL of the previously treated target cells (BT-20, HT-29 or SK-BR-3) were added. Control wells included target cells only (10,000), NK cells only (20,000, 40,000 or 60,000), target and lysis buffer, media only, and media and lysis buffer. Assay plates were incubated at 37 °C for 4 hours, after which the assay plate was centrifuged at 250 g for 5
25 minutes and 50 µL of assay supernatant was transferred to a 96-well flat-bottom plate with dark walls and clear bottoms. 50 µL of LDH reaction mixture was added, and after incubation at room temperature for 30 minutes, 50 µL of stop solution was added. Spectrophotometric absorbance was measured at 490 and 680 nm wavelengths using a SpectraMax i3x (Molecular Devices) spectrophotometer.

30 **[00305]** Corrected values were generated by subtracting the average value of the culture medium background control from average values of the experimental, effector cell spontaneous, LDH release controls and target cell spontaneous LDH release control. The

average value of the volume correction control was then subtracted from the average value of the target cell lysis LDH release control. Percent cytotoxicity was calculated using the following formula: % cytotoxicity= (experimental value-effector cell spontaneous control-target cell spontaneous control) * 100 /(target cell maximum control-target cell spontaneous control).

[00306] Results are shown in FIGURE 15. FIGURE 15A depicts targeted killing of BT-20 cells, FIGURE 15B depicts targeted killing of HT-29 cells, and FIGURE 15C depicts targeted killing of SKBR3 cells. As depicted, ADCC was maintained for the ASCs and was comparable to that of trastuzumab.

[00307] For ADCP assays, the source of effector cells was cytokine-induced and cultured M2-like macrophages generated from CD14+ monocytes. PBMCs were isolated from Leukopaks (ZenBio) by Ficoll density gradient (GE Healthcare Biosciences) following the manufacturer's protocol. From the PBMCs, CD14+ monocytes were isolated using magnetic beads and cultured for 5 days in RPMI-1640 medium containing 20% heat-inactivated fetal bovine serum, antibiotics, and 50 ng/mL recombinant human M-CSF. On day 7, M0/M2-like macrophages were lifted off the culture dish by Accutase treatment and gentle scrapping and reseeded on a 24-well tissue culture dish (50,000 cells per well) using the same culture media supplemented with IL-10 (20 ng/mL), TGF- β (50 ng/mL), and M-CSF (20 ng/ml), and incubated at 37 °C for 48 hours for polarization to M2 phenotypes. On the day of phagocytosis assays, polarized M2-like macrophages were lifted off by treatment with Accutase and gentle scrapping, washed, and counted.

[00308] BT-20 (breast), HT-29 (colorectal) and SK-BR-3 (breast) tumor cell lines were used as target cells. Target tumor cell lines were cultured in appropriate media supplemented with 10% heat-inactivated fetal bovine serum, antibiotics, non-essential amino acids, pyruvic acid and grown to logarithmic growth phase by passaging them 2-3 times. A day prior to phagocytosis assays, target cells (BT-20, HT-29 and SK-BR-3) were harvested by treating with Accutase, washed, counted, and labeled with carboxyfluorescein succinimidyl ester (CFSE). Target tumor cells then underwent treatment overnight with trastuzumab, Janus Trastuzumab 2, Janus-LOF, or isotype control (IgG) at concentrations of 10 and 30 μ g/mL. Treatment with PBS was used as a control.

[00309] Internalization/phagocytosis of target cells by phagocytes (M2-like macrophages) result in CFSE-positive phagocytes. % Phagocytosis or % killing was calculated by

measuring CFSE+ M2-like macrophages by flow cytometry. All phagocytosis assays were done in triplicates. Phagocytosis assays were set up in flat-bottom 48-well plates in triplicate at an effector:target (E:T) ratio of 1:5 (50,000 effector cells and 250,000 target cells). The assay plate was incubated at 37 °C for 2 hours, after which cells were scraped off the assay plate, washed and stained for live/dead, CD45, and CD14, and fixed using 4% paraformaldehyde for 10 minutes at room temperature. Cells were washed in PBS twice and resuspended in FACS staining buffer. Single-stained M2 cells and CFSE labeled only target cells were used as controls. Cells were run for flow cytometry using a BD FACS Celesta (Becton Dickinson) FACS analyzer. Results were analyzed using the FloJo (Tree Star/Becton Dickinson) software program and % killing was calculated. The results are shown in FIGURE 16.

[00310] FIGURE 16A depicts percent killing by phagocytosis of BT-20 cells, FIGURE 16B depicts percent killing by phagocytosis of HT-29 cells and FIGURE 16C depicts percent killing by phagocytosis of SKBR-3. As shown, ADCP was maintained for the ASCs and was comparable to trastuzumab.

Example 6

[00311] This Example describes the in vivo administration of anti-HER2 antibody sialidase conjugates (ASCs).

[00312] Janus Trastuzumab 2, as described above in Example 2, 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, and Janus LOF, as described above in Example 2, 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: 250, encoded by nucleotide sequence SEQ ID NO: 251, were made and tested in this Example.

[00313] Janus Trastuzumab 2 was compared to isotype control antibody, trastuzumab, and Janus LOF 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 6 groups of 8 animals each when tumors reached a mean ~ 75 -100 mm³ and treated as shown in **TABLE 14**.

TABLE 14

Group	Treatment	Dose	Route	Schedule
1	Isotype Control	10 mg/kg	IP	Twice per week; 6 doses
2	Trastuzumab	5 mg/kg		
3	Janus LOF	10 mg/kg		
4	Janus Trastuzumab 2	1 mg/kg		
5	Janus Trastuzumab 2	3 mg/kg		
6	Janus Trastuzumab 2	10 mg/kg		

5

[00314] Mice were treated with intraperitoneal injections of the indicated test article and dosed twice per week and tumor volume (mm³) was recorded.

[00315] Tumor volumes for individual mice are shown in FIGURES 17A-17F. Average tumor volumes for mice treated with Janus Trastuzumab 2 (10 mg/kg) or Janus LOF (10 mg/kg) are shown FIGURE 18A. Survival curves for mice treated with Janus Trastuzumab 2, Janus LOF or trastuzumab are shown in FIGURE 18B. As shown, treatment with Janus Trastuzumab 2 resulted in reduced tumor growth relative to treatment with Janus LOF. Additionally, treatment with Janus Trastuzumab 2 resulted in increased survival relative to treatment with Janus LOF or trastuzumab.

15

INCORPORATION BY REFERENCE

[00316] The entire disclosure of each of the patent and scientific documents referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[00317] 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
5 description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

SEQUENCE LISTING

[00318] SEQ ID NO: 1:

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 5 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 IQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVEVETGEQRRVVTLNARSHLRARVQAQS
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[00319] SEQ ID NO: 2:

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 15 YRKLHPAQKPTPFAFCFISLDHGHTWKLGNFVAENSLEQCQVAEVEVGTGAQRMVYLNARSFLGA
 RVQAQSPNDGLDFQDNRVVSKLVEPPHGCHGSSVAFHNPISKPHALDTWLLYTHPTDSNRNT
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20 [00320] SEQ ID NO: 3:

EDLRP

[00321] SEQ ID NO: 4:

MEDLRP

[00322] SEQ ID NO: 5:

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 EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
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30 [00323] SEQ ID NO: 6:

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 AGCTTCATCGATACCGCTGCCGCCAGATCTACCGATGGCGGCAAGACCTGGAACAAGAAGAT
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 AGAACGGCACCATCTCTGCCATGCTCGGCGGCGTTGGATCTGGCCTGCAACTGAATGATGGC
 40 AAGCTGGTGTTCCTCGTGAGATGGTCCGAACAAAGATATCACCACCGTGCTGAATACCAG
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 5 CAAAGTGGGCAATGCCAGCGGAGCCGGCTACAGCTGTCTGAGCTACCGGAAAAATGTGGACA
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10 ENDFGLVQPLVTMEQLLWVSGRQIGSVDTFRILITATPRGTLTLLAFAEARKMSSSDEGAKFI
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 20 RLCFIYSQDAGCSWSEVRDLTEEVIKHWATFAVGPGHGIQLQSGRLVIPAYTYIIPSW
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 30 KHWATFAVGPGHGIQLQSGRLVIPAYTYIIPSWFFCFQLPCKTRPHSLMIYSDDLGVTHHGR
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 40 FGKICRTSPHSFAFYSDDHGRTWRCGLVNLRSQCQLAAVDGGQAGSFLYCNARSPLGSR
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5 PAYTYRVDRRECFGKICRTSPHSFAFYSDDHGRTWRCGGLVPNLRSGECQLAAVDGGQAGSF
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- 10 [00329] SEQ ID NO: 12:
MASLP
- [00330] SEQ ID NO: 13:
ASLP
- [00331] SEQ ID NO: 14:
15 TVEKSVVF
- [00332] SEQ ID NO: 15:
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- [00333] SEQ ID NO: 16:
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- 20 [00334] SEQ ID NO: 17:
STDGGKWTW
- [00335] SEQ ID NO: 18:
PRPPAPEA
- [00336] SEQ ID NO: 19:
25 QTPLEAAC
- [00337] SEQ ID NO: 20:
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- [00338] SEQ ID NO: 21:
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- 30 [00339] SEQ ID NO: 22:
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[00340] SEQ ID NO: 23:

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CCACAGAACCATGAATCCTTGTCTGTGTGGGAGCAGAAAAGCGGCTGCGTGTTCTGTTCT
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5 AGACTGTGCTTCATCTACAGCCAGGATGCCGGCTGCTCTTGGAGCGAAGTTTCGGGATCTGAC
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15 CTCTCACCCACCAGCAGAAAGCAGAGAGTGGACCTGGGCATCTACCTGAATCAGACCCCTC
TGGAAGCCGCTGTTGGAGCAGACCTTGGATTCTGCACTGTGGCCCTTGCGGCTACTCTGAT
CTGGCCGCTCTGGAAGAAGAGGGCTGTTCCGGCTGCCTGTTTGAGTGCGGCACAAAGCAAGA
GTGCGAGCAGATCGCCTTCCGGCTGTTACCCACAGAGAGATCTGAGCCATCTGCAGGGCG
ACTGCACAAGCCCAGGCAGAAATCCCAGCCAGTTCAAGAGCAAC

20 **[00343]** SEQ ID NO: 26:

ATGGGCGTGCCAGAACACCCAGCAGAACCGTGCTGTTGAGAGAGAGAGAGGACCGGCCCTGAC
CTACAGAGTGCCCTTCTCTGCTGCCTGTGCCTCCTGGACCTACACTGCTGGCCTTCGTGGAAC
AGAGACTGAGCCCCGATGATTCTCACGCCCACAGACTGGTGCTGAGAAGAGGAACACTGGCT
GGCGGCTCTGTTAGATGGGGAGCACTGCATGTGCTGGGCACAGCTGCTCTTGCCGAGCACAG
25 ATCCATGAATCCCTGTCCTGTGCACGACGCCGGAACCGGCACAGTGTTTCTGTTCTTTATCG
CCGTGCTGGGCCACACACCTGAGGCCGTTCAAATTGCCACCGGCAGAAATGCCGCCAGACTG
TGTTGTGTGGCCTCCAGAGATGCCGGCCTGTCTTGGGGATCTGCCAGAGATCTGACCGAGGA
AGCCATTGGCGGAGCCGTTGAGGATTGGGCCACATTTGCTGTTGGACCTGGACACGGCGTGC
AGCTGCCAAGTGGTAGACTGCTGGTGCCTGCCTACACATACAGAGTGGATCGGAGAGAGTGC
30 TTCGGAAGATCTGCCGACAAGCCCTCACAGCTTCGCCTTCTACTCCGACGATCACGGCCG
GACTTGGAGATGTGGTGGCCTGGTGCCTAATCTGAGAAGCGGCGAATGTCAACTGGCCGCCG
TTGATGGTGGACAGGCTGGCAGCTTCTGTACTGCAACGCCAGATCTCCTCTGGGCTCTAGA
GTGCGAGGCCCTGTCTACCGATGAGGGCACCAAGTTTCTGCCCCGCCGAAAGAGTTGCCTCTCT
GCCTGAAACAGCCTGGGGCTGTCAGGGCTCTATCGTGGGATTTCTGCTCCTGCTCCAAACA
35 GACCCCGGACGATTCTTGGAGTGTGCGCCCTGGATCTCCACTGCAGCCTCCATTGCTTGGA
CCAGGCGTTACAGAGCCACCTGAAGAGGCTGCCGTTGATCCTAGAGGCGGACAAGTTCTTG
CGGCCCTTTTAGCAGACTGCAGCCAAGAGGCGACGGCCCTAGACAACCTGGACCAAGACCTG
GCGTCAGCGGAGATGTTGGCTCTTGGACACTGGCCCTGCCTATGCCTTTTGCCGCTCCTCCT
CAGTCTCCTACCTGGCTGCTGTACTCTACCCCTGTTGGCAGACGGGCCAGACTGCACATGGG
40 CATCAGACTGTCTCAGAGCCCTCTGGACCCCAGAAGCTGGACAGAGCCTTGGGTCTATATG
AGGGCCCTAGCGGCTACAGCGATCTGGCCTCTATTGGCCCAGCTCCTGAAGGCGGACTGGTG
TTCGCTTGTCTGTATGAGAGCGGCGCCAGAACCAGCTACGACGAGATCAGCTTCTGCACCTT
CAGCCTGCGCGAGGTGCTGGAAAATGTGCCCGCCTCTCCTAAGCCTCCTAACCTGGGCGATA
AGCCTAGAGGCTGTTGCTGGCCATCT

45

[00344] SEQ ID NO: 27:

MTGERPSTALPDRRWGPRILGFWGGCRVWVFAAIFLLLSLAASWSKA

[00345] SEQ ID NO: 28:

MDMRVPAQLLGLLLLWLPGARC

5 [00346] SEQ ID NO: 29:

YGTL

[00347] SEQ ID NO: 30:

10 MTVEKSVVFKAEGEHFTDQKGNTIVGSGSGGTTKYFRIPAMCTTSKGTIVVFADARHNTASD
QSFIDTAAARSTDGGKTWNKKIAIYNDRVNSKLSRVMPTCIVANIQGRETILVMVGKWNND
DKTWGAYRDKAPDWDVLVLYKSTDDGVTFSKVTNIHDIIVTKNGTISAMLGGVGSGQLQND
GKLVFPVQMVRTKNITTVLNTSFIYSTDGITWSLPSGYCEGFGSENNIIEFNASLVNNIRNS
GLRRSFETKDFGKTWTEFPPMDKKVDNRNHGVQGSTITIPSGNKLVAAHSSAQNKNNDYTRS
DISLYAHNLYSGEVKLIDDFYPKVGNASGAGYSCLSYRKNVDKETLYVVYEANGSIEFQDLS
RHLFVIKSYN

15

[00348] SEQ ID NO: 31:

20 EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00349] SEQ ID NO: 32:

25 DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFL
TSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00350] SEQ ID NO: 33:

30 EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00351] SEQ ID NO: 34:

35 ATGAGACCTGCGGACCTGCCCCGCGCCCCATGGAAGAATCCCCGGCGTCCAGCTCTGCCCC
GACAGAGACGGAGGAGCCGGGGTCCAGTGCAGAGGTCATGGAAGAAGTGACAACATGCTCCT
TCAACAGCCCTCTGTTCCGGCAGGAAGATGACAGAGGGATTACCTACCGGATCCCAGCCCTG
CTCTACATACCCCCACCCACACCTTCCTGGCCTTTGCAGAGAAGCGTTCTACGAGGAGAGA
TGAGGATGCTCTCCACCTGGTGCTGAGGCGAGGGTTGAGGATTGGGCAGTTGGTACAGTGGG
40 GGCCCCCTGAAGCCACTGATGGAAGCCACACTACCGGGGCATCGGACCATGAACCCCTGTCCT
GTATGGGAGCAGAAGAGTGTTGTGTGTTCTCTCATCTGTGTGCGGGGCCATGTCAC

AGAGCGTCAACAGATTGTGTCAGGCAGGAATGCTGCCCGCCTTTGCTTCATCTACAGTCAGG
ATGCTGGATGTTTCATGGAGTGAGGTGAGGGACTTGACTGAGGAGGTCATTGGCTCAGAGCTG
AAGCACTGGGCCACATTTGCTGTGGGCCCAGGTCATGGCATCCAGCTGCAGTCAGGGAGACT
GGTCATCCCTGCGTATACCTACTACATCCCTTCCTGGTTCTTTTGTCTCCAGCTACCATGTA
5 AAACCAGGCCTCATTCTCTGATGATCTACAGTGATGACCTAGGGGTCACATGGCACCATGGT
AGACTCATTAGGCCCATGGTTACAGTAGAATGTGAAGTGGCAGAGGTGACTGGGAGGGCTGG
CCACCCTGTGCTATATTGCAGTGCCCGACACCAAACAGGTGCCGGGCAGAGGCGCTCAGCA
CTGACCATGGTGAAGGCTTTCAGAGACTGGCCCTGAGTCGACAGCTCTGTGAGCCCCCACAT
GGTTGCCAAGGGAGTGTGGTAAGTTTCCGGCCCCCTGGAGATCCCACATAGGTGCCAGGACTC
10 TAGCAGCAAAGATGCACCCACCATTTCAGCAGAGCTCTCCAGGCAGTTCACTGAGGCTGGAGG
AGGAAGCTGGAACACCGTCAGAATCATGGCTCTTGTACTCACACCAACCAGTAGGAAACAG
AGGGTTGACCTAGGTATCTATCTCAACCAGACCCCTTGAGGCTGCCTGCTGGTCCCGCC
CTGGATCTTGCACGTGTGGGCCCTGTGGCTACTCTGATCTGGCTGCTCTGGAGGAGGAGGGCT
TGTTTGGGTGTTTGTGTTGAATGTGGGACCAAGCAAGAGTGTGAGCAGATTGCCTTCCGCTG
15 TTTACACACCGGGAGATCCTGAGTCACCTGCAGGGGGACTGCACCAGCCCTGGTAGGAACCC
AAGCCAATTCAAAGCAAT

[00352] SEQ ID NO: 35:

ATGATGAGCTCTGCAGCCTTCCCAAGGTGGCTGAGCATGGGGGTCCCTCGTACCCCTTCACG
20 GACAGTGCTCTTCGAGCGGGAGAGGACGGGCTGACCTACCGCGTGCCCTCGCTGCTCCCCG
TGCCCCCGGGCCCCACCCTGCTGGCCTTTGTGGAGCAGCGGCTCAGCCCTGACGACTCCAC
GCCACCGCCTGGTGCTGAGGAGGGGCACGCTGGCCGGGGGCTCCGTGCGGTGGGGTCCCT
GCACGTGCTGGGGACAGCAGCCCTGGCGGAGCACCGGTCCATGAACCCCTGCCCTGTGCACG
ATGCTGGCACGGGCACCGTCTTCCTCTTCTTCATCGCGGTGCTGGGCCACACGCCTGAGGCC
25 GTGCAGATCGCCACGGGAAGGAACGCCGCGCCCTCTGCTGTGTGGCCAGCCGTGACGCCGG
CCTCTCGTGGGGCAGCGCCCGGGACCTCACCGAGGAGGCCATCGGTGGTGGCGTGCAAGACT
GGGCCACATTGCTGTGGGTCCCGGCCACGGTGTGCAGCTGCCCTCAGGCCGCTGCTGGTA
CCCGCCTACACCTACCGCGTGACCGCCGAGAGTGTGTTGGCAAGATCTGCCGGACAGCCC
TCACTCCTTCGCCTTCTACAGCGATGACCACGGCCGCACCTGGCGCTGTGGAGGCCTCGTGC
30 CCAACCTGCGCTCAGGCGAGTGCCAGCTGGCAGCGGTGGACGGTGGGCAGGCCGGCAGCTTC
CTCTACTGCAATGCCCCGAGCCCACTGGGCAGCCGTGTGCAGGCGCTCAGCACTGACGAGGG
CACCTCCTTCTGCCCCGAGAGCGCGTGGCTTCCCTGCCCCGAGACTGCCTGGGGCTGCCAGG
GCAGCATCGTGGGCTTCCAGCCCCCGCCCCAACAGGCCACGGGATGACAGTTGGTCAGTG
GGCCCCGGGAGTCCCCTCCAGCCTCCACTCCTCGGTCTGGAGTCCACGAACCCCCAGAGGA
35 GGCTGCTGTAGACCCCGTGGAGGCCAGGTGCCTGGTGGGCCCTTCAGCCGTCTGCAGCCTC
GGGGGGATGGCCCCAGGCAGCCTGGCCCCAGGCCTGGGGTCAGTGGGGATGTGGGGTCTTG
ACCCTGGCACTCCCCATGCCCTTTGCTGCCCCGCCCCAGAGCCCCACGTGGCTGCTGTACTC
CCACCCAGTGGGGCGCAGGGCTCGGCTACACATGGGTATCCGCCTGAGCCAGTCCCCGCTGG
ACCCGCGCAGCTGGACAGAGCCCTGGGTGATCTACGAGGGCCCCAGCGGCTACTCCGACCTG
40 GCGTCCATCGGGCCGGCCCCCTGAGGGGGGCTGGTTTTTCCTGCTGCTGTACGAGAGCGGGC
CAGGACCTCCTATGATGAGATTTCTTTTGTACATTCTCCCTGCGTGAGGTCTGGAGAACG
TGCCCCCAGCCCCAAACCGCCCCAACCTTGGGGACAAGCCTCGGGGGTGCTGCTGGCCCTCC

[00353] SEQ ID NO: 36:

45 MRFKNVKKTALMLAMFGMATSSNAALFDYNATGDTEFDSPAKQGWMDNTNNGSGVLTNADG
MPAWLVQIGGGAQWTYSLSTNQHAQASSFGWRMTTEMKVLSSGMITNYANGTQRLPIIS
LDSSGNLVVEFEGQTGRTVLATGTAATEYHKFELVFLPGSNPSASFYFDGKLIRDNIQPTAS
KQNMIVWNGSSNTDGVAAAYRDIKFEIQGDVIFRGPDRIPSIVASSVTPGVVTAFAEKRVGG
GDPGALSNTNDIITRTSRDGGITWDELNLTEQINVSDEFDFSDPRPIYDPSNTVLVSAR

WPTDAAQNGDRIKPWMPNGIFYSVYDVASGNWQAPIDVTDQVKERSFQIAGWGGSELYRRNT
SLNSQQDWQSNAKIRIVDGAANQIQVADGSRKYVVTLSIDESGGLVANLNGVSAPIILQSEH
AKVHSFHDYELQYSALNHTTTLFVDGQQITTWAGEVVSQENNIQFGNADAQIDGRLHVQKIVL
TQQGHNLFVDAFYLAQQTPEVEKDLEKLWTKIKTGNTMSLYGNASVNP GP GHGITLTRQQ
5 NISGSQNGRLIYPAIVLDRFFLNVMSIYSDDGGSNWQTGSTLPIPFWRKSSSILETLEPSEA
DMVELQNGDLLLTARLDFNQIVNGVNYSRQQFLSKDGGITWSLLEANNANVFSNISTGTVD
ASITRFEQSDGSHFLFTNPQGNPAGTNGRQNLGLWFSFDEGVTWKGP IQLVNGASAYSIDIY
QLDSENAIVIVETDNSNMRILRMPITLLKQKLTLSQN

10 [00354] SEQ ID NO: 37:

TTGTCAATCAAGATGACTTCACAACGAAGAAGAGCATCGATTACAAGGAAACAGATTCTAA
TATAAAGGGAGTAGATATGCGTTTCAAAAACGTAAAAGAAAACCGCTTTAATGCTTGCAATGT
TCGGTATGGCGACAAGCTCAAACGCCGACATTTTGTACTATAACGCAACGGGTGACACTGAG
TTTGACAGTCCAGCCAAACAGGGATGGATGCAAGACAACACGAATAATGGCAGCGGCGTTTT
15 AACCAATGCAGATGGAATGCCCGCTTGGTTGGTGCAAGGTATTGGAGGGAGAGCTCAATGGA
CATATTCTCTCTCTACTAATCAACATGCCCAAGCATCAAGTTTCGGTTGGCGAATGACGACA
GAAATGAAAGTGCTCAGTGGTGGAATGATCACAACACTACTACGCCAACGGCACTCAGCGTGT
CTTACCCATCATTTTCATTAGATAGCAGTGGTAACCTTAGTTGTTGAGTTTGAAGGGCAAACCTG
GACGCACCGTTTTTGGCAACCGGCACAGCAGCAACGGAATATCATAAATTTGAATTGGTATTC
20 CTTCTGGAAGTAACCCATCCGCTAGCTTTTACTTCGATGGCAAACCTCATTTCGTGACAACAT
CCAGCCGACTGCATCAAAACAAAATATGATCGTATGGGGGAATGGCTCATCAAATACGGATG
GTGTCGCCGCTTATCGTGATATTAAGTTTGAAATTC AAGGCGACGTCATCTTCAGAGGCCCA
GACCGTATACCGTCCATTGTAGCAAGTAGCGTAACACACGAGGGGTGGTAACCGCATTTGCAGA
GAAACGTGTGGGGGAGGAGATCCCGGTGCTCTGAGTAATACCAATGACATAATCACTCGTA
25 CCTCACGAGATGGCGGTATAACTTGGGATACCGAGCTCAACCTCACTGAGCAAATCAATGTC
AGTGATGAGTTTGATTTCTCCGATCCTCGGCCTATCTATGATCCTTCTCCAATACGGTTCT
TGTCTCTTATGCTCGATGGCCGACCGATGCCGCTCAAAACGGAGATCGAATAAAACCATGGA
TGCCAAACGGTATTTTTTACAGCGTCTATGATGTTGCATCAGGGAACCTGGCAAGCGCCTATC
GATGTTACCGATCAGGTGAAAGAACGCAGTTTCCAATCGCTGGTTGGGGTGGTTTCAGAGCT
30 GTATCGCCGAAATACCAGCCTAAATAGCCAGCAAGACTGGCAATCAAACGCTAAGATCCGAA
TTGTTGATGGTGCAGCGAACCAGATACAAGTTGCCGATGGTAGCCGAAAATATGTTGT CACA
CTGAGTATTGATGAATCAGGTGGTCTAGTCGCTAATCTAAACGGTGTTAGTGCTCCGATTAT
CCTGCAATCTGAACACGCAAGGTACACTCTTTCCATGACTACGAACCTCAATATTCCGGCT
TAAACCACACCACAACGTTATTTCGTGGATGGTCAGCAAATCACAACCTGGGCTGGCGAAGTA
35 TCGCAGGAGAAACAACATT CAGTTTGTAATGCGGATGCCCAAATGACGGCAGACTGCATGT
GCAAAAAATTTGTTCTCACACAGCAAGGCCATAACCTCGTGGAGTTTGATGCTTTCTATTTAG
CACAGCAAACCCCTGAAGTAGAGAAAGACCTTGAAAAGCTTGGTTGGACAAAAATTTAAACG
GGCAACACCATGAGTTTGTATGGAATGCCAGTGTCAACCCAGGACCGGGTCATGGCATCAC
CCTTACTCGACAACAAAATATCAGTGGCAGCCAAAACGGCCGCTTGATCTACCCAGCGATTG
40 TGCTTGATCGTTTTCTTCTTGAACGTCATGTCTATTTACAGTGATGATGGCGGTTCAAACCTGG
CAAACCGGTTCAACACTCCCTATCCCTTTTCGCTGGAGAGTTTCGAGTATCCTAGAAACTCT
CGAACCTAGTGAAGCTGATATGGTTGAACCTCCAAACGGTGATCTACTCCTTACTGCACGCC
TTGATTTTAACCAAATCGTTAATGGTGTGAACCTATAGCCCACGCCAGCAATTTTTGAGTAAA
GATGGTGGAATCACGTGGAGCCTACTTGAGGCTAACAAACGCTAACGCTTTTAGCAATATCAG
45 TACTGGTACCGTTGATGCTTCTATTACTCGGTTTCGAGCAAAGTGACGGTAGCCATTTCTTAC
TCTTTACTAACCACAAAGGAAACCTGCGGGGACAAATGGCAGGCAAATCTAGGCTTATGG
TTTAGCTTCGATGAAGGGGTGACATGGAAGGACCAATTCAACTTGTTAATGGTGCATCGGC
ATATTCTGATATTTATCAATTGGATTCGGAATGCGATTGTCATTGTTGAAACGGATAATT
CAAATATGCGAATTCTTCGTATGCCTATCACATTGCTAAAACAGAAGCTGACCTTATCGCAA
50 AACTAA

[00355] SEQ ID NO: 38:

MVGADPTRPRGPLSYWAGRRGQGLAAIFLLLVSAAESEARAEDDFSLVQPLVTMEQLLWVSG
 KQIGSVDTFRITPLITATPRGTLTLLAFAEARKKSASDEGAKFIAMRRSTDQGSTWSSTAFIVDD
 5 GEASDGLNLGAVVNDVDTGIVFLIYTLCAHKVNCQVASTMLVWSKDDGISWSPPRNLSVDIG
 TEMFAPGPGSGIQKQREPGKGRILIVCGHGTLELDGVFCLLSDDHGASWHYGTGVSGIFPGQP
 KHDHDFNPDECQPYELPDGSVIINARNQNNYHCRCRIVLRSYDACDTLRPRDVTFDPELVDP
 VVAAGALATSSGIVFFSNPAHPEFRVNLTLRWSFSNGTSLWKERVQVWPGPSGYSSLTALEN
 STDGKKQPPQLFVLYEKGLNRYTESISMVKISVYGTL

10

[00356] SEQ ID NO: 39:

MTVQPSPWFSDLRPMATCPVLQKETLFRITGVHAYRIPALLYLKKQKTLLAFAEKRASKTDEH
 AELIVLRRGSYNEATNRVKWPPEEVVTAQLEGHRSMNPCPLYDKQTKTLFLFFIAVPGRVS
 15 EHHQLHTKVNVTRLCCVSSTDHGRTWSPIQDLTETTIGSTHQEWATFAVGPGHCLQLRNPAG
 SLLVPAYAYRKLHPAQKPTPFAFCFISLDHGHTWKLGNFVAENSLECQVAEVTGAQRMVYL
 NARSFLGARVQAQSPNDGLDFQDNRVVSKLVEPPHGCHGSVVAFHNPISKPHALDTWLLYTH
 PTDNRNRNLGVYLNQMPLDPTAWSEPTLLAMGICAYSDLQNMGGQPDGSPQFGCLYESGNY
 EEIIFLIFFTLKQAFPTVFDAQ

20

[00357] SEQ ID NO: 40:

MEEVPPYSLSSTLFLQEEQSGVTYRIPALLYLPPTHFLAFAEKRTSVRDEDAACLVLRRLGL
 MKGRSVQWGPQRLLEATLPGHRTMNPVWEKNTGRVYLFFICVRGHVTERCQIVWGKNAA
 25 RLCFLCSEDAGCSWGEVKDLTEEVIIGSEVKRWATFAVGPGHGIQLHSGRLIIPAYAYYVSRW
 FLCFACSVKPHSLMIYSDDFGVTWHHGKFIQVTGECQVAEVAGTAGNPVLYCSARTPSRF
 RAEAFSTDSGGCFQKPTLNPQLHEPRTGCQGSVVSFRPLKMPNTYQDSIGKGAPATQKCPLL
 DSPLEVEKGAETPSATWLLYSHPTS KRKRINLGIYYNRNPLEVNCWSRPWILNRGPSGYSDL
 AVVEEQDLVACLFECEKNEYERIDFCLFSDHEVLSCEDCTSPSSD

30

[00358] SEQ ID NO: 41:

METAGAPFCFHVDSLVPSCSYWKVMGPTRVPRRTVLFQRERTGLTYRVPALLCVPPRPTLLAF
 AEQRLSPDDSHAHRLVLRGTLTRGSVRWGTLVLETAVLEEHRSMNCPVLDEHSGTIFLF
 35 FIAVLGHTPEAVQIATGKNAARLCCVTSCDAGLTWGSVRDLTEEAIGAALQDWATFAVGPGH
 GVQLRSGRLLVPAYTYHVDRECFGKICWTSPhSLAFYSDDHGISWHCGGLVPLNRSGECQL
 AAVDGDFLYCNARSPLGNRVQALSADGTSFLPGELVPTLAETARGCQGSIVGFLAPPSIEP
 QDDRWTGSPRNTPHSPCFNLRVQESSGEGARGLLERWMPRLPLCYPQSRSPENHGLEPGSDG
 DKTSWTPECPMSSDSMLQSPTWLLYSHPAGRRARLHMGIIYLSRSPLDPHSWTEPWVIYEGPS
 40 GYSDLAFLGPMPGASLVFACLFESGTRTSYEDISFCLFSLADVLENVPTGLEMLSLRDKAQG
 HCWPS

[00359] SEQ ID NO: 42:

GGGTCACATGCTGATGGACTAATTGGAGTCGCGGCAGCGGGGCTGCGGCCCCCAAGGGGAG
 GGGTCGGAGTGACGTGCGCGCTTTTAAAGGGCCGAGGTGAGCTGACGGCTTGCCACCGGTGA
 CCAGTTCCTGGACAGGGATCGCCGGGAGCTATGGTGGGGGCAGACCCGACCAGACCCGGGG
 ACCGCTGAGCTATTGGGCGGGCCGTCGGGGTCAGGGGCTCGCAGCGATCTTCCTGCTCCTGG
 TGTCCGCGGCGGAATCCGAGGCCAGGGCAGAGGATGACTTCAGCCTGGTGAGCCGCTGGTG
 50 ACCATGGAGCAGCTGCTGTGGGTGAGCGGGAAGCAGATCGGCTCTGTAGACACTTCCGCAT
 CCCGCTCATCACAGCCACCCCTCGGGGCAGCTCCTGGCCTTCGCTGAGGCCAGGAAAAAT

117

GCACAGACATACAATCAGGCCAAAATATTCATACACATAAAAATAAAATAATTTAAAACAAAAG
CAAAAATCAGGACCTAAGAAAAAAATCTATTCCTGATTCTTTTATGTTTTGTTTGTATTTTA
TCAAGACAGGGTTGTTTTCTCTGTATAGCCCTGGCTGTCTTGGAATTCAGTCTGTAGACCAGG
CTGGCCTCAAACCTCAGAAATCCTCCTGCCTTTGCCTTCCAAGTGCTGGAATTAAAGGCATGC
5 GCCACC

[00360] SEQ ID NO: 43:

GACATGACCCAAACGGCCCCCTGGCTGCAAGGTAATATCGGAAGTTGACTAAGAATGGACGCC
10 CCACCACTGACTGACCCGCCCCCTGAGTCTGAGATTGGACTTGTCTCTGGATACAGTCATAC
TTTGAGGTTACTACAAGTTAGAACTGTTAGGTTACTCAGTTCAGTCCATGACAGTCCAACCT
TCTCCATGGTTTTCCGATCTCAGGCCATGGCGACCTGCCCTGTCTGCAGAGAGACACT
GTTCCGCACAGGCGTCCATGCTTACAGAATCCCTGCTCTGCTCTACCTGAAGAAGCAGAAGA
CCCTGCTGGCCTTTGCGGAAAAGCGAGCCAGCAAGACGGATGAGCACGCAGAGTTGATTGTC
15 CTGAGAAGAGGAAGCTACAACGAAGCCACCAACCGTGTCAAGTGGCAGCCTGAGGAAGTGGT
GACCCAAGCCCAGCTGGAAGGCCACCGCTCCATGAATCCATGTCCCTTGTATGACAAGCAAA
CAAAGACCTCTTCCTTTTCTTCATCGCTGTCCCTGGGCGTGTATCAGAACATCATCAGCTC
CACACTAAGGTTAATGTACACGGCTGTGCTGTGTGTCAGCAGCACTGACCATGGGAGGACCTG
GAGCCCCATCCAGGACCTCACAGAGACCACCATTTGGCAGCACTCATCAGGAATGGGCCACAT
20 TTGCTGTGGGTCTCTGGGCATTGTCTGCAGCTGCGGAACCCAGCTGGGAGCCTGCTGGTACCT
GCTTATGCCTACCGGAAACTGCACCCTGCTCAGAAGCCTACCCCCCTTTGCCTTCTGCTTCAT
CAGCCTTGACCATGGGCACACATGGAAGCTAGGCAACTTTGTGGCTGAAAACCTCACTGGAGT
GCCAGGTGGCTGAGGTTGGCACTGGAGCTCAGAGGATGGTATATCTCAATGTAGGAGCTTC
CTGGGAGCCAGGGTCCAGGCACAAAGTCCCTAATGATGGTCTGGATTTCAGGACAACCGGGT
25 AGTGAGTAAGCTTGTAGAGCCCCCCCCACGGGTGTCTATGGAAGTGTGGTTGCCTTCCACAACC
CCATCTCTAAGCCACATGCCTTAGACACATGGCTTCTTTATACACACCCTACAGACTCCAGG
AATAGAACCAACCTGGGTGTGTACCTAAACCAGATGCCACTAGATCCCACAGCCTGGTCAGA
GCCCACCCTGCTGGCCATGGGCATCTGTGCCTACTCAGACTTACAGAACATGGGGCAAGGCC
CTGATGGCTCCCCACAGTTTGGGTGTCTGTATGAATCAGGTAACCTATGAAGAGATCATTTTC
30 CTCATATTCACCCTGAAGCAAGCTTTCCCCACTGTATTTGATGCCCAGTGATCTCAGTGCAC
GTGGCCCCAAAGGGCTTCCTTGTGCTTCAAACACCCATCTCTCTTTGCTTCCAGCATCCTCT
GGACTCTTGAGTCCAGCTCTTGGGTAACCTCCTCAGGAGGATGCAGAGAATTTGGTCTCTTG
ACTCTCTGCAGGCCTTATTGTTTCAGCCTCTGGTTCTCTTTTCAGCCCAGAAATCAAAGGAG
CCTGGCTTTCTCAGCCTGTTGGCAGGGCAGGTGGGGACAGTATATATAGAGGCTGCCATTC
35 TGCATGTCGGTTGTCACTATGCTAGTTTAACCTGCCTGTTTCCCCATGCCTAGTGTTTGAAT
GAGTATTAATAAAATATCCAACCCAGGCCATTTCTCTCTGGAAAAAAA

[00361] SEQ ID NO: 44:

ACTGCGCGGTGAAGGGGCGTGGCCTGGCCGGGGAGGTTGACACCCAGACGCTGCTCTCAGTC
40 CTCTGGCGCCTGCTCCCCAGCGCATTCCTTCTGCTCCTGGGATATTTGTCTCATTACTGCCA
GTTCTTTGCGCAGCGGTCACTGGGTTCGTTTCAGCGTCTGTGGTTTCTGTGCTGTTATCCAG
TCTCCATCGCCCCAGCTCAGCTTCAGGCCTTCTTCCGAGACTCCACGGGAGAGCCCAGAGAG
CCTCCGGAGCCGAAGCCATGGAGGAAGTCCCACCCTACTCCCTCAGCAGCACCCCTGTTCCAG
45 CAGGAAGAACAGAGTGGGGTGACCTACCGGATCCCAGCCCTGCTGTACCTTCTCTCCACCCA
CACCTTCCTGGCCTTTGCAGAGAAGCGGACCTCAGTCAGAGATGAGGATGCTGCCTGCCTGG
TGCTCAGACGAGGGCTGATGAAGGGGCGCTCTGTACAGTGGGGCCCCCAACGGCTACTGATG
GAGGCCACATTACCTGGGCATCGACCATGAACCCCTGCCCTGTGTGGGAGAAAAATACTGG
CCGTGTGTACCTGTTTTTCATCTGTGTGCGGGGCCATGTTACTGAGAGGTGCCAGATTGTGT
50 GGGGCAAAAATGCCGCCCGTCTCTGCTTCTTTGCAGTGAAGATGCCGGCTGCTCTTGGGGT
GAAGTGAAAGACTTGACCGAGGAGGTCAATTGGCTCAGAGGTGAAGCGCTGGGCCACATTTGC

[00362] SEQ ID NO: 45:

45 GGACAGTGTGCATCACGGAGCTTGTGGCCAGACTGTGCCTGGCAGACCCAGAGGACCTAAG
GCTTGGCTCTAGTGGTGGTCAGCACAGCCCTCGGTGGTCTGCGGAGCCTGATATTGCTTTAC
GTAAGGGCTGTTCTGCTGTGCATCTCCTGTGTCTGAAGCTATTGCGCATGGAGACTGCTGGA
GCTCCCTTCTGCTTCCATGTGGACTCCCTGGTACCTTGCTCCTACTGGAAGGTTATGGGGCC
50 CACGCGTGTGCCAGGAGAACGGTGCTCTCCAGAGGGAAGGACGGCGCTGACCTACCGTG
TGCGTCGCTTACTCTGTGTGCCTCCAGGCCCTACTCTGCTGGCCTTCGCGGAACAGCGACTT

120

- CCTGGATTTAAATTTTCAGCACCCACATGGCAGCTCACAACAACCCATAAATCCAGTTTCAG
AGGATCCAACCTCTGATATACCATGTCAGCCAGAGCAGACACGGCTGAAGGTGGTTTGATCC
CCGTATGGAGAGGTGACAATTGGGAAGAGAGAAAAGATCAACTTAACCATGCAAGGAACAGGA
AGTTAAATACTGAACAGGGAAGGTAAAGGCAGGAAGTAGATGTAGAGGGCAAATCAATGAAA
5 CCCAAACATAACCCAAATTACGCTAAACACACACTGACATGCCAATTTAAAGGACAAATTGGC
TCCACTGGCAAAACCAAAACAGACACTGAAGATCCAAACAGTCACATGCCAACTACCGCGGA
GGGAGACAGACACAGAGAAGACCGTGACAGACACTTGGACACTCTTGAGAGTGGATGTGCAG
GAAGAGAGCTCTGCCAGTGGAGAAGAAAGCACTCAGAAGAAAAGTGACAGCAGCTGTAAATTT
GTATTCTGCTAATGTTATGTTCCAAAGTTGAAAGCAAAATTGTACCAATTCATAAGAACAAA
10 CAGGCTGACTCTCAGTTGTGACTGAACGCTCTCTCAGTAACTGACGGGGCGAGCAGGCCAAAG
GAGAGTCGGCTCAGAAGGGTGCATAGCCACGCCAAATCAAATAAGCAAGTACAACCGGCAGG
CTCTATTTCTAGCACAAAGGGTCTGTGCCTCATTCTGTGCTTGGGTGAGAGCTTGGGTCTC
TCATTTGGATGTAAGTGGTGTAGTGGAGAAGCAGGAAATAATCCGGAGCGCATATTTTGATT
TTAACATAAGTGCTGATTTGGGAGGGAGTTTTGTCAAATTGTGTTTTTACAATGTTTTTTTT
15 TTTTTAAATGATGCTTTTTTTGTAAAGTGTACAAATGTGATATAAGATTGGTTCTGCTACATT
CAGTTTCTATAAAAGTGGTTCTAAAATATTGTACTGTCAATCATCTCATGATTATTCTACTG
TACACATTACTGACTTTGTATGTAATAATTAATATTAGAAGAAAATATAATTTATTTGAATA
TAAAAAAAAAAAAAAAAAAAAA
- 20 **[00363]** SEQ ID NO: 46:
- X₁ASLPX₂LQX₃ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
AX₄THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₅QTGTLFLFFIAIPGQVTEQQQLQTRANV
TRLQVVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
25 LHPX₆QRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQVAEVETGEQRVVTLNARSHLRARVQ
AQSTNDGLDFQESQLVKKLVEPPPX₇GCQGSVISFSPSRSGPGSPAQWLLYTHPTHX₈X₉QRA
DLGAYLNPRPPAPEAWSEPVLLAKGSX₁₀AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX₁₁FX
12MFTLKQAFPAEYLPQ
- 30 **[00364]** SEQ ID NO: 47:
- X₁X₂SX₃X₄X₅LQX₆ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX₇X₈DEHAELIVX₉RR
GDYDAX₁₀THQVQWQAQEVVAQAX₁₂LDGHRSMNPCPLYDX₁₃QTGTLFLFFIAIPX₁₄X₁₅VT
EX₁₆QQQLQTRANVTRLX₁₇X₁₈VTSTDHGRTWSSPRDLTDAAIGPX₁₉YREWSTFAVGPGHX₂₀LQ
35 LHDX₂₁RSLVVPAYAYRKLHPX₂₂QRPIPSAFX₂₃FLSHDHGRTWARGHFVAQDTX₂₄ECQVAE
VETGEQRVVTLNARSHLRARVQAQX₂₅NX₂₆GLDFQX₂₇SQLVKKLVEPPPX₂₈GX₂₉QGSVISF
PSPSRSGPGSPAQX₃₀LLYTHPTHX₃₁X₃₂QRADLGAYLNPRPPAPEAWSEPX₃₃LLAKGSX₃₄AYS
DLQSMGTGPDGSPLFGX₃₅LYEANDYEEIX₃₆FX₃₇MFTLKQAFPAEYLPQ
- 40 **[00365]** SEQ ID NO: 48:
- DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
45 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPPQGCQGSVISFSPSRSGPGSPAQWLLYTHPTHX₃₂QRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00366] SEQ ID NO: 49:

DASLPYLQDESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 5 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA
 FPAEYLPQ

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[00367] SEQ ID NO: 50:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 15 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQ

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[00368] SEQ ID NO: 51:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 25 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQ

30

[00369] SEQ ID NO: 52:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 35 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQ

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[00370] SEQ ID NO: 53:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 45 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQ

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[00371] SEQ ID NO: 54:

5 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQ

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[00372] SEQ ID NO: 55:

15 ASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
 HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
 QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
 QRPPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQST
 NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAYL
 LNPRPPAPEAWSEPVLLAKGSCAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
 PAEYLPQ

[00373] SEQ ID NO: 56:

25 MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSCAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQ

[00374] SEQ ID NO: 57:

30 ASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
 HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
 QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
 QRPPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQST
 NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAYL
 35 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
 PAEYLPQ

[00375] SEQ ID NO: 58:

40 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 45 FPAEYLPQ

[00376] SEQ ID NO: 59:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 5 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQ

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[00377] SEQ ID NO: 60:

AASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 15 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQ

20 [00378] SEQ ID NO: 61:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 25 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQ

[00379] SEQ ID NO: 62:

AASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 35 LNPRPPAPEAWSEPVLLAKGSCAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQ

[00380] SEQ ID NO: 63:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYAD
 40 SVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLVTVSSASTK
 GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
 SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
 KPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
 VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLV
 45 KGFYPDSI AVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
 LHNHYTQKSLSLSPGK

[00381] SEQ ID NO: 64:

DIQMTQSPSSLSASVGDRVTTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRF
 5 SGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQ
 LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADY
 EKHKVYACEVTHQGLSPVTKSFNRGEC

[00382] SEQ ID NO: 65:

EVQLVESGGGLVQPGGSLRLSCAASGFINIKDTYIHWRQAPGKGLEWVARIYPTNGYTRYAD
 10 SVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLTVTVSSGGGG
 SGGGGSGGGGSDIQMTQSPSSLSASVGDRVTTITCRASQDVNTAVAWYQQKPGKAPKLLIYSA
 SFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

[00383] SEQ ID NO: 66:

15 DIQMTQSPSSLSASVGDRVTTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRF
 SGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQ
 LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADY
 EKHKVYACEVTHQGLSPVTKSFNRGEC

[00384] SEQ ID NO: 67:

EVQLVESGGGLVQPGGSLRLSCAASGFINIKDTYIHWRQAPGKGLEWVARIYPTNGYTRYAD
 SVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLTVTVSSASTK
 GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
 25 SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
 KPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
 VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLV
 KGFYPSPDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEHA
 LHNHYTQKSLSLSPGK

[00385] SEQ ID NO: 68:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 35 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLTKQA
 40 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSPDIAVEWESNGQPE
 NNYKTTPPVLDSDGSFFLTSLKLTVDKSRWQQGNVFSQSVMEHALHNHYTQKSLSLSPGK

[00386] SEQ ID NO: 69:

45 DASLPYLQDES VFQSGAHAYRIPALLYLPGQQSLLAFQAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP

KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA
 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 5 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTPPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00387] SEQ ID NO: 70:

10 DASLPYLQKESV FQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 15 LNPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTPPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK
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[00388] SEQ ID NO: 71:

DASLPYLQKESV FQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 25 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 30 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTPPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00389] SEQ ID NO: 72:

DASLPYLQKESV FQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
 35 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 40 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTPPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

45 **[00390]** SEQ ID NO: 73:

DASLPYLQKESV FQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL

CQVSTSDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 5 FPAEYLPQGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTTPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

10 **[00391]** SEQ ID NO: 74:

DASLPYLQKESV FQSGAHAYRIPALLYLPGQQSLLAF AEQRASKKDEHAELIVLRRGDYDAN
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVSTSDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCVAEVETGEQRVVTLNARSHLRARVQAQS
 15 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 20 NNYKTTTPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00392] SEQ ID NO: 75:

X₁ASLPX₂LQX₃ESV FQSGAHAYRIPALLYLPGQQSLLAF AEQRASKKDEHAELIVLRRGDYD
 25 AX₄THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₅QTGTLFLFFIAIPGQVTEQQQLQTRANV
 TRLCQVSTSDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
 LHPX₆QRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCVAEVETGEQRVVTLNARSHLRARVQ
 AQSTNDGLDFQESQLVKKLVEPPPX₇GCQGSVISFPSRSGPGSPAQWLLYTHPTHX₈X₉QRA
 DLGAYLNPRPPAPEAWSEPVLLAKGSX₁₀AYS DLQSMGTGPDGSPLFGCLYEANDYEEIX₁₁FX
 30 ₁₂MFTLKQAFPAEYLPQGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRT
 PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
 YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLS
 LSPGK
 35

[00393] SEQ ID NO: 76:

X₁X₂SX₃X₄X₅LQX₆ESV FQSGAHAYRIPALLYLPGQQSLLAF AEQRASX₇X₈DEHAELIVX₉RR
 GDYDAX₁₀THQVQWX₁₁AQEVVAQAX₁₂LDGHRSMNPCPLYDX₁₃QTGTLFLFFIAIPX₁₄X₁₅VT
 40 EX₁₆QQQLQTRANVTRLX₁₇X₁₈VTSDHGRTWSSPRDLTDAAIGPX₁₉YREWSTFAVGPGHX₂₀LQ
 LHDRX₂₁RSLVVPAYAYRKLHPX₂₂QRPIPSAFX₂₃FLSHDHGRTWARGHFVAQDTX₂₄ECQVAE
 VETGEQRVVTLNARSHLRARVQAQX₂₅NX₂₆GLDFQX₂₇SQLVKKLVEPPPX₂₈GX₂₉QGSVISF
 PSRSGPGSPAQX₃₀LLYTHPTHX₃₁X₃₂QADLGAYLNPRPPAPEAWSEPX₃₃LLAKGSX₃₄AYS
 DLQSMGTGPDGSPLFGX₃₅LYEANDYEEIX₃₆FX₃₇MFTLKQAFPAEYLPQGGGSGGGGSDKT
 45 HTPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
 NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
 VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLT SK
 LTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00394] SEQ ID NO: 77:

5 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
 10 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCVMHEALHNHYTQKSLSLSPGKGGG
 GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
 IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
 15 GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
 PGKAPKLLIYSASFLYSGVPSRFSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
 TKVEIK

[00395] SEQ ID NO: 78:

20 DASLPYLQDES VFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 25 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLGCLYEANDYEEIRFIMFTLKQA
 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 30 NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCVMHEALHNHYTQKSLSLSPGKGGG
 GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
 IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
 GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
 PGKAPKLLIYSASFLYSGVPSRFSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
 35 TKVEIK

[00396] SEQ ID NO: 79:

40 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
 45 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCVMHEALHNHYTQKSLSLSPGKGGG
 GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
 50 IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ

GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

5 **[00397]** SEQ ID NO: 80:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
10 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKHTCPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
15 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
20 PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

[00398] SEQ ID NO: 81:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
30 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKHTCPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGKGGG
35 GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQG
TKVEIK

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[00399] SEQ ID NO: 82:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
45 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKHTCPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
50 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE

NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
 GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIDKTYIHWRQAPGKGLEWVAR
 IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
 GTLVTVSSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
 5 PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
 TKVEIK

[00400] SEQ ID NO: 83:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRGDDYDAN
 THQVQWQAQEVVAQARLDGHRSMNCPPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
 KQRPISAFCLFLSHDHGRTWARGHFVAQDTLECCQVAEVETGEQVRVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPPAGCQGSVISFSPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 15 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIISRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGG
 20 GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIDKTYIHWRQAPGKGLEWVAR
 IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
 GTLVTVSSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
 PGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQG
 TKVEIK
 25

[00401] SEQ ID NO: 84:

X₁ASLPX₂LQX₃ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRGDDYD
 AX₄THQVQWQAQEVVAQARLDGHRSMNCPPLYDX₅QTGTLFLFFIAIPGQVTEQQQLQTRANV
 30 TRLCQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRK
 LHPX₆QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECCQVAEVETGEQVRVTLNARSHLRARVQ
 AQSTNDGLDFQESQLVKKLVEPPPX₇GCQGSVISFSPSRSGPGSPAQWLLYTHPTHX₈X₉QRA
 DLGAYLNPRPPAPEAWSEPVLLAKGSX₁₀AYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIX₁₁FX
 1₂MFTLKQAFPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIISRT
 35 PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
 YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
 WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
 LSPGKGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIDKTYIHWRQAPG
 KGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 40 YAMDYWGQGTTLVTVSSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNT
 AVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYT
 TPPTFGQGTKEIK

[00402] SEQ ID NO: 85:

X₁X₂SX₃X₄X₅LQX₆ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX₇X₈DEHAELIVX₉RR
 GDYDAX₁₀THQVQWX₁₁AQEVVAQAX₁₂LDGHRSMNCPPLYDX₁₃QTGTLFLFFIAIPX₁₄X₁₅VT
 EX₁₆QQQLQTRANVTRLX₁₇X₁₈VTSTDHGRTWSSPRDLTDAAIGPX₁₉YREWSTFAVGPGHX₂₀LQ
 LHDX₂₁RSLVVPAYAYRKLHPX₂₂QRPIPSAFX₂₃FLSHDHGRTWARGHFVAQDTX₂₄ECQVAE
 50 VETGEQVRVTLNARSHLRARVQAQX₂₅NX₂₆GLDFQX₂₇SQLVKKLVEPPPX₂₈GX₂₉QGSVISF
 PSRSGPGSPAQX₃₀LLYTHPTHX₃₁X₃₂QRADLGAYLNPRPPAPEAWSEPX₃₃LLAKGSX₃₄AYS

DLQSMGTGPDGSPLFGX₃₅LYEANDYEEIX₃₆FX₃₇MFTLKQAFPAEYLPQGGGSGGGGSDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSK
5 LTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGSGGGGSGGGGSEVQLVESGG
GLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTIS
ADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRTVITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPS
RFSGSRSGTDFTLTITSSLPEDFATYYCQGHYTPPTFGQGTKVEIK

10

[00403] SEQ ID NO: 86:

GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCAGCGTGGGAGACAGAGTGACCAT
CACCTGTAGAGCCAGCCAGGACGTGAACACAGCCGTGGCTTGGTATCAGCAGAAGCCTGGCA
15 AGGCCCTAAGCTGCTGATCTACAGCGCCAGCTTTCTGTACTCCGGCGTGCCAGCAGATTC
AGCGGCTCTAGAAGCGGCACCGACTTCACCCTGACCATAAGCAGTCTGCAGCCCAGGACTT
CGCCACCTACTACTGTCTCAGCAGCACTACACCACACCTCCAACCTTTGGCCAGGGCACCAAGG
TGGAAATCAAGCGTACGGTGGCTGCACCATCTGTCTTCATCTTCCC GCCATCTGATGAGCAG
TTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAA
20 AGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGC
AGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAGACTAC
GAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAA
GAGCTTCAACAGGGGAGAGTGT

25 **[00404]** SEQ ID NO: 87:

GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGCCTGGCGGATCTCTGAGACTGTC
TTGTGCCGCCAGCGCTTCAACATCAAGGACACCTACATCCACTGGGTCCGACAGGCCCCCTG
GCAAAGGACTTGAATGGGTGCGCAGAATCTACCCCAACCGCTACACCAGATACGCCGAC
30 TCTGTGAAGGGCAGATTACCATCAGCGCCGACACCAGCAAGAACACCGCCTACCTGCAGAT
GAACAGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTTCTAGATGGGAGGCGACGGCT
TCTACGCCATGGATTATTGGGGCCAGGGCACCTGGTCACCGTTTCTTCTGCTagcACCAAG
GGCCCATC_cGTCTTCCCCCTGGCACCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCT
GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTC_cTGGAAGTACAGGCGCTC
35 TGACCAGCGGCGTGACACCTTCCCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGC
AGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA
CAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACCTCACA
CATGCCCACCGTGCCAGCACCTGAACCTCTGGGGGACCGTCAGTCTTCTCTTCCCCCA
AAACCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGT
40 GAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGAGGTGCATAATG
CCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACC
GTCTTGACACAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
CCCAGCCCCCATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcT
ACACCTTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTACGCTGtactGCCTGGTC
45 AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAA
CTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTATAGCAAGCTCA
CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

50 **[00405]** SEQ ID NO: 88:

GATGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCACGCCTACAG
AATTCCCCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGG
CCAGCAAGAAGGATGAGCACGCCGAACCTGATCGTGCTGCGGAGAGGCGATTACGACGCCGGC
5 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATGAACAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTC AAGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
10 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCTGTTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGGCG
AGCAGAGAGTCTGTGACCCTGAACGCCAGATCTCACCTGAGAGCCAGAGTGCAGGCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCC
15 ACAGGGCTGT CAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CGCTGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCTCTGATGTTACCCCTGAAGCAGGCC
20 TTTCCAGCCGAGTACCTGCCTCAAGGCGGAGGTGGAAGTGGCGGAGGCGGATCCGACAAAAC
TCACACATGCCCACCGTGCCAGCACCTGAACCTCGGGGGACCGTCAGTCTTCTCTTCC
CCCCAAAACCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTG
GACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGAGGTGCA
TAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCC
25 TCACCGTCTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA
GCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACA
GGTCTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCC
TGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAG
AACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACTAGCAA
30 GCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATG
AGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00406] SEQ ID NO: 89:

GATGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCACGCCTACAG
AATTCCCCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGG
CCAGCAAGAAGGATGAGCACGCCGAACCTGATCGTGCTGCGGAGAGGCGATTACGACGCCGGC
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATGAACAGACCGGCACACTGTTTCTGTTCTTTATCG
40 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
TGTC AAGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
45 CAGAGGACATTTCTGTTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGGCG
AGCAGAGAGTCTGTGACCCTGAACGCCAGATCTCACCTGAGAGCCAGAGTGCAGGCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCC
ACAGGGCTGT CAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
50 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
CGCTGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT

GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAA

[00407] SEQ ID NO: 90:

5 TVEKSVVFKAEGEHFTDQKGNTIVGSGSGGTTKYFRIPAMCTTSKGTIVVFADARHNTASDQ
SFIDTAAARSTDGGKTWNKKIAIYNDRVNSKLSRVMDPTCIVANIQGRETIILVMVGKWNND
KTWGAYRDKAPDTDWDLVLYKSTDDGVTFSKVETNIHDIIVTKNGTISAMLGCVGSGQLQNDG
KLVPVQMVRTKNITTVLNTSFIYSTDGITWSLPSGYCEGFGSENNIEFNASLVNNIRNSG
10 LRRSFETKDFGKTWTEFFPMDKKVDNRNHGVQGSTITIPSGNKLVAHSSAQNKNDYTRSD
ISLYAHNLYSGEVKLIDDFYPKVGNASGAGYSCLSYRKNVDKETLYVVYEANGSIEFQDLRSR
HLPVIKSYNGGGSGGGGSDKTHTCPPCAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
15 ENNYKTTTPVLDSGSSFLLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00408] SEQ ID NO: 91:

ACAGTGGAAAAGTCCGTGGTGTTCAGGCCGAGGGCGAGCACTTCACCGACCAGAAAGGCAA
TACCATCGTCGGCTCTGGCAGCGCGGCACCACCAAGTACTTTAGAATCCCCGCCATGTGCA
CCACCAGCAAGGGCACCATTGTGGTGTTCGCCGACGCCAGACACAACACCGCCAGCGATCAG
20 AGCTTCATCGATACCGCTGCCGCCAGATCTACCGATGGCGGCAAGACCTGGAACAAGAAGAT
CGCCATCTACAACGACCGCGTGAACAGCAAGCTGAGCAGAGTGATGGACCTACCTGCATCG
TGGCCAAACATCCAGGGCAGAGAAACCATCCTGGTCACTGGTTCGGAAAAGTGGAACAACAACGAT
AAGACCTGGGGCGCCTACAGAGACAAGGCCCTGATACCGATTGGGACCTCGTGCTGTACAA
GAGCACCGATGACGGCGTGACCTTCAGCAAGGTGGAACAAACATCCACGACATCGTGACCA
25 AGAAGCGCACCATCTCTGCCATGCTCGGCGGCGTTGGATCTGGCCTGCAACTGAATGATGGC
AAGCTGGTGTTCCTCGTGAGATGGTCCGAACAAAGAATATCACCAACCGTGCTGAATACCAG
CTTCATCTACAGCACCGACGGCATCACATGGTCCCTGCCTAGCGGCTACTGTGAAGGCTTTG
GCAGCGAGAACAACATCATCGAGTTCAACGCCAGCCTGGTCAACAACATCCGGAACAGCGGC
CTGCGGAGAAGCTTCGAGACAAAGGACTTCGGAAAGACGTGGACCGAGTTTCCTCCAATGGA
30 CAAGAAGGTGGACAACCGGAACACGGCGTGACGGGCAGCACAATCACAATCCCTAGCGGCA
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CAAAGTGGGCAATGCCAGCGGAGCCGGCTACAGCTGTCTGAGCTACCGGAAAAATGTGGACA
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35 CATCTGCCCCGTGATCAAGAGCTACAACGgcgagggtggaagtggcgaggcgatccgacaa
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45 caagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgc
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[00409] SEQ ID NO: 92:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYAD
SVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
5 KPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTKSKAGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHEA
LHNHYTQKSLSLSPGKGGGGSGGGSGGGGSTVEKSVVFKAEGEHFTDQKGNTIVGSGSGGT
TKYFRIPAMCTTSKGTIVVFADARHNTASDQSFIDTAAARSTDGGKTNWKKIAIYNDRVNSK
10 LSRVMDPTCIVANIQGRETIILVMVGKWNNDKTWGAIRDKAPDWDVLVLYKSTDDGVTFSK
VETNIHDIVTKNGTISAMLGVGSGQLNDGKLVFPVQMVRTKNITTVLNTSFIYSTDGITW
SLPSGYCEGFGSENNIIIEFNASLVNNIRNSGLRRSFETKDFGKTWTEFPPMDKKVDNRNHGV
QGSTITIPSGNKLVAAHSSAQNKNDYTRSDISLYAHNLYSGEVKLIDDFYPKVGNASGAGY
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15

[00410] SEQ ID NO: 93:

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20 tctgtgaagggcagattcaccatcagcgccgacaccagcaagaacaccgcctacctgcagat
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 5 gcgaagtgaagctgatcgacgacttctaccccaaagtgggcaatgccagcggagccggctac
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[00411] SEQ ID NO: 94:

10 TVEKSVVFKAEGEHFTDQKGNITIVSGSGGTTKYFRIPAMCTTSKGTIVVFADARHNTASDQ
 SFIDTAAARSTDGGKTWNKKIAIYNDRVNSKLSRVMPTCIVANIQGRETIILVMVGKWNND
 KTWGAYRDKAPDWDVLVLYKSTDDGVTFSKVETNIHDIIVTKNGTISAMLGGVGSGLQLNDG
 KLVFPVQMVRTKNITTVLNTSFIYSTDGITWSLPSGYCEGFGSENNIIIEFNASLVNNIRNSG
 15 LRRSFETKDFGKTWTEFPPMDKKVDNRNHGVQGSTITIPSGNKLVAHSSAQNKNNDYTRSD
 ISLYAHNLYSGEVKLIDDFYPKVGNASGAGYSCLSYRKNVDKETLYVVYEANGSIEFQDLR
 HLPVIKSYNGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
 VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
 KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
 20 ENNYKTTTPVLDSGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGG
 GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFINIKDTYIHWVRQAPGKLEWVA
 RIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRRAEDTAVYYCSRWGGDGFYAMDYWG
 QGTLVTVSSGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTVITCRASQDVNTAVAWYQQ
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 25 GTKVEIK

[00412] SEQ ID NO: 95:

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 AGCTTCATCGATACCGCTGCCGCCAGATCTACCGATGGCGGCAAGACCTGGAACAAGAAGAT
 CGCCATCTACAACGACCGCGTGAACAGCAAGCTGAGCAGAGTGATGGACCCTACCTGCATCG
 TGGCCAACATCCAGGGCAGAGAAACCATCCTGGTCATGGTCGGAAGTGGAACAACAACGAT
 35 AAGACCTGGGGCGCCTACAGAGACAAGGCCCTGATACCGATTGGGACCTCGTGCTGTACAA
 GAGCACCGATGACGGCGTGACCTTCAGCAAGGTGGAACAAAACATCCACGACATCGTGACCA
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 AAGCTGGTGTTCCTCGTGAGATGGTCCGAACAAAGAATATCACCACCGTGCTGAATACCAG
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 40 GCAGCGAGAACAAACATCATCGAGTTCAACGCCAGCCTGGTCAACAACATCCGGAACAGCGGC
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 45 CAAAGTGGGCAATGCCAGCGGAGCCGGCTACAGCTGTCTGAGCTACCGGAAAAATGTGGACA
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 5 GAGAACAACACTACAAGACCACGCCTCCCGTGTGGACTCCGACGGCTCCTTCTTCTCTATAG
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 GGAGGATCTGGCGGAGGTGGAAGTGGCGGAGGCGGATCTGAGGTGCAGCTGGTTGAATCTGG
 CGGAGGACTGGTTACGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTTCAACA
 10 TCAAGGACACCTACATCCACTGGGTCCGACAGGCCCCCTGGCAAAGGACTTGAATGGGTGCGC
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 15 AGGCGGATCTGACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCAGCGTGGGAGACA
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 CAGCAGATTGAGCGGCTCTAGAAGCGGCACCGACTTCACCCTGACCATAAGCAGTCTGCAGC
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 20 GGCACCAAGGTGGAAATCAAG

[00413] SEQ ID NO: 96:

TVEKSVVFKAEGEHFTDQKGNITIVGSGSGGTTKYFRIPAMCTTSKGTIVVFADARHNTASDQ
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 25 KTWGAYRDKAPDTDWDLVLYKSTDDGVTFSKVETNIHDIIVTKNGTISAMLGGVGSLQLNDG
 KLVFPVQMVRTKNITTVLNTSFIYSTDGITWSLPSGYCEGFGSVNNIIEFNASLVNNIRNSG
 LRRSFETKDFGKTWTEFPPMDKKVDNRNHGVQGSTITIPSGNKLVAHSSAQNKNNDYTRSD
 ISLYAHNLYSGEVKLIDDFYPKVGNASGAGYSCLSYRKNVDKETLYVVYEANGSIEFQDLR
 HLPVIKSYNGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
 30 VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
 KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
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[00414] SEQ ID NO: 97:

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[00415] SEQ ID NO: 98:

20 ASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
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 QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
 QRPISAFCLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQST
 NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAYL
 25 NPRPPAPEAWSEPVLAKGSCAYSDLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQAF
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 EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
 PPVLDSDGSFFLTSTKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
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[00416] SEQ ID NO: 99:

ASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
 HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
 35 QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
 QRPISAFCLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQST
 NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAYL
 NPRPPAPEAWSEPVLAKGSAAYSDLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQAF
 PAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHED
 40 PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
 EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
 PPVLDSDGSFFLTSTKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00417] SEQ ID NO: 100:

45 AASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPISAFCLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQST
 50 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLAKGSAAYSDLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA

FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSTKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSLSLSPGK

5

[00418] SEQ ID NO: 101:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
10 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLAKGSAAYSDLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
15 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSTKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSLSLSPGK

[00419] SEQ ID NO: 102:

AASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
20 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
25 LNPRPPAPEAWSEPVLAKGSCAYSDLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSTKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSLSLSPGK

30

[00420] SEQ ID NO: 103:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
35 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLAKGSCAYSDLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
40 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLTSTKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSLSLSPGK

[00421] SEQ ID NO: 104:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
45 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY

LNPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 5 TPPVLDSGDSFFLTSTKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00422] SEQ ID NO: 105:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTFLFFIAIPGQVTEQQQLQTRANVTRL
 10 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQVRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 15 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSGDSFFLTSTKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00423] SEQ ID NO: 106:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTFLFFIAIPGQVTEQQQLQTRANVTRL
 20 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQVRVVTLNARSHLRARVQAQS
 25 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 30 TPPVLDSGDSFFLTSTKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00424] SEQ ID NO: 107:

DASLPYLQDES VFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 35 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQVRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA
 40 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSGDSFFLTSTKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00425] SEQ ID NO: 108:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 50 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQVRVVTLNARSHLRARVQAQS

TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSP LFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 5 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00426] SEQ ID NO: 109:

10 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 15 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSP LFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00427] SEQ ID NO: 110:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 25 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSP LFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 30 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00428] SEQ ID NO: 111:

35 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECCQVAEVETGEQRVVTLNARSHLRARVQAQS
 40 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSP LFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 45 TPPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00429] SEQ ID NO: 112:

50 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP

KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 5 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLTSLKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00430] SEQ ID NO: 113:

10 ASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
 HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
 QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVVPAYAYRKLHPK
 QRPPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQST
 15 NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAYL
 NPRPPAPEAWSEPVLLAKGSCAYSSDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQAF
 PAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
 VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
 LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 20 NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00431] SEQ ID NO: 114:

25 ASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
 HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
 QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVVPAYAYRKLHPK
 QRPPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQST
 NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAYL
 NPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQAF
 30 PAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
 VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
 LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00432] SEQ ID NO: 115:

35 AASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVVPAYAYRKLHP
 40 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSSDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 45 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00433] SEQ ID NO: 116:

50 DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL

CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCVAEVETGEQ RVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 5 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

10 **[00434]** SEQ ID NO: 117:

AASLPYLQKESV FQSGAHAYRIPALLYLPGQQSLLAF AEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCVAEVETGEQ RVVTLNARSHLRARVQAQS
 15 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSCAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 20 NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

[00435] SEQ ID NO: 118:

DASLPYLQKESV FQSGAHAYRIPALLYLPGQQSLLAF AEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 25 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCVAEVETGEQ RVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSCAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 30 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

[00436] SEQ ID NO: 119:

MASLPYLQKESV FQSGAHAYRIPALLYLPGQQSLLAF AEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCVAEVETGEQ RVVTLNARSHLRARVQAQS
 35 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSCAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 40 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 45 NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

[00437] SEQ ID NO: 120:

MASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 5 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 10 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTFPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEALHNHYTQKSLSLSPGK

[00438] SEQ ID NO: 121:

15 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
 20 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 25 NNYKTTFPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEALHNHYTQKSLSLSPGK

[00439] SEQ ID NO: 122:

DASLPYLQDES VFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 30 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA
 35 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTFPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEALHNHYTQKSLSLSPGK

[00440] SEQ ID NO: 123:

40 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 45 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK

ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK

[00441] SEQ ID NO: 124:

5 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHP
KQRPPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRRVVTLNARSHLRARVQAQS
10 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
15 NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK

[00442] SEQ ID NO: 125:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
20 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHP
KQRPPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
25 FPAEYLPQGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK

[00443] SEQ ID NO: 126:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHP
35 KQRPPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
40 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK

[00444] SEQ ID NO: 127:

45 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHP
KQRPPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
50 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV

DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

5 [00445] SEQ ID NO: 128:

ASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQGTGLFLFFIAIPGQVTEQQQLQTRANVTRLC
QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHPK
10 QRPPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQST
NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAYL
NPRPPAPEAWSEPVLLAKGSCAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
PAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
15 EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

[00446] SEQ ID NO: 129:

ASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAPT
HQVQWQAQEVVAQARLDGHRSMNPCPLYDAQGTGLFLFFIAIPGQVTEQQQLQTRANVTRLC
QVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHPK
QRPPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQST
NDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAYL
25 NPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQAF
PAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
30

[00447] SEQ ID NO: 130:

AASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQGTGLFLFFIAIPGQVTEQQQLQTRANVTRL
35 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHP
KQRPPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQST
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHED
40 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

[00448] SEQ ID NO: 131:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQGTGLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVVPAYAYRKLHP
KQRPPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQST
50 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA

FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSLSLSPGK

5

[00449] SEQ ID NO: 132:

AASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
10 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQVRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLAKGSCAYSIDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
15 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSLSLSPGK

[00450] SEQ ID NO: 133:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
20 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQVRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLAKGSCAYSIDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
25 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSLSLSPGK

30 **[00451]** SEQ ID NO: 134:

MASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQVRVVTLNARSHLRARVQAQS
35 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLAKGSCAYSIDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
40 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSLSLSPGK

[00452] SEQ ID NO: 135:

MASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
45 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQVRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY

LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 5 TPPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00453] SEQ ID NO: 136:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 10 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQ RVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 15 FPAEYLPQEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

20 **[00454]** SEQ ID NO: 137:

DASLPYLQDES VFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 25 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQ RVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIRFIMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 30 IEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00455] SEQ ID NO: 138:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQ RVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 40 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

45 **[00456]** SEQ ID NO: 139:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 50 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQ RVVTLNARSHLRARVQAQS

TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 5 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00457] SEQ ID NO: 140:

10 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECCQVAEVETGEQ RVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 15 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
 20

[00458] SEQ ID NO: 141:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 25 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECCQVAEVETGEQ RVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 30 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00459] SEQ ID NO: 142:

35 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARS LVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECCQVAEVETGEQ RVVTLNARSHLRARVQAQS
 40 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHRKQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 45 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00460] SEQ ID NO: 143

:
 X₁X₂SX₃X₄X₅LQX₆ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX₇X₈DEHAELIVX₉RR
 50 GDYDAX₁₀THQVQWX₁₁AQEVVAQAX₁₂LDGHRSMNPCPLYDX₁₃QTGTLFLFFIAIPX₁₄X₁₅VT
 EX₁₆QQQLQTRANVTRLX₁₇X₁₈VTSTDHGRTWSSPRDLTDAAIGPX₁₉YREWSTFAVGPGHX₂₀LQ

LHDX₂₁RSLVVPAYAYRKLHPX₂₂QRPIPSAFX₂₃FLSHDHGRTWARGHFVAQDTX₂₄ECQVAE
 VETGEQRRVVTNLNARSHLRARVQAQXS₂₅NX₂₆GLDFQX₂₇SQLVKKLVEPPX₂₈GX₂₉QGSVISF
 PPSRSGPGSPAQX₃₀LLYTHPTHX₃₁X₃₂QRADLGAYLNPRPPAPEAWSEPX₃₃LLAKGSX₃₄AYS
 DLQSMGTGPDGSPLFGX₃₅LYEANDYEEIX₃₆FX₃₇MFTLKQAFPAEYLPQX₃₈DKTHTCPPCPA
 5 PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
 EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
 EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSTKLTVDKSRW
 QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00461] SEQ ID NO: 144:

10 X₁ASLPX₂LQX₃ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
 AX₄THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₅QTGTFLFLFFIAIPGQVTEQQQLQTRANV
 TRLCQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
 LHPX₆QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRRVVTNLNARSHLRARVQ
 15 AQSTNDGLDFQESQLVKKLVEPPX₇GCQGSVISFPPSRSGPGSPAQWLLYTHPTHX₈X₉QRA
 DLGAYLNPRPPAPEAWSEPVLLAKGSX₁₀AYSDDLQSMGTGPDGSPLFGCLYEANDYEEIX₁₁FX
₁₂MFTLKQAFPAEYLPQX₁₃DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 20 NNYKTTPPVLDSDGSFFLTSTKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00462] SEQ ID NO: 145:

GGGGS

25

[00463] SEQ ID NO: 146:

EPKSS

30 [00464] SEQ ID NO: 147:

EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
 YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
 KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
 35 GSFFLTSTKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00465] SEQ ID NO: 148:

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
 40 EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
 EPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
 YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00466] SEQ ID NO: 149:

45 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTFLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRRVVTNLNARSHLRARVQAQ
 50 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPPSRSGPGSPAQWLLYTHPTHARQADLGAY

LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

[00467] SEQ ID NO: 150:

5

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVEVETGEQVRVVTLNARSHLRARVQAQS
10 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTTHARQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
15 NNYKTTPPVLDSDGSFFLT SKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00468] SEQ ID NO: 151:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
20 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVEVETGEQVRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTTHARQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
25 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLT SKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

30 **[00469] SEQ ID NO: 152:**

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
35 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVEVETGEQVRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTTHARQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
40 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00470] SEQ ID NO: 153:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
45 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVEVETGEQVRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTTHARQRADLGAY
50 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE

DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

5 **[00471]** SEQ ID NO: 154:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVVPAYAYRKLHP
10 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQVRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLTKQA
FPAEYLPQ

15 **[00472]** SEQ ID NO: 155:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVVPAYAYRKLHP
20 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQVRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLTKQA
FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
25 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTPPVLDSDGSFFLT SKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

[00473] SEQ ID NO: 156:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQVRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
35 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLTKQA
FPAEYLPQEPKSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLT SKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
40

[00474] SEQ ID NO: 157:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVVPAYAYRKLHP
45 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQVRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLTKQA
50 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK

ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00475] SEQ ID NO: 158:

5 DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
10 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
15 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00476] SEQ ID NO: 159:

20 DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
25 FPAEYLPQ

[00477] SEQ ID NO: 160:

30 DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
35 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTPPVLDSDGSFFLT SKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00478] SEQ ID NO: 161:

40 DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
45 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
50 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLT SKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00479] SEQ ID NO: 162:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 5 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 10 FPAEYLPQGGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTPPVLDSGDSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK

[00480] SEQ ID NO: 163:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 15 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRFRVQAQS
 20 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 25 TPPVLDSGDSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK

[00481] SEQ ID NO: 164:

X₁ASLPX₂LQX₃ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
 30 AX₄THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₅QTGTLFLFFIAIPGQVTEQQQLQTRANV
 TRLCX₆VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLLVPAYAYRK
 LHPX₇QRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRX₈RV
 QAQSTNDGLDFQESQLVKKLVEPPPX₉GCQGSVISFPSRSGPGSPAQWLLYTHPTHX₁₀X₁₁Q
 RADLGAYLNPRPPAPEAWSEPVLLAKGSX₁₂AYSDDLQSMGTGPDGSPLFGCLYEANDYEEIX₁₃
 35 FX₁₄MFTLKQAFPAEYLPQX₁₅DKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
 VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
 NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
 PENNYKTTPPVLDSGDSFFLTSLKTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK

[00482] SEQ ID NO: 165:

X₁X₂SX₃X₄X₅LQX₆ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX₇X₈DEHAELIVX₉RR
 GDYDAX₁₀THQVQWX₁₁AQEVVAQAX₁₂LX₁₃GHRSMNPCPLYDX₁₄QTGTLFLFFIAIPX₁₅X₁₆V
 TEX₁₇QQQLQTRANVTRLX₁₈X₁₉VTSTDHGRTWSSPRDLTDAAIGPX₂₀YREWSTFAVGPGHX₂₁L
 45 QLHDX₂₂X₂₃RSLVVPAYAYRKLHPX₂₄X₂₅X₂₆PIPSAFX₂₇FLSHDHGRTWARGHFVX₂₈QDTX₂₉
 ECQVAEVX₃₀TGEQRVVTLNARSX₃₁X₃₂X₃₃X₃₄RX₃₅QAQX₃₆NX₃₇GLDFQX₃₈X₃₉QX₄₀VKKL
 X₄₁EPPPX₄₂GX₄₃QGSVISFPSRSGPGSPAQX₄₄LLYTHPTHX₄₅X₄₆QRADLGAYLNPRPPAP
 EAWSEPX₄₇LLAKGSX₄₈AYSDDLQSMGTGPDGSPLFGX₄₉LYEANDYEEIX₅₀FX₅₁MFTLKQAFP
 AEYLPQX₅₂DKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
 50 FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT I

SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVL
DSDGSFFLTSLKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

[00483] SEQ ID NO: 166:

5 DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQVRVVTLNARSHLRARVQAQS
10 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTTHARQADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKHTCPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
15 NNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSRSGTDFTLTISSLQPEDFATYYCQGHYTTPTFGQG
20 TKVEIK

[00484] SEQ ID NO: 167:

25 DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQVRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
30 FPAEYLPQGGGGSGGGGSDKHTCPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGG
GSGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
35 IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
PGKAPKLLIYSASFLYSGVPSRFSRSGTDFTLTISSLQPEDFATYYCQGHYTTPTFGQG
TKVEIK

[00485] SEQ ID NO: 168:

40 DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
45 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQVRVVTLNARSHLRFRVQAQS
TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQGGGGSGGGGSDKHTCPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
50 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE

NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGKGGG
 GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
 IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
 GTLVTVSSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
 5 PGKAPKLLIYSASFLYSGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQG
 TKVEIK

[00486] SEQ ID NO: 169:

10 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRWTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVPAAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 15 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
 20 GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
 GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLT
 VSSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
 KLLIYSASFLYSGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKEI
 K

25

[00487] SEQ ID NO: 170:

DASLPYLQDES VFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 30 CQVTSTDHGRWTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVPAAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLGCLYEANDYEEIRFIMFTLKQA
 FPAEYLPQEPKSSDKTHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 35 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGKGGGGSGGG
 GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
 GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLT
 40 VSSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
 KLLIYSASFLYSGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKEI
 K

[00488] SEQ ID NO: 171:

45 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAN
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRWTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVPAAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 50 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA

FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGSGGG
 5 GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
 GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTTLVT
 VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
 KLLIYSASFVLYSGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKEI
 K

10

[00489] SEQ ID NO: 172:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAP
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 15 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTRKQRADLGAY
 LNPRPPAPEAWSEPVLAKGSAAYSSDLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 20 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGSGGG
 GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
 25 GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTTLVT
 VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
 KLLIYSASFVLYSGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKEI
 K

[00490] SEQ ID NO: 173:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAS
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
 35 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTRKQRADLGAY
 LNPRPPAPEAWSEPVLAKGSAAYSSDLQSMGTGPDGSPFLGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 40 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGSGGG
 GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
 GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTTLVT
 VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
 KLLIYSASFVLYSGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKEI
 45 K

[00491] SEQ ID NO: 174:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAT
 50 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSVVPAYAYRKLHP

KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
5 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTI SKAKGQPREPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSGSSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLLV
10 VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGRSGTDFTLTLSISLQPEDFATYYCQQHYTTPPTFGQGTKEI
K

[00492] SEQ ID NO: 175:

15 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQAEQRASKKDEHAELIVLRRGDYDAN
THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
20 TNDGLDFQESQLVKKLVEPPPAGCQGSVISFPSRSGPGSPAQWLLYTHPTHKQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTI SKAKGQPREPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
25 TPPVLDSGSSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLLV
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGRSGTDFTLTLSISLQPEDFATYYCQQHYTTPPTFGQGTKEI
30 K

[00493] SEQ ID NO: 176:

35 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHARQADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
40 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTI SKAKGQPREPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSGSSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGSGGG
GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
45 GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLLV
VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
KLLIYSASFLYSGVPSRFSGRSGTDFTLTLSISLQPEDFATYYCQQHYTTPPTFGQGTKEI
K

50 [00494] SEQ ID NO: 177:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFQAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 5 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 10 TPPVLDSGSEFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGGSGGG
 GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
 GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLLV
 VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
 KLLIYSASFLYSGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKEI
 15 K

[00495] SEQ ID NO: 178:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFQAEQRASKKDEHAELIVLRRGDYDAG
 20 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 25 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSGSEFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGGSGGG
 GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
 30 GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLLV
 VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
 KLLIYSASFLYSGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKEI
 K

35 [00496] SEQ ID NO: 179:

X₁ASLPX₂LQX₃ESVVFQSGAHAYRIPALLYLPGQQSLLAFQAEQRASKKDEHAELIVLRRGDYD
 AX₄THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₅QTGTLFLFFIAIPGQVTEQQQLQTRANV
 40 TRLCX₆VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRK
 LHPX₇QRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRX₈RV
 QAQSTNDGLDFQESQLVKKLVEPPPX₉GCQGSVISFPSRSGPGSPAQWLLYTHPTHX₁₀X₁₁Q
 RADLGAYLNPRPPAPEAWSEPVLAKGSX₁₂AYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIX₁₃
 FX₁₄MFTLKQAFPAEYLPQX₁₅DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
 VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
 45 NKALPAPIEKTISKAKGQPREPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
 PENNYKTPPVLDSGSEFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
 GGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWV
 ARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDY
 50 GQGTLLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQ
 QKPGKAPKLLIYSASFLYSGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFG
 QGTKEI

[00497] SEQ ID NO: 180:

X₁X₂SX₃X₄X₅LQX₆ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX₇X₈DEHAELIVX₉RR
 GDYDAX₁₀THQVQWX₁₁AQEVVAQAX₁₂LX₁₃GHRSMNPCPLYDX₁₄QTGTLFLFFIAIPX₁₅X₁₆V
 5 TEX₁₇QQLQTRANVTRLX₁₈X₁₉VTSTDHGRTWSSPRDLTDAAIGPX₂₀YREWSTFAVGPGHX₂₁L
 QLHDX₂₂X₂₃RSLVVPAYAYRKLHPX₂₄X₂₅X₂₆P I P S A F X₂₇FLSHDHGRTWARGHFVX₂₈QDTX₂₉
 ECQVAEVX₃₀TGEQVRVVTLNARSX₃₁X₃₂X₃₃X₃₄RX₃₅QAQX₃₆NX₃₇GLDFQX₃₈X₃₉QX₄₀VKKL
 X₄₁EPPPX₄₂GX₄₃QGSVISFSPSRSGPGSPAQX₄₄LLYTHPTHX₄₅X₄₆QRADLGAYLNPRPPAP
 EAWSEPX₄₇LLAKGSX₄₈AYSDLQSMGTGPDGSPLFGX₄₉LYEANDYEEIX₅₀FX₅₁MFTLKQAFP
 10 AEYLPQX₅₂DKHTCPCPPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
 FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT I
 SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL
 DSDGSEFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGSGGGGSGGG
 GSEVQLVESGGGLVQPGGSLRLSCAASGFTNIDTYIHWRVQAPGKGLEWVARIYPTNGYTRY
 15 ADSVKGRFTISADTSKNTAYLQMNSLRAREDVAVYYCSRWGGDGFYAMDYWGQGLTVTVSSGG
 GSGGGGSGGGGSDIQMTQSPSSLSASVGRVITITCRASQDVNTAVAWYQQKPGKAPKLLIY
 SASFLYSGVPSRFSGRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

[00498] SEQ ID NO: 181:

20 gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 AATTCCTCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGG
 CCAGCAAGAAGGATGAGCACGCCGAAGTATCTGCTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGCCACAG
 25 ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCGACTG
 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCCTATAGAAAGCTGCACCCC
 30 AAACAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 CAGAGGACATTTCTGTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGGCG
 AGCAGAGAGTCTGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCAGAGC
 ACAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCC
 AaccGGCTGTGAGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
 35 CTCAGTGGCTGTGTATACACACCCACACAGCTGGCAGAGAGCCGATCTGGGCGCCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCTGAAGCAGGCC
 TTTCCAGCCGAGTACCTGCCTCAA

[00499] SEQ ID NO: 182:

45 X₁X₂SX₃X₄X₅LQX₆ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASX₇X₈DEHAELIVX₉RR
 GDYDAX₁₀THQVQWX₁₁AQEVVAQAX₁₂LX₁₃GHRSMNPCPLYDX₁₄QTGTLFLFFIAIPX₁₅X₁₆V
 TEX₁₇QQLQTRANVTRLX₁₈X₁₉VTSTDHGRTWSSPRDLTDAAIGPX₂₀YREWSTFAVGPGHX₂₁L
 QLHDX₂₂X₂₃RSLVVPAYAYRKLHPX₂₄X₂₅X₂₆P I P S A F X₂₇FLSHDHGRTWARGHFVX₂₈QDTX₂₉
 ECQVAEVX₃₀TGEQVRVVTLNARSX₃₁X₃₂X₃₃X₃₄RX₃₅QAQX₃₆NX₃₇GLDFQX₃₈X₃₉QX₄₀VKKL
 X₄₁EPPPX₄₂GX₄₃QGSVISFSPSRSGPGSPAQX₄₄LLYTHPTHX₄₅X₄₆QRADLGAYLNPRPPAP
 EAWSEPX₄₇LLAKGSX₄₈AYSDLQSMGTGPDGSPLFGX₄₉LYEANDYEEIX₅₀FX₅₁MFTLKQAFP
 50 AEYLPQ

[00500] SEQ ID NO: 183:

X₁ASLPX₂LQX₃ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYD
 AX₄THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₅QTGTLFLFFIAIPGQVTEQQQLQTRANV
 5 TRLCX₆VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
 LHPX₇QRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRX₈RV
 QAQSTNDGLDFQESQLVKKLVEPPPX₉GCQGSVISFSPSPRSGPGSPAQWLLYTHPTHX₁₀X₁₁Q
 RADLGAYLNP RPPEAWSEPVLLAKGSX₁₂AYS DLQSMGTGPDGSPLFGCLYEANDYEEIX₁₃
 FX₁₄MFTLKQAFPAEYLPQ

10

[00501] SEQ ID NO: 184:

GGGGS

15 [00502] SEQ ID NO: 185:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 20 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFSPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNP RPPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
 DEPVKENWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 25 IEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK

[00503] SEQ ID NO: 186:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 AATTCCCCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGG
 CCAGCAAGAAGGATGAGCACGCCGAAGTATCGTGTCTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 35 CTATCCCCGGCCAAAGTGACCGAGCAGCAGCTGCAGACAAGAGCCAACGTGACCCAGACTG
 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 40 CAGAGGACATTTCTGTTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGGCG
 AGCAGAGAGTCTGACCTGAACGCCAGATCTCACCTGAGAGCCAGAGTGCAGGCCAGAGC
 ACAAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCC
 AaccGGCTGTGAGGAAGCGTGATCAGCTTTCATCTCCTAGAAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 45 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 CgctGCCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCACC
 GTGCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCCTCTTCCCCCAAACCCAAAGG
 50 ACACCCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAA
 GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCTGGAGGTGCATAATGCCAAGACAAA

GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCC
 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGtaCTGCCTGGTCAAAGGCTTCT
 5 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACC
 ACGCTCCCGTGTCTGGACTCCGACGGCTCCTTCTCCTCtatAGCAAGCTCACCGTGGACAA
 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGTAAA

10 **[00504]** SEQ ID NO: 187:

DASLPYLGKESVVFQSGAHAYRIPALLYLPQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAIGPAYREWSTFAVGPQHCLQLHDRARSLVVPAYAYRKLHP
 15 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFSPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKENWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 20 IEKTIISKAKQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00505] SEQ ID NO: 188:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 AATCCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGG
 CCAGCAAGAAGGATGAGCACGCCGAACCTGATCGTGTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 30 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 35 CAGAGGACATTTCTGGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGGCG
 AGCAGAGAGTCTGTGACCCTGAACGCCAGATCTCACCTGAGAttcAGAGTGCAGGCCCAGAGC
 ACAAACGACGGCCTGGATTTCGAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
 AaccGGCTGTGAGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 40 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCACC
 GTGCCAGCACCTGAACCTCCTGGGGGACCGTCAGTCTTCTCTCCCCCAAACCCAAGG
 45 ACACCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAA
 GACCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCC
 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 50 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGtaCTGCCTGGTCAAAGGCTTCT
 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACC

ACGCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTCCTCtatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

5 [00506] SEQ ID NO: 189:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYAD
SVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
10 SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFCFSVMHEA
LHNHYTQKSLSLSPGK

15

[00507] SEQ ID NO: 190:

GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGCCTGGCGGATCTCTGAGACTGTC
TTGTGCCGCCAGCGGCTTCAACATCAAGGACACCTACATCCACTGGGTCCGACAGGCCCCCTG
20 GCAAAGGACTTGAATGGGTGCGCCAGAATCTACCCACCAACGGCTACACCAGATACGCCGAC
TCTGTGAAGGGCAGATTACCATCAGCGCCGACACCAGCAAGAACACCGCCTACCTGCAGAT
GAACAGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTTCTAGATGGGGAGGCGACGGCT
TCTACGCCATGGATTATTGGGGCCAGGGCACCCCTGGTCACCGTTTCTTCTGCTagcACCAAG
GGCCCCATCgGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCT
25 GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCcTGGAACCTCAGGCGCtC
TGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTACTCCCTCAGC
AGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA
CAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACCTCACA
CATGCCCACCGTGCCAGCACCTGAACCTCCTGGGGGGACCGTCAGTCTTCTCTTCCCCCCA
30 AAACCCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGGTGCACATGCGTGGTGGTGGACGT
GAGCCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG
CCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACC
GTCTTGACACAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
CCCAGCCCCCATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcT
35 ACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTACAGCCTGACCTGCCTGGTC
AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAA
CTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCacTAGCAAGCTCA
CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

40

[00508] SEQ ID NO: 191:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
45 CYVTSTDHGRTWSSPRDLTDAAGPAYREWSTFAVGPQHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQVAEVETGEQRVVTLNARSHLRARVQAQS
TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
FPAEYLPQ

50

[00509] SEQ ID NO: 192:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 5 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 10 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSGDSFFLTSLKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00510] SEQ ID NO: 193:

15 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 20 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSGDSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
 25

[00511] SEQ ID NO: 194:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 30 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 35 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSGDSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGGSGGG
 GSGGGGSEVQLVESGGGLVQPGGSLRLS CAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
 GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLT
 40 VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
 KLLIYSASFYSGVPSRFSGRSGTDFTLT ISSLQPEDFATYYCQQHYTTPPTFGQGTKEI
 K

[00512] SEQ ID NO: 195:

45 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRARVQAQS
 50 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA

FPAEYLPQGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTTPVLDSDGSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

5

[00513] SEQ ID NO: 196:

DASLPYLQKESV FQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 10 CYVTSTDHGR TWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGR TWARGHFVAQDTLE CQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSP LFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 15 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTTPVLDSDGSFFLY SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00514] SEQ ID NO: 197:

DASLPYLQKESV FQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 20 CYVTSTDHGR TWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGR TWARGHFVAQDTLE CQVAEVETGEQRVVTLNARSHLRARVQAQS
 25 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSP LFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGSGGGGSDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 30 NNYKTTTPVLDSDGSFFLY SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGKGGG
 GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
 IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
 GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
 PGKAPKLLIYSASFLYSGVPSRFSGRSGTDFTLTISSLQPEDFATYYCQHHYTTPTFGQG
 35 TKVEIK

[00515] SEQ ID NO: 198:

DASLPYLQKESV FQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
 40 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGR TWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGR TWARGHFVAQDTLE CQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSP LFGCLYEANDYEEIVFLMFTLKQA
 45 FPAEYLPQ

[00516] SEQ ID NO: 199:

X₁X₂SX₃X₄X₅LQX₆ESV FQSGAHAYRIPALLYLPGQQSLLAFAEQRX₇SX₈X₉DEHAELIVX₁₀R
 50 RGDYDAX₁₁THQVQWX₁₂AQEVVAQAX₁₃LX₁₄GHRSMNPCPLYDX₁₅QTGTLFLFFIAIPX₁₆X₁₇
 VTEX₁₈QQQLQTRANVTRLX₁₉X₂₀VTSTDHGR TWSSPRDLTDAAIGPX₂₁YREWSTFAVGPGHX₂₂

LQLHDX₂₃X₂₄RSLVVPAYAYRKLHPX₂₅X₂₆X₂₇PIPSAFX₂₈FLSHDHGRTWARGHFVX₂₉QDTX
 30ECQVAEVX₃₁TGEQRVVTLNARSX₃₂X₃₃X₃₄X₃₅RX₃₆QAQX₃₇NX₃₈GLDFQX₃₉X₄₀QX₄₁VKK
 LX₄₂EPPPX₄₃GX₄₄QGSVISFSPRSGPGSPAQX₄₅LLYTHPTHX₄₆X₄₇QRADLGAYLNPRPPA
 5 PEAWSEPX₄₈LLAKGSX₄₉AYSDLQSMGTGPDGSPLFGX₅₀LYEANDYEEIX₅₁FX₅₂MFTLKQAF
 PAEYLPQ

[00517] SEQ ID NO: 200:

X₁ASLPX₂LQX₃ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX₄SKKDEHAELIVLRRGDYD
 10 AX₅THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₆QTGTFLFLFFIAIPGQVTEQQQLQTRANV
 TRLCX₇VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
 LHPX₈QRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQVAEVETGEQRVVTLNARSHLRX₉RV
 QAQSTNDGLDFQESQLVKKLVEPPPX₁₀GCQGSVISFSPRSGPGSPAQWLLYTHPTHX₁₁X₁₂
 15 QRADLGAYLNPRPPAPEAWSEPVLLAKGSX₁₃AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX
 14FX₁₅MFTLKQAFPAEYLPQ

[00518] SEQ ID NO: 201:

X₁X₂SX₃X₄X₅LQX₆ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX₇SX₈X₉DEHAELIVX₁₀R
 20 RGDYDAX₁₁THQVQWX₁₂AQEVVAQAX₁₃LX₁₄GHRSMNPCPLYDX₁₅QTGTFLFLFFIAIPX₁₆X₁₇
 VTEX₁₈QQLQTRANVTRLX₁₉X₂₀VTSTDHGRTWSSPRDLTDAAIGPX₂₁YREWSTFAVGPGHX₂₂
 LQLHDX₂₃X₂₄RSLVVPAYAYRKLHPX₂₅X₂₆X₂₇PIPSAFX₂₈FLSHDHGRTWARGHFVX₂₉QDTX
 30ECQVAEVX₃₁TGEQRVVTLNARSX₃₂X₃₃X₃₄X₃₅RX₃₆QAQX₃₇NX₃₈GLDFQX₃₉X₄₀QX₄₁VKK
 LX₄₂EPPPX₄₃GX₄₄QGSVISFSPRSGPGSPAQX₄₅LLYTHPTHX₄₆X₄₇QRADLGAYLNPRPPA
 25 PEAWSEPX₄₈LLAKGSX₄₉AYSDLQSMGTGPDGSPLFGX₅₀LYEANDYEEIX₅₁FX₅₂MFTLKQAF
 PAEYLPQX₅₃DKTHTCPPELPGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
 KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
 ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
 30 LDSGFSFFLTSLKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00519] SEQ ID NO: 202:

X₁ASLPX₂LQX₃ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX₄SKKDEHAELIVLRRGDYD
 35 AX₅THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₆QTGTFLFLFFIAIPGQVTEQQQLQTRANV
 TRLCX₇VTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
 LHPX₈QRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQVAEVETGEQRVVTLNARSHLRX₉RV
 QAQSTNDGLDFQESQLVKKLVEPPPX₁₀GCQGSVISFSPRSGPGSPAQWLLYTHPTHX₁₁X₁₂
 40 QRADLGAYLNPRPPAPEAWSEPVLLAKGSX₁₃AYSDLQSMGTGPDGSPLFGCLYEANDYEEIX
 14FX₁₅MFTLKQAFPAEYLPQX₁₆DKTHTCPPELPGPSVFLFPPKPKDTLMISRTPEVT
 CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
 VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
 GQPENNYKTTPVLDSDGFSFFLTSLKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
 45 K

[00520] SEQ ID NO: 203:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTFLFLFFIAIPGQVTEQQQLQTRANVTRL
 50 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQVAEVETGEQRVVTLNARSHLRFRVQAQS

TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 5 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00521] SEQ ID NO: 204:

10 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 15 LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKTHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPE
 NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

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[00522] SEQ ID NO: 205:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 25 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 30 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00523] SEQ ID NO: 206:

35 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRFRVQAQS
 40 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKTHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPE
 45 NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00524] SEQ ID NO: 207:

50 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHADRARSLVVPAYAYRKLHP

KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 5 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTPPVLDSGDSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00525] SEQ ID NO: 208:

10 DASLPYLQKESVFQSGAHAYRIPALLYLPQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
 15 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 20 TPPVLDSGDSFFLT SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00526] SEQ ID NO: 209:

25 DASLPYLQKESVFQSGAHAYRIPALLYLPQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 30 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTPPVLDSGDSFFLY SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

35 **[00527] SEQ ID NO: 210:**

DASLPYLQKESVFQSGAHAYRIPALLYLPQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 40 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 45 IEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSGDSFFLY SKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00528] SEQ ID NO: 211:

50 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
 YSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF

LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSCSV
MHEALHNHYTQKSLSLSPGK

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[00529] SEQ ID NO: 212:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSCSV
MHEALHNHYTQKSLSLSPGK

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15 [00530] SEQ ID NO: 213:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSCSV
MHEALHNHYTQKSLSLSPGK

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[00531] SEQ ID NO: 214:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
YCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSCSV
MHEALHNHYTQKSLSLSPGK

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[00532] SEQ ID NO: 215:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSCSV
MHEALHNHYTQKSLSLSPGK

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[00533] SEQ ID NO: 216:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
YCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSCSV
MHEALHNHYTQKSLSLSPGK

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[00534] SEQ ID NO: 217:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 AATTCCCCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
 ggAGCAAGAAGGATGAGCACGCCGAAGTATCGTGTGCGGAGAGGCGATTACGACGCCggc
 5 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
 10 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 CAGAGGACATTTCTGTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGCGC
 AGCAGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTTCAGAGTGCAGGCCAGAGC
 ACAAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCC
 15 AaccGGCTGTGAGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 20 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTCTGACAAAACCTCACACATGCCCACC
 GTGCCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCTCTTCCCCCAAACCCAAGG
 ACACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAA
 GACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCTGCACC
 25 AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
 ATCGAGAAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTGACCTGACCTGCCTGGTCAAAGGCTTCT
 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACC
 ACGCCTCCCGTGTGACTCCGACGGCTCCTTCTCCTCtatAGCAAGCTCACCGTGGACAA
 30 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00535] SEQ ID NO: 218:

35 DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 40 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQKSLSLSPGK
 45

[00536] SEQ ID NO: 219:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 AATTCCCCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
 50 ggAGCAAGAAGGATGAGCACGCCGAAGTATCGTGTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG

ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 TGTTacGTGACCTCCACCGACCACGGCAGAACCCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTGGACCTGGACACTGTCTCC
 5 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 CAGAGGACATTTTCGTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
 AGCAGAGAGTTCGTGACCCTGAACGCCAGATCTCACCTGAGATTTCAGAGTGCAGGCCAGAGC
 ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACTCCTCC
 10 AaccGGCTGTGAGGAAGCGTGATCAGCTTTCCATCTCCTAGAAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGGAGCTGGAGCGAACCTGTTCTGCTGGCCAAAGGCGAG
 CgctGCCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 15 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTcTGACAAAACCTCACACATGCCCACC
 GTGCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCCTCTTCCCCCAAACCCAAAGG
 ACACCCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
 GACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCGCGGGAGGAGCAGTACgcAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
 20 AGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCTGACCTGCCTGGTCAAAGGCTTCT
 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGAGCCGGAGAACAACTACAAGACC
 ACGCCTCCCGTGTGGACTCCGACGGCTCCTTCTTCTCTATAGCAAGCTCACCGTGGACAA
 25 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTAAGcTTGTCTCCGGGTAAA

[00537] SEQ ID NO: 220:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQGTFLFLFFIAIPGQVTEEQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAGIPAYREWSTFAVGPQHCLQLHDRARSLVVPAYAYRKLHP
 KQRPISAFcFLSHDHGRTWARGHFVAQDTLEcQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
 35 LNPRPPAPEAWSEPVLAKGSAAYSSDLQSMGTGPDGSPLFGLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGK

40

[00538] SEQ ID NO: 221:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCACGCCTACAG
 AATTCCCCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTTCGCTGAACAGCGGc
 45 ggAGCAAGAAGGATGAGCAGCCGAATGATCGTGTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGACGTGGCAGGCTCAAGAGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGgaaCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 TGTTacGTGACCTCCACCGACCACGGCAGAACCCTGGTCTAGCCCTAGAGATCTGACCGACGC
 50 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC

AACACGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 CAGAGGACATTTCTGTTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGGCG
 AGCAGAGAGTTCGTGACCCTGAACGCCAGATCTCACCTGAGATTTCAGAGTGCAGGCCCAGAGC
 ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCC
 5 AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 10 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACC
 GTGCCCAGCACCTGAACCTCCTGGGGGACCGTCAGTCTTCTCTTCCCCCAAACCCAAAGG
 ACACCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAA
 GACCTTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCTCACCCTCCTGCACC
 15 AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCAGCCCCC
 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTACGCTGACCTGCCTGGTCAAAGGCTTCT
 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACC
 ACGCTCCCGTGTCTGGACTCCGACGGCTCCTTCTTCTCtatAGCAAGCTCACCGTGGACAA
 20 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTA

[00539] SEQ ID NO: 222:

25 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAGPAYREWSTFAVGPGLHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVCTGEQVRVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPCQWLLYTHPTHSWQRADLGAY
 30 LNRPFPAPPAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
 35

[00540] SEQ ID NO: 223:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCACGCCTACAG
 AATTCCCCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCTGCTGAACAGCGGc
 40 ggAGCAAGAAGGATGAGCACGCCGAAGTATCGTGTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 45 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 CAGAGGACATTTCTGTTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTgtgTACCGGCG
 AGCAGAGAGTTCGTGACCCTGAACGCCAGATCTCACCTGAGATTTCAGAGTGCAGGCCCAGAGC
 50 ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCC
 AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAAGCGGCCCTGGCTCTCCTt

gtCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCTGAAGCAGGCC
 5 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCCACC
 GTGCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCTCTCCCCCAAAACCAAGG
 ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
 GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCTGCACC
 10 AGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCCGGGAGGAGATGACCAAGAACCAGGTGACCGTGACCTGCCTGGTCAAAGGCTTCT
 ATCCCGAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACATAAGACC
 ACGCCTCCCGTGTCTGGACTCCGACGGCTCCTTCTTCTCtataGCAAGCTCACCGTGGACAA
 15 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00541] SEQ ID NO: 224:

20 ASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAGT
 HQVQWQAQEVVAQARLDGHRSMNPNPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRLC
 YVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHPK
 QRPISAFCLSHDHGRTWARGHFVAQDTLECCQVAEVETGEQRVVTLNARSHLRFVRVQAQST
 NDGLDFQESQLVKKLVEPPPTGCQGSVISFSPSRSGPGSPAQWLLYTHPTHSWQRADLGLAYL
 25 NRPPEAPEAWSEPVLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQAF
 PAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHED
 PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
 EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
 PPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

30

[00542] SEQ ID NO: 225:

GCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAGAAT
 TCCCGCTCTGCTGTATCTGCCAGGCCAGCTCTCTGCTGGCTTTCGCTGAACAGCGGcgga
 35 GCAAGAAGGATGAGCACGCCGAAGTATCGTGTGCTGCGGAGAGGCGATTACGACGCCggcACA
 CATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGCCACAGATC
 TATGAACCCCTGTCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCGCTA
 TCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTGTGT
 tacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGCCGC
 40 CATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTGGACCTGGACACTGTCTCCAGC
 TGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCCTACGCCTATAGAAAGCTGCACCCAAA
 CAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGCCAG
 AGGACATTTCTGTTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGGCGAGC
 AGAGAGTCGTGACCCTGAACGCCAGATCTCACCTGAGATTGAGAGTGCAGGCCAGAGCACA
 45 AACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCCAac
 cGGCTGTGAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTGCTC
 AGTGGCTGTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTACCTG
 AATCCTAGACCTCCTGCTCCTGAGGCTTGAGCGAACCTGTTCTGCTGGCCAAGGGCAGCgc
 tGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCTGTC
 50 TGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCTGAAGCAGGCCTTT
 CCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACCGTG

CCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCC AAAACCCAAGGACA
 CCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGAC
 CCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCC
 GCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGG
 5 ACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATC
 GAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCCCCC
 ATCCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTATC
 CCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACATAAGACCACG
 CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCGTGGACAAGAG
 10 CAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT
 ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00543] SEQ ID NO: 226:

15 DASLPVLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAIGPAYREWSTFAVGPQHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 20 LNRPPEAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTI SKAKGQPREPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK
 25

[00544] SEQ ID NO: 227:

gatGCATCTCTGCCTgtgCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 AATTCCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTTCGCTGAACAGCGGc
 30 ggAGCAAGAAGGATGAGCACGCCGAAGTATCGTGTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 TGTTacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 35 CGCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTGAGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGGCTGCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 CAGAGGACATTTTCGTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGGCG
 AGCAGAGAGTTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
 40 ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGTGGTCAAGAACTGGTGGAACCTCCTCC
 AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 45 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 TTTCAGCCGAGTACCTGCCTCAAGAGGCCAAATCTTCTGACAAAACACACATGCCACC
 GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCC AAAACCCAAGG
 ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
 GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 50 GCCCGGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCTGCACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCCAGCCCC

ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTcAGCCTGACCTGCCTGGTCAAAGGCTTCT
 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACC
 ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTCCTCtatAGCAAGCTCACCGTGGACAA
 5 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00545] SEQ ID NO: 228:

10 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRASKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDPHGRTWSSPRDLTDAAGPAYREWSTFAVGPCHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECCQVAEVETGEQVRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
 15 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSTMHEALHNHYTQKSLSLSPGK
 20

[00546] SEQ ID NO: 229:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 25 AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGG
 CCAGCAAGAAGGATGAGCACGCCGAACCTGATCGTGTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGCCACAG
 ATCTATGAACCCCTGTCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 30 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 CAGAGGACATTTCTGGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGGCG
 35 AGCAGAGAGTCTGACCTGAACGCCAGATCTACCTGAGATTACAGAGTGCAGGCCACAGC
 ACAAAACGACGGCTGGATTTCGAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
 AaccGGCTGTGAGGAAGCGTGATCAGCTTTCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 40 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCACC
 GTGCCAGCACCTGAACCTCTGGGGGACCGTCAGTCTTCCTCTTCCCCCAAACCCAAGG
 ACACCCTCATGATCTCCCGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAA
 45 GACCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCTGCACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCAGCCCCC
 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTcAGCCTGACCTGCCTGGTCAAAGGCTTCT
 50 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACC
 ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTCCTCtatAGCAAGCTCACCGTGGACAA

GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00547] SEQ ID NO: 230:

5 DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAP
THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQQRVVTLNARSHLRFRVQAQS
10 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFSPSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
LNPRPPAPEAWSEFVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLTKQA
FPAEYLPQEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
15 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK

[00548] SEQ ID NO: 231:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
20 AATTCCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTTCGCTGAACAGCGGc
ggAGCAAGAAGGATGAGCACGCCGAAGTATCGTGCTGCGGAGAGGCGATTACGACGCCcct
ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCACTG
25 TGTTacGTGACCTCCACCGACCACGGCAGAACCCTGGTCTAGCCCTAGAGATCTGACCGACGC
CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCCGTTGGACCTGGACACTGTCTCC
AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCCTATAGAAAGCTGCACCCC
AAACAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
CAGAGGACATTTCTGTTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGGCG
30 AGCAGAGAGTCTGACCCCTGAACGCCAGATCTCACCTGAGATTACAGAGTGCAGGCCCAGAGC
ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCC
AaccGGCTGTACAGGAAGCGTGATCAGCTTTCCATCTCCTAGAAAGCGGCCCTGGCTCTCCTG
CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
35 CgttGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCACC
GTGCCACGACCTGAACCTCCTGGGGGACCGTCAGTCTTCCTCTTCCCCCAAACCCAAAGG
ACACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAA
40 GACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCTGCACC
AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
ATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAACACAGGTcTACACCCTGCC
CCCATCCCGGGAGGAGATGACCAAGAACCAGGTACGCTGACCTGCCTGGTCAAAGGCTTCT
45 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
ACGCCCTCCCGTGTGACTCCGACGGCTCCTTCTTCTCCTctatAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

50 [00549] SEQ ID NO: 232:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDAQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRFRVQAQS
 5 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKENWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIISKAKGQPREPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 10 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKSLSLSPGK

[00550] SEQ ID NO: 233:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 15 AATTCCTCGTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
 ggAGCAAGAAGGATGAGCACGCCGAAGTATCGTGTCTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCCTCTGTACGATgccCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 20 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCTTATTCCTAGCGCCTTCTGCTTTCTGAGCCACGATCAGGCAGGACATGGGC
 CAGAGGACATTTCTGTTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGCGC
 25 AGCAGAGAGTCTGTGACCCTGAACGCCAGATCTCACCTGAGATTTCAGAGTGCAGGCCCAGAGC
 ACAAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACTCCTCC
 AaccGGCTGTGAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 30 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACC
 GTGCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCTCTTCCCCCAAACCCAAGG
 ACACCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAA
 35 GACCTTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCCGGGGAGGAGCAGTACAACAGCACGTACCCTGTGGTCAGCGTCCTCACCCTCCTGCACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCAGCCCCC
 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTACGCTGACCTGCCTGGTCAAAGGCTTCT
 40 ATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACC
 ACGCCTCCCGTGTCTGGACTCCGACGGCTCCTTCTTCTCtatAGCAAGCTCACCCTGGACAA
 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

45 [00551] SEQ ID NO: 234:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CQVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 50 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY

LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 5 TPPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00552] SEQ ID NO: 235:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCCAGTCTGGCGCCACGCCTACAG
 10 AATTC CCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTTCGCTGAACAGCGGc
 ggAGCAAGAAGGATGAGCACGCCGAAC TATCGTGCTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGCCACAG
 ATCTATGAACCCCTGTCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 15 TGTcagGTGACCTCCACCGACCACGGCAGAACCCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 CAGAGGACATTTTCGTGGCC CAGGACACACTGGAATGCCAGGTGGCCGAAGTGAAACCGGCG
 20 AGCAGAGAGTTCGTGACCCTGAACGCCAGATCTCACCTGAGATT CAGAGTGCAGGCCAGAGC
 ACAAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAAACTGGTGGAACCTCCTCC
 AaccGGCTGT CAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCTAGACCTCCTGCTCCTGAGGCTTGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 25 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACC
 GTGCCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCCTCTTCCCCCAAACCCAAGG
 ACACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAA
 30 GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGT CAGCCTGACCTGCCTGGTCAAAGGCTTCT
 35 ATCCACGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
 ACGCCTCCCGTGTCTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCCTGGACAA
 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

40 **[00553] SEQ ID NO: 236:**

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPQHCLQLHDRARSLVVPAYAYRKLHP
 45 IQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQVAEVETGEQRRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 50 IEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[00554] SEQ ID NO: 237:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 5 AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
 ggAGCAAGAAGGATGAGCACGCCGAAGTATCGTGTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 10 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTACGCCTATAGAAAGCTGCACCCC
 atcCAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 CAGAGGACATTTCTGGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGAAACCGGCG
 15 AGCAGAGAGTCTGACCCCTGAACGCCAGATCTCACCTGAGATTcAGAGTGCAGGCCCAGAGC
 ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCC
 AaccGGCTGTcAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 20 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTcACCCTGAAGCAGGCC
 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACC
 GTGCCCAGCACCTGAACCTCCTGGGGGACCGTCAGTCTTCTCCTCTCCCCCAAACCAAGG
 ACACCCCTCATGATCTCCCGGACCCCTGAGGTcACATGCGTGGTGGTGGACGTGAGCCACGAA
 25 GACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCCGGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTcAGCGTCCTCACCGTCTGCACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
 ATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCCGGGAGGAGATGACCAAGAACCAGGTcAGCCTGACCTGCCTGGTCAAAGGCTTCT
 30 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACC
 ACGCCTCCCGTGTCTGGACTCCGACGGCTCCTTCTCCTCtatAGCAAGCTCACCGTGGACAA
 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAG

35 **[00555]** SEQ ID NO: 238:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNCPPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVSTSDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 40 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRARVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNRPPPAPEAWSEPVLLAKGSAAYSDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 45 IEKTIKAKGQPREPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNQGPNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00556] SEQ ID NO: 239:

50 gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc

ggAGCAAGAAGGATGAGCACGCCGAACCTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 5 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 CAGAGGACATTTCTGTTGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAACCGGCG
 10 AGCAGAGAGTTCGTGACCTGAACGCCAGATCTCACCTGAGAgccAGAGTGCAGGCCCAGAGC
 ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCC
 AaccGGCTGTGAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 15 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACC
 GTGCCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCTCTTCCCCCAAACCCAAGG
 ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
 20 GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCTGCACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
 ATCGAGAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCTGGCC
 CCCATCCCCGGGAGGAGATGACCAAGAACCAGGTACGCTGACCTGCCTGGTCAAAGGCTTCT
 25 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACC
 ACGCCTCCCGTGTGACTCCGACGGCTCCTTCTTCTCtatAGCAAGCTCACCGTGGACAA
 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGTAAA

30 [00557] SEQ ID NO: 240:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAIGPAYREWSTFAVGPQHCLQLHDRARSLVVPAYAYRKLHP
 35 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPQGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 40 IEKTIKAKAQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00558] SEQ ID NO: 241:

45 gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 AATTCCCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
 ggAGCAAGAAGGATGAGCACGCCGAACCTGATCGTGCTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 50 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC

CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 CAGAGGACATTTCTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
 5 AGCAGAGAGTTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC
 ACAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACTCCTCC
 AcagGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 10 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 TTTCCAGCCAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTACACATGCCACC
 GTGCCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGG
 ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
 15 GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCTGCACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
 ATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTcAGCCTGACCTGCCTGGTCAAAGGCTTCT
 20 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
 ACGCCTCCCGTGTCTGGACTCCGACGGCTCCTTCTTCTCtatAGCAAGCTCACCGTGGACAA
 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGTAAA

25 [00559] SEQ ID NO: 242:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAGPAYREWSTFAVGPHCLQLHDRARSLVVPAYAYRKLHP
 30 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSCAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLTKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 35 IEKTIISKAKGQPREPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK

[00560] SEQ ID NO: 243:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 AATTCCCCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCTGCTGAACAGCGGc
 ggAGCAAGAAGGATGAGCACGCCGAAGTATCGTGTCTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 45 CTATCCCCGGCCAAGTGACCGAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 TGTTacGTGACCTCCACCGACACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTAGCGCCTTCTGCTTTCTGAGCCACGATCACGGCAGGACATGGGC
 50 CAGAGGACATTTCTGGCCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGGAAACCGGCG
 AGCAGAGAGTTCGTGACCCTGAACGCCAGATCTCACCTGAGATTCAGAGTGCAGGCCCAGAGC

ACAAACGACGGCCTGGATTTC AAGAGAGCCAGCTGGTCAAGAACTGGTGGAACCTCCTCC
 AaccGGCTGTCAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAAGCGGCCCTGGCTCTCCTG
 CTCAGTGCGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 5 CtgtGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTTCTGACAAAACCTCACACATGCCACC
 GTGCCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCCTCTTCCCCCAAAACCAAGG
 ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
 10 GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCCTCCTGCACC
 AGGACTGCAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAGCCCTCCGAGCCCCC
 ATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCT
 15 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACC
 ACGCCTCCCGTGTGGACTCCGACGGCTCCTTCTTCCTCtatAGCAAGCTCACCCTGGACAA
 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGTAAA

20 [00561] SEQ ID NO: 244:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNCPPLYDEQGTGLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 25 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQCQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVPEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNRPPEPAEAWSEPVLLAKGSAAYS DLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVV
 DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
 30 ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
 NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGKGGG
 GSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAR
 IYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQ
 GTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQK
 35 PGKAPKLLIYSASFLYSGVPSRFSRSGTDFTLTISSLQPEDFATYYCQQHYTTPTFTGQG
 TKVEIK

[00562] SEQ ID NO: 245:

GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGCCTGGCGGATCTCTGAGACTGTC
 TTGTGCCGCCAGCGGCTTCAACATCAAGGACACCTACATCCACTGGGTCCGACAGGCCCCCTG
 GCAAAGGACTTGAATGGGTCGCCAGAATCTACCCCAACACGGCTACACCAGATACGCCGAC
 TCTGTGAAGGGCAGATTACCATCAGCGCCGACACCAGCAAGAACACCGCCTACCTGCAGAT
 GAACAGCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTCTTAGATGGGGAGGCGACGGCT
 45 TCTACGCCATGGATTATTGGGGCCAGGGCACCCCTGGTCACCGTTTCTTCTGCTagcACCAAG
 GGCCCATCcgTCTTCCCCCTGGCACCCCTCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCT
 GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCcTGGAACCTCAGGCGCtC
 TGACCAGCGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTACTCCCTCAGC
 AGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA
 50 CAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACCTCACA
 CATGCCCACCGTGCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCCTCTTCCCCCA

AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGT
 GAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG
 CCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACC
 5 GTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
 CCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcT
 ACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGACCTGACCTGCCTGGTC
 AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAA
 CTACAAGACCACGCCTCCCGTGTGGACTCCGACGGCTCCTTCTTCCTCaccAGCAAGCTCA
 10 CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
 CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

[00563] SEQ ID NO: 246:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 15 AATTCCTCGCTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
 ggAGCAAGAAGGATGAGCACGCCGAAGTATCGTGTCTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 20 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTTAGCGCCTTCTGCTTTCTGAGCCACGATCAGGCAGGACATGGGC
 CAGAGGACATTTCTGGGCCAGGACACACTGGAATGCCAGGTGGCCGAAGTGAAACCGGCG
 25 AGCAGAGAGTCTGTGACCCTGAACGCCAGATCTCACCTGAGATTGAGAGTGCAGGCCCAGAGC
 ACAAAACGACGGCCTGGATTTCGAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACTCCTCC
 AaccGGCTGTGAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 30 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAAATCTCTGACAAAACCTCACACATGCCCACC
 GTGCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCTCTTCCCCCAAACCCAAGG
 ACACCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
 35 GACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCCAGCCCCC
 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTGACCTGtaCTGCCTGGTCAAAGGCTTCT
 40 ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACC
 ACGCCTCCCGTGTCTGGACTCCGACGGCTCCTTCTTCTCtatAGCAAGCTCACCGTGGACAA
 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

45 [00564] SEQ ID NO: 247:

X₁ASLPX₂LQX₃ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX₄SKKDEHAELIVLRRGDYD
 AX₅THQVQWQAQEVVAQARLDGHRSMNPCPLYDX₆QTGTLFLFFIAIPGQVTEQQQLQTRANV
 50 TRLCX₇VTSTDHGRTWSSPRDLTDAAGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRK
 LHPX₈QRPIPSAFCFLSHDHGRTWARGHFVAQDTLECQVAEVETGEQRVVTLNARSHLRX₉RV
 QAQSTNDGLDFQESQLVKKLVEPPPX₁₀GCQGSVISFSPSPRSGPSPAQWLLYTHPTHX₁₁X₁₂

QRADLGAYLNPRPPAPEAWSEPVLLAKGSX₁₃AYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIX
₁₄FX₁₅MFTLKQAFPAEYLPQX₁₆DKHTCPCPPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
 CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
 VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
 5 GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
 KGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLE
 WVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMD
 YWQGQTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAW
 YQQKPGKAPKLLIYSASFLYSGVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPT
 10 FGQGTKVEIK

[00565] SEQ ID NO: 248:

X₁X₂SX₃X₄X₅LQX₆ESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRX₇SX₈X₉DEHAELIVX₁₀R
 15 RGDYDAX₁₁THQVQWX₁₂AQEVVAQAX₁₃LX₁₄GHRSMNPCPLYDX₁₅QTGTLFLFFIAIPX₁₆X₁₇
 VTEX₁₈QQLQTRANVTRLX₁₉X₂₀VTSTDHGRTWSSPRDLTDAAIGPX₂₁YREWSTFAVGPGHX₂₂
 LQLHDX₂₃X₂₄RSLVVPAYAYRKLHPX₂₅X₂₆X₂₇PIPSAFX₂₈FLSHDHGRTWARGHFVX₂₉QDTX
₃₀ECQVAEVX₃₁TGEQRVVTLNARSX₃₂X₃₃X₃₄X₃₅RX₃₆QAQX₃₇NX₃₈GLDFQX₃₉X₄₀QX₄₁VKK
 LX₄₂EPPIX₄₃GX₄₄QGSVISFSPRSGPGSPAQX₄₅LLYTHPTHX₄₆X₄₇QRADLGAYLNPRPPA
 20 PEAWSEPX₄₈LLAKGSX₄₉AYSDDLQSMGTGPDGSPFLFGX₅₀LYEANDYEEIX₅₁FX₅₂MFTLKQAF
 PAEYLPQX₅₃DKHTCPCPPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
 KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
 ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
 LDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGG
 25 GGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTR
 YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQTLVTVSSG
 GGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAPKLLI
 YSASFLYSGVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

30 [00566] SEQ ID NO: 249:

DASLPYLQKESVFQSGAHAYRIPALLYLPGQQSLLAFAEQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPGQVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 35 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLEQVAEVETGEQRVVTLNARSHLRFRVQAQS
 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFSPRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPFLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKHTCPCPPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 40 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGGSGGG
 GSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN
 GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQTLVTV
 VSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQDVNTAVAWYQQKPGKAP
 45 KLLIYSASFLYSGVPSRFSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

[00567] SEQ ID NO: 250:

DASLPYLQKESVVFQSGAHAYRIPALLYLPGQQSLLAFQRRSKKDEHAELIVLRRGDYDAG
 THQVQWQAQEVVAQARLDGHRSMNPCPLYDEQTGTLFLFFIAIPQOVTEQQQLQTRANVTRL
 CYVTSTDHGRTWSSPRDLTDAAIGPAYREWSTFAVGPGHCLQLHDRARSLVVPAYAYRKLHP
 KQRPIPSAFCFLSHDHGRTWARGHFVAQDTLACQVAEVETGEQRVVTLNARSHLRFRVQAQS
 5 TNDGLDFQESQLVKKLVEPPPTGCQGSVISFPSRSGPGSPAQWLLYTHPTHSWQRADLGAY
 LNPRPPAPEAWSEPVLLAKGSAAYSDDLQSMGTGPDGSPLFGCLYEANDYEEIVFLMFTLKQA
 FPAEYLPQEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
 DPEVKENWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTIKAKGQPREPQVYITLPPSREEMTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKT
 10 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK

[00568] SEQ ID NO: 251:

gatGCATCTCTGCCTTACCTGCAGAAAGAAAGCGTGTTCAGTCTGGCGCCACGCCTACAG
 15 AATTCCTCGTCTGCTGTATCTGCCAGGCCAGCAGTCTCTGCTGGCTTTCGCTGAACAGCGGc
 ggAGCAAGAAGGATGAGCACGCCGAAGTATCGTGTCTGCGGAGAGGCGATTACGACGCCggc
 ACACATCAGGTGCAGTGGCAGGCTCAAGAGGTGGTGGCTCAGGCTAGACTGGACGGCCACAG
 ATCTATGAACCCCTGTCCTCTGTACGATgaaCAGACCGGCACACTGTTTCTGTTCTTTATCG
 CTATCCCCGGCCAAGTGACCGAGCAGCAGCAGCTGCAGACAAGAGCCAACGTGACCAGACTG
 20 TGTtacGTGACCTCCACCGACCACGGCAGAACCTGGTCTAGCCCTAGAGATCTGACCGACGC
 CGCCATCGGACCTGCCTATAGAGAGTGGTCCACCTTCGCCGTTGGACCTGGACACTGTCTCC
 AGCTGCACGACAGGGCTAGATCTCTGGTGGTGCCTGCCTACGCCTATAGAAAGCTGCACCCC
 AAACAGCGGCCTATTCTCTAGCGCCTTCTGCTTTCTGAGCCACGATCAGGCAGGACATGGGC
 CAGAGGACATTTCTGCGCCAGGACACACTGGCCTGCCAGGTGGCCGAAGTGGAACCGGCG
 25 AGCAGAGAGTCTGTGACCCTGAACGCCAGATCTCACCTGAGATTGAGAGTGCAGGCCCAGAGC
 ACAAAACGACGGCCTGGATTTCCAAGAGAGCCAGCTGGTCAAGAACTGGTGGAACTCCTCC
 AaccGGCTGTGAGGGAAGCGTGATCAGCTTTCCATCTCCTAGAAGCGGCCCTGGCTCTCCTG
 CTCAGTGGCTGCTGTATACACACCCACACACAGCTGGCAGAGAGCCGATCTGGGCGCCTAC
 CTGAATCCTAGACCTCCTGCTCCTGAGGCTTGAGCGAACCTGTTCTGCTGGCCAAGGGCAG
 30 CgctGCCTACAGCGATCTGCAGTCTATGGGCACAGGCCCTGATGGCAGCCCTCTGTTTGGCT
 GTCTGTACGAGGCCAACGACTACGAAGAGATCGTGTTCCTGATGTTACCCCTGAAGCAGGCC
 TTTCCAGCCGAGTACCTGCCTCAAGAGCCCAATCTTCTGACAAAACCTCACACATGCCCACC
 GTGCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCTCTTCCCCCAAACCCAAGG
 ACACCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA
 35 GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
 GCCCGGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTGCAGCGTCCCTACCGTCTGACC
 AGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCCAGCCCCC
 ATCGAGAAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTcTACACCCTGCC
 CCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGtaCTGCCTGGTCAAAGGCTTCT
 40 ATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACC
 ACGCCTCCCGTGTGACTCCGACGGCTCCTTCTTCTCtatAGCAAGCTCACCGTGGACAA
 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
 ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTA

WHAT IS CLAIMED IS:

1. A fusion protein comprising:
 - (a) a recombinant mutant human sialidase, wherein the sialidase comprises a
5 substitution of an alanine residue at a position corresponding to position 42 of
wild-type human Neu2 (A42); and
 - (b) an anti-HER2 immunoglobulin antigen-binding domain.
2. The fusion protein of claim 1, wherein the alanine residue at a position corresponding to
position 42 of wild-type human Neu2 is substituted by arginine (A42R).
- 10 3. The fusion protein of claim 1 or 2, 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);
 - 15 (c) a substitution of a lysine residue at a position corresponding to position 44 of wild-
type human Neu2 (K44);
 - (d) a substitution of a lysine residue at a position corresponding to position 45 of wild-
type human Neu2 (K45);
 - (e) a substitution of a leucine residue at a position corresponding to position 54 of
20 wild-type human Neu2 (L54);
 - (f) a substitution of a proline residue at a position corresponding to position 62 of
wild-type human Neu2 (P62);
 - (g) a substitution of a glutamine residue at a position corresponding to position 69 of
wild-type human Neu2 (Q69);
 - 25 (h) a substitution of an arginine residue at a position corresponding to position 78 of
wild-type human Neu2 (R78);
 - (i) a substitution of an aspartic acid residue at a position corresponding to position 80
of wild-type human Neu2 (D80);
 - (j) a substitution of an alanine residue at a position corresponding to position 93 of
30 wild-type human Neu2 (A93);
 - (k) a substitution of a glycine residue at a position corresponding to position 107 of
wild-type human Neu2 (G107);

- (l) a substitution of a glutamine residue at a position corresponding to position 108 of wild-type human Neu2 (Q108);
- (m) a substitution of a glutamine residue at a position corresponding to position 112 of wild-type human Neu2 (Q112);
- 5 (n) a substitution of a cysteine residue at a position corresponding to position 125 of wild-type human Neu2 (C125);
- (o) a substitution of a glutamine residue at a position corresponding to position 126 of wild-type human Neu2 (Q126);
- (p) a substitution of an alanine residue at a position corresponding to position 150 of wild-type human Neu2 (A150);
- 10 (q) a substitution of a cysteine residue at a position corresponding to position 164 of wild-type human Neu2 (C164);
- (r) a substitution of an arginine residue at a position corresponding to position 170 of wild-type human Neu2 (R170);
- 15 (s) a substitution of an alanine residue at a position corresponding to position 171 of wild-type human Neu2 (A171);
- (t) a substitution of a glutamine residue at a position corresponding to position 188 of wild-type human Neu2 (Q188);
- (u) a substitution of an arginine residue at a position corresponding to position 189 of wild-type human Neu2 (R189);
- 20 (v) a substitution of an alanine residue at a position corresponding to position 213 of wild-type human Neu2 (A213);
- (w) a substitution of a leucine residue at a position corresponding to position 217 of wild-type human Neu2 (L217);
- 25 (x) a substitution of a glutamic acid residue at a position corresponding to position 225 of wild-type human Neu2 (E225);
- (y) a substitution of a histidine residue at a position corresponding to position 239 of wild-type human Neu2 (H239);
- (z) a substitution of a leucine residue at a position corresponding to position 240 of wild-type human Neu2 (L240);
- 30 (aa) a substitution of an arginine residue at a position corresponding to position 241 of wild-type human Neu2 (R241);
- (bb) a substitution of an alanine residue at a position corresponding to position 242 of

- wild-type human Neu2 (A242);
- (cc) a substitution of a valine residue at a position corresponding to position 244 of wild-type human Neu2 (V244);
- (dd) a substitution of a threonine residue at a position corresponding to position 249 of wild-type human Neu2 (T249);
- (ee) a substitution of an aspartic acid residue at a position corresponding to position 251 of wild-type human Neu2 (D251);
- (ff) a substitution of a glutamic acid residue at a position corresponding to position 257 of wild-type human Neu2 (E257);
- (gg) a substitution of a serine residue at a position corresponding to position 258 of wild-type human Neu2 (S258);
- (hh) a substitution of a leucine residue at a position corresponding to position 260 of wild-type human Neu2 (L260);
- (ii) a substitution of a valine residue at a position corresponding to position 265 of wild-type human Neu2 (V265);
- (jj) a substitution of a glutamine residue at a position corresponding to position 270 of wild-type human Neu2 (Q270);
- (kk) a substitution of a tryptophan residue at a position corresponding to position 292 of wild-type human Neu2 (W292);
- (ll) a substitution of a serine residue at a position corresponding to position 301 of wild-type human Neu2 (S301);
- (mm) a substitution of a tryptophan residue at a position corresponding to position 302 of wild-type human Neu2 (W302);
- (nn) a substitution of a valine residue at a position corresponding to position 363 of wild-type human Neu2 (V363); or
- (oo) 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.
4. The fusion protein of any one of claims 1-3, wherein the sialidase comprises a substitution of K9, P62, A93, Q126, A242, Q270, S301, W302, V363, or L365, or a combination of any of the foregoing substitutions.
5. The fusion protein of claim 3 or 4, wherein, 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);
- 5 (c) the lysine residue at a position corresponding to position 44 of wild-type human Neu2 is substituted by arginine (K44R) or glutamic acid (K44E);
- (d) 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);
- (e) the leucine residue at a position corresponding to position 54 of wild-type human Neu2 is substituted by methionine (L54M);
- 10 (f) 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);
- (g) the glutamine residue at a position corresponding to position 69 of wild-type human Neu2 is substituted by histidine (Q69H);
- 15 (h) the arginine residue at a position corresponding to position 78 of wild-type human Neu2 is substituted by lysine (R78K);
- (i) the aspartic acid residue at a position corresponding to position 80 of wild-type human Neu2 is substituted by proline (D80P);
- 20 (j) the alanine residue at a position corresponding to position 93 of wild-type human Neu2 is substituted by glutamic acid (A93E) or lysine (A93K);
- (k) the glycine residue at a position corresponding to position 107 of wild-type human Neu2 is substituted by aspartic acid (G107D);
- (l) the glutamine residue at a position corresponding to position 108 of wild-type human Neu2 is substituted by histidine (Q108H);
- 25 (m) the glutamine residue at a position corresponding to position 112 of wild-type human Neu2 is substituted by arginine (Q112R) or lysine (Q112K);
- (n) the cysteine residue at a position corresponding to position 125 of wild-type human Neu2 is substituted by leucine (C125L);
- 30 (o) 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);

- (p) the alanine residue at a position corresponding to position 150 of wild-type human Neu2 is substituted by valine (A150V);
- (q) the cysteine residue at a position corresponding to position 164 of wild-type human Neu2 is substituted by glycine (C164G);
- 5 (r) the arginine residue at a position corresponding to position 170 of wild-type human Neu2 is substituted by proline (R170P);
- (s) the alanine residue at a position corresponding to position 171 of wild-type human Neu2 is substituted by glycine (A171G);
- 10 (t) the glutamine residue at a position corresponding to position 188 of wild-type human Neu2 is substituted by proline (Q188P);
- (u) the arginine residue at a position corresponding to position 189 of wild-type human Neu2 is substituted by proline (R189P);
- (v) 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
15 threonine (A213T);
- (w) the leucine residue at a position corresponding to position 217 of wild-type human Neu2 is substituted by alanine (L217A) or valine (L217V);
- (x) the glutamic acid residue at a position corresponding to position 225 of wild-type human Neu2 is substituted by proline (E225P);
- 20 (y) the histidine residue at a position corresponding to position 239 of wild-type human Neu2 is substituted by proline (H239P);
- (z) 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);
- 25 (aa) 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);
- (bb) the alanine residue at a position corresponding to position 242 of wild-type human Neu2 is substituted by cysteine (A242C), phenylalanine (A242F), glycine
30 (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);

- (cc) the valine residue at a position corresponding to position 244 of wild-type human Neu2 is substituted by isoleucine (V244I) or proline (V244P);
- (dd) the threonine residue at a position corresponding to position 249 of wild-type human Neu2 is substituted by alanine (T249A);
- 5 (ee) the aspartic acid residue at a position corresponding to position 251 of wild-type human Neu2 is substituted by glycine (D251G);
- (ff) the glutamic acid residue at a position corresponding to position 257 of wild-type human Neu2 is substituted by proline (E257P);
- (gg) the serine residue at a position corresponding to position 258 is substituted by
10 cysteine (S258C);
- (hh) 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);
- (ii) the valine residue at a position corresponding to position 265 of wild-type human
15 Neu2 is substituted by phenylalanine (V265F);
- (jj) 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);
- (kk) the tryptophan residue at a position corresponding to position 292 of wild-type
20 human Neu2 is substituted by arginine (W292R);
- (ll) 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
25 (S301Q), arginine (S301R), threonine (S301T), valine (S301V), tryptophan (S301W), or tyrosine (S301Y);
- (mm) 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
30 (W302I), lysine (W302K), leucine (W302L), methionine (W302M), asparagine (W302N), proline (W302P), glutamine (W302Q), arginine (W302R), serine (W302S), threonine (W302T), valine (W302V), or tyrosine (W302Y);
- (nn) the valine residue at a position corresponding to position 363 of wild-type human

- Neu2 is substituted by arginine (V363R); or
- (oo) 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);
- 5 or the sialidase comprises a combination of any of the foregoing substitutions.
6. The fusion protein of claim 5, wherein the sialidase comprises a substitution selected from the K9D, P62G, P62N, P62S, P62T, A93E, Q126Y, A242F, A242W, A242Y, Q270A, Q270T, S301A, S301R, W302K, W302R, V363R, and L365I substitutions, or a combination of any of the foregoing substitutions.
- 10 7. The fusion protein of any one of claims 1-6, wherein the sialidase 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);
- 15 (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.
- 20 8. The fusion protein of claim 7, wherein, in the sialidase:
- (a) the methionine residue at a position corresponding to position 1 of wild-type human Neu2 is deleted (Δ M1), 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);
- 25 (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);
- 30 or the sialidase comprises a combination of any of the foregoing substitutions.
9. The fusion protein of claim 8, wherein the sialidase comprises the M1D, V6Y, A42R,

P62G, A93E, Q126Y, I187K, A242F, Q270T, and C332A substitutions.

10. The fusion protein of any one of claims 1-9, wherein the sialidase is selected from Neu1, Neu2, Neu3, and Neu4.

11. The fusion protein of claim 10, wherein the sialidase is Neu2.

5 12. The fusion protein of any one of claims 1-11, wherein the sialidase has a different substrate specificity than the corresponding wild-type sialidase.

13. The fusion protein of claim 12, wherein the sialidase can cleave α 2,3, α 2,6, and/or α 2,8 linkages.

14. The fusion protein of claim 13, wherein the sialidase can cleave α 2,3 and α 2,8 linkages.

10 15. The fusion protein of any one of claims 1-14, wherein the sialidase comprises SEQ ID NO: 198.

16. The fusion protein of any one of claims 1-15, wherein the sialidase comprises a mutation or combination of mutations set forth in any one of **TABLES 1-11**.

15 17. The fusion protein of any one of claims 1-16, wherein the fusion protein further comprises an immunoglobulin Fc domain.

18. The fusion protein of claim 17, wherein the immunoglobulin Fc domain is derived from a human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM Fc domain.

19. The fusion protein of claim 18, wherein the immunoglobulin Fc domain is derived from a human IgG1, IgG2, IgG3, or IgG4 Fc domain.

20 20. The fusion protein of claim 19, wherein the immunoglobulin Fc domain is derived from a human IgG1 Fc domain.

21. The fusion protein of any one of claims 1-20, wherein the anti-HER2 immunoglobulin antigen-binding domain is associated with a second anti-HER2 immunoglobulin antigen-binding domain to produce an anti-HER2 antigen-binding site.

25 22. The fusion protein of any one of claims 1-21, wherein the anti-HER2 immunoglobulin antigen-binding domain is derived from an antibody selected from trastuzumab, pertuzumab, CT-P6, trastuzumab-dkst, MGAH22 (margetuximab), PF-05280014, ertumaxomab, gancotamab, timigutuzumab, Ontruzant, ABP-980, SB3, DS-8201, MYL-1410, BCD-022, and HD201.

23. The fusion protein of claim 22, wherein the anti-HER2 immunoglobulin antigen-binding domain is derived from trastuzumab.
24. The fusion protein of any one of claims 1-23, wherein the sialidase and the immunoglobulin Fc domain and/or the anti-HER2 immunoglobulin antigen-binding domain are linked by a peptide bond or an amino acid linker.
25. The fusion protein of any one of claims 1-24, wherein the fusion protein comprises any one of SEQ ID NOs: 203-208.
26. An antibody conjugate comprising the fusion protein of any one of claims 1-25.
27. The antibody conjugate of claim 26, wherein the antibody conjugate comprises a single sialidase.
28. The antibody conjugate of claim 26, wherein the antibody conjugate comprises two sialidases.
29. The antibody conjugate of claim 28, wherein the two sialidases are identical.
30. The antibody conjugate of any one of claims 26-29, wherein the antibody conjugate comprises a single anti-HER2 antigen-binding site.
31. The antibody conjugate of any one of claims 26-29, wherein the antibody conjugate comprises two anti-HER2 antigen-binding sites.
32. The antibody conjugate of claim 31, wherein the two anti-HER2 antigen-binding sites are identical.
33. The antibody conjugate of any one of claims 26-32, wherein the antibody conjugate has a molecular weight from about 135 kDa to about 165 kDa.
34. The antibody conjugate of any one of claims 26-32, wherein the antibody conjugate has a molecular weight from about 215 kDa to about 245 kDa.
35. The antibody conjugate of any one of claims 26-34, 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 linked together, and wherein the first polypeptide and the second polypeptide together define an anti-HER2 antigen-binding site.

36. The antibody conjugate of claim 35, wherein the third polypeptide comprises the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation.
37. The antibody conjugate of claim 35 or 36, wherein the first polypeptide comprises SEQ ID NO: 66.
38. The antibody conjugate of any one of claims 35-37, wherein the second polypeptide comprises any one of SEQ ID NOs: 67 or 189.
39. The antibody conjugate of any one of claims 35-38, wherein the third polypeptide comprises any one of SEQ ID NOs: 203-208.
40. The antibody conjugate of any one of claims 35-39, wherein 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.
41. The antibody conjugate of any one of claims 26-34, wherein the fusion protein 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 anti-HER2 antigen-binding site, and the third polypeptide and the fourth polypeptide together define a second anti-HER2 antigen-binding site.
42. The antibody conjugate of claim 41, wherein 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.

43. The antibody conjugate of any one of claims 26-34, wherein the fusion protein 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 a second single chain variable fragment (scFv);
- 5 wherein the first and second polypeptides are covalently linked together, and wherein the first scFv defines a first anti-HER2 antigen-binding site, and the second scFv defines a second anti-HER2 antigen-binding site.
44. The antibody conjugate of claim 43, wherein the first polypeptide comprises the first sialidase, the first immunoglobulin Fc domain, and the first scFv in an N- to C-terminal orientation, and the second polypeptide comprises the second sialidase, the second immunoglobulin Fc domain, and the second scFv in an N- to C-terminal orientation.
- 10 45. The antibody conjugate of claims 43 or 44, wherein the first polypeptide comprises SEQ ID NO: 244 or SEQ ID NO: 249 and/or wherein the second polypeptide comprises SEQ ID NO: 244 or SEQ ID NO: 249.
- 15 46. The antibody conjugate of any one of claims 26-34, wherein 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;
- 20 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 anti-HER2 antigen-binding site and the scFv defines a second anti-HER2 antigen-binding site.
- 25 47. The antibody conjugate of claim 46, wherein the second polypeptide comprises the immunoglobulin heavy chain and the scFv in an N- to C-terminal orientation, and the third polypeptide comprises the sialidase and the immunoglobulin Fc domain in an N- to C-terminal orientation.
- 30 48. An isolated nucleic acid comprising a nucleotide sequence encoding the fusion protein of

any one of claims 1-25, or at least a portion of the antibody conjugate of any one of claims 26-47.

49. An expression vector comprising the nucleic acid of claim 48.

50. A host cell comprising the expression vector of claim 49.

5 51. A pharmaceutical composition comprising the fusion protein of any one of claims 1-25 or the antibody conjugate of any one of claims 26-47.

52. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of the fusion protein of any one of claims 1-25, the antibody conjugate of any one of claims 26-47, or the pharmaceutical composition of
10 claim 51.

53. The method of claim 52, wherein the cancer is selected from lung bronchioloalveolar carcinoma (BAC), bladder cancer, a female genital tract malignancy (*e.g.*, uterine serous carcinoma, endometrial carcinoma, vulvar squamous cell carcinoma, and uterine sarcoma), an ovarian surface epithelial carcinoma (*e.g.*, clear cell carcinoma of the ovary, epithelial
15 ovarian cancer, fallopian tube cancer, and primary peritoneal cancer), breast carcinoma, non-small cell lung cancer (NSCLC), a male genital tract malignancy (*e.g.*, testicular cancer), retroperitoneal or peritoneal carcinoma, gastroesophageal adenocarcinoma, esophagogastric junction carcinoma, liver hepatocellular carcinoma, esophageal and esophagogastric junction carcinoma, cervical cancer, cholangiocarcinoma, pancreatic adenocarcinoma, extrahepatic
20 bile duct adenocarcinoma, a small intestinal malignancy, gastric adenocarcinoma, cancer of unknown primary (CUP), colorectal adenocarcinoma, esophageal carcinoma, prostatic adenocarcinoma, kidney cancer, head and neck squamous carcinoma, thymic carcinoma, non-melanoma skin cancer, thyroid carcinoma (*e.g.*, papillary carcinoma), a head and neck cancer, anal carcinoma, non-epithelial ovarian cancer (non-EOC), uveal melanoma, malignant pleural
25 mesothelioma, small cell lung cancer (SCLC), a central nervous system cancer, a neuroendocrine tumor, and a soft tissue tumor.

54. The method of claim 52 or 53, wherein the cancer is breast cancer.

55. The method of claim 52 or 53, wherein the cancer is non-small cell lung cancer.

56. The method of claim 52 or 53, wherein the cancer is bladder cancer.

30 57. The method of claim 52 or 53, wherein the cancer is kidney cancer.

58. The method of claim 52 or 53, wherein the cancer is colon cancer.
59. The method of claim 52 or 53, wherein the cancer is melanoma.
60. A method of promoting infiltration of immune cells into a tumor in a subject in need thereof, the method comprising administering to the subject an effective amount of the fusion protein of any one of claims 1-25, the antibody conjugate of any one of claims 26-47, or the pharmaceutical composition of claim 51.
61. The method of claim 60, wherein the immune cells are T-cells.
62. The method of claim 61, wherein the T-cells are CD4⁺ T-cells and/or CD8⁺ T-cells.
63. The method of claim 62, wherein the CD8⁺ T-cells are CD69⁺CD8⁺ and/or GzmB⁺CD8⁺ T-cells.
64. The method of claim 60, wherein the immune cells are natural killer (NK) cells.
65. A method of increasing the number of circulating natural killer (NK) cells in a subject in need thereof, the method comprising administering to the subject an effective amount of the fusion protein of any one of claims 1-25, the antibody conjugate of any one of claims 26-47, or the pharmaceutical composition of claim 51, so as to increase the number of circulating NK cells relative to prior to administration of the fusion protein, antibody conjugate or pharmaceutical composition.
66. A method of increasing the number of T-cells in the draining lymph node in subject in need thereof, the method comprising administering to the subject an effective amount of the fusion protein of any one of claims 1-25, the antibody conjugate of any one of claims 26-47, or the pharmaceutical composition of claim 51, so as to increase the number of T-cells in the draining lymph node relative to prior to administration of the fusion protein, antibody conjugate or pharmaceutical composition.
67. The method of claim 66, wherein the T-cells are CD4⁺ T-cells and/or CD8⁺ T-cells.
68. A method of increasing expression of Cd3, Cd4, Cd8, Cd274, Ctl4, Icos, Pdcd1, Lag3, Il6, Il1b, Il2, Ifng, Ifna1, Mx1, Gzmb, Cxcl9, Cxcl12, and/or Ccl5 in a cell, tissue, or subject, the method comprising contacting the cell, tissue, or subject with an effective amount of the fusion protein of any one of claims 1-25, the antibody conjugate of any one of claims 26-47, or the pharmaceutical composition of claim 51, so as to increase the expression of Cd3, Cd4, Cd8, Cd274, Ctl4, 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 fusion protein, antibody conjugate or pharmaceutical composition.