

IL-18 FUSION PROTEINS AND METHODS OF PRODUCING IL-18

CROSS-REFERENCE TO RELATED APPLICATIONS

[01] This application includes a claim of priority under 35 U.S.C. §119(e) to U.S. provisional patent application No. 63/395,476, filed August 5, 2022, and 63/463,505, filed May 2, 2023, the entirety of both are hereby incorporated by reference.

REFERENCE TO SEQUENCE LISTING

[02] This application contains a Sequence Listing submitted as a computer readable form named "096034_000002WOPT_SequenceListing.xml", having a size in bytes of 366,973 bytes, and created on August 3, 2023 (Production Date). The information contained in this computer readable form is hereby incorporated by reference in its entirety.

FIELD OF INVENTION

[03] This invention relates to new compositions allowing for enhanced production (including expression, secretion, and purification) of recombinantly produced IL-18 cytokine, for example in mammalian cells, for masking and de-masking of the biological activity of IL-18, and/or for improved binding specificity of produced IL-18 to its receptor over its binding protein, while at least maintaining the binding affinity to its receptor, as well as methods for preparing the compositions.

BACKGROUND

[04] Members of the interleukin (IL)-1 cytokine family have established roles in host-defense responses and in inflammatory responses that contribute to disease. IL-18 belongs to the IL-1 superfamily, and is a proinflammatory cytokine that facilitates type 1 immunity responses. IL-18, also known as interferon-gamma inducing factor, is encoded in humans by the *IL-18* gene. IL-18 gene, similar to other IL-1 family members, lacks a signal peptide. The *IL-18* gene encodes for a 193 amino acid precursor protein, first synthesized as an inactive 24 kDa precursor with no signal peptide, which is cytosolic and accumulates in cell cytoplasm. WO 97/24441 discloses a 193 amino acid protein corresponding to IL-18 precursor and encoding DNA. The IL-18 precursor (also referred to as Pro-IL-18) is processed intracellularly (e.g., by caspase 1 (CASP1), chymase, and proteinase B) into its mature biologically active molecule of 18 kDa (157 amino acids; i.e., amino acid residues 37-193 of Uniprot ID Q14116). That is, upon cleavage, the propeptide breaks away from the rest of the precursor, resulting in mature IL-18 and the propeptide which formerly inactivated the precursor IL-18.

[05] Without wishing to be bound by a particular theory, the mature form of IL-18 is secreted and released into the extracellular milieu via at least three unconventional pathways. This is as opposed to signal

peptide-dependent and ER-Golgi trafficking-mediated conventional secretion. The unconventional pathways listed below are in no particular order of frequency. The first is called secretory autophagy, a process involved in the secretion of cytosolic proteins without a signal peptide (leaderless cargoes). Here, IL-18 interacts with cargo receptor transmembrane emp24 domain-containing protein 10 (TMED10), and the interaction mediates the translocation from the cytoplasm into the endoplasmic reticulum (ER)-Golgi intermediate compartment (ERGIC), a compartment contributing membranes to the forming autophagosome, which acts as a mechanism for secretory cargo entry into the vesicle, thereby secretion. The second and third reported mechanisms of release of IL-18 from cells include rupture of dead cells that have undergone apoptosis and/or gasdermin D-dependent plasma membrane permeabilization (*see* Tapia et al., *IMMUNOLOGY*, volume 294, issue 21, p8325-8335, 2019).

[006] Mature IL-18 binds the ligand receptor IL-18 receptor alpha (IL-18R α), inducing the recruitment of IL-18R β (also called IL-18 receptor accessory protein (IL-18RAP)) to form a high affinity complex (approximately 18 nM, *see* Torigoe et al., *Membranes and Bioenergetics*, vol. 272, issue 41, pp25737-25742, 1997), which signals through the toll/interleukin-1 receptor (TIR) domain. This signaling domain recruits MyD88 adaptor protein that activates proinflammatory programs and NF- κ B pathway. The activity of IL-18 can be suppressed by extracellular interleukin 18 binding protein (IL-18BP) that binds soluble IL-18 with a higher affinity (approximately 0.4 pM, *see* Kim et al., *Proc Natl Acad Sci USA*. 2000;97(3):1190-1195) than IL-18R α thus prevents IL-18 binding to IL-18 receptor.

[007] Therefore, it is an objective of the present invention to provide compositions of matter that allow for improved production (including expression, secretion, and purification) of recombinantly produced IL-18.

[008] It is another objective of the present invention to provide compositions of matter that allow for enhanced production of recombinantly produced IL-18, including modified IL-18 or a fragment thereof, which maintains a similar binding affinity to IL-18R α /b compared to natural IL-18, and has a reduced binding affinity to IL-18BP compared to natural IL-18 (i.e. binding to both at ~18 nM); or more preferably, the binding affinity to IL-18BP is weaker than that to IL-18R α /b (i.e. binding to IL-18BP <18 nM, binding to IL-18R α /b ~18 nM), for the produced IL-18 (or its fragment); as well as methods for preparing these compositions.

[009] It is another objective of the present invention to provide variants of IL-18 (or its fragment).

[010] It is another objective of the present invention to provide compositions allowing for masked activity in normal tissues and the circulation and specific release of IL-18 (or its fragment) by proteases in a tumor microenvironment.

[011] All publications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

SUMMARY OF THE INVENTION

[012] The following embodiments and aspects thereof are described and illustrated in conjunction with compositions and methods which are meant to be exemplary and illustrative, not limiting in scope.

[013] Various embodiments provide for a fusion protein, comprising: a first polypeptide or protein capable of translocating into an endoplasmic reticulum (ER) or a fragment thereof; and an interleukin 18 (IL-18), a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant, wherein the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant is on the C-terminus end of the fusion protein relative to the first polypeptide or protein capable of translocating into the ER.

[014] In various embodiments, the IL-18 variant can have an amino acid sequence comprising amino acid positions 37-193 of SEQ ID NO:250 with one to five amino acid substitutions at positions E42, M87, K89, M96, and M149 of SEQ ID NO:250.

[015] In various embodiments, the IL-18 variant can have an amino acid sequence comprising positions 37-193 of SEQ ID NO:251 with one to five amino acid substitutions at positions E42, M87, K89, M96, and M149 of SEQ ID NO:251.

[016] In various embodiments, the IL-18 variant can have an amino acid sequence comprising positions 37-193 of SEQ ID NO:251 with one or more amino acid substitutions at positions C74, C104, C112, and C164 and one to five amino acid substitutions at positions E42, M87, K89, M96, and M149, of SEQ ID NO:251.

[017] In various embodiments, the amino acid substitutions at one or more of C74, C104, C112, and C164 can be each independently to valine, alanine or serine.

[018] In various embodiments, the one to five amino acid substitutions can be one or more of: E42K, E42R, E42A, E42H, or E42Q; M87K, or M87H; K89G, K89A, or K89E; M96L, or M96I; or M149V or M149I.

[019] In various embodiments, the one to five amino acid substitutions can be E42K, E42R, E42A, E42H, or E42Q; M87K, or M87H; K89G, K89A, or K89E; M96L, or M96I; and M149V or M149I.

[020] In various embodiments, the IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant further comprises its propeptide (PP) or a PP variant.

[021] In various embodiments, the IL-18 propeptide variant comprises a polypeptide having AAEPVEDNX₁INFVAMKFIDNTLYFIAEDDEN (SEQ ID NO:238), wherein X₁ can be any amino acid except cysteine.

[022] In various embodiments, X₁ can be alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine or tryptophan (SEQ ID NO:239). In various embodiments, X₁ can be valine (SEQ ID NO:78). In various embodiments, X₁ can be serine, threonine, asparagine, or glutamine (SEQ ID NO:240). In various embodiments, X₁ can be serine (SEQ ID NO:76).

[023] In various embodiments, the fusion protein does not comprise a polypeptide consisting of the sequence X_1 - X_2 - X_3 - X_4 between the propeptide or propeptide variant, and the mature IL-18 or mature IL-18 variant, wherein X_1 is L or absent, X_2 is E or absent, X_3 is S or absent, and X_4 is D or absent, and when X_1 , X_2 , X_3 , and X_4 are present, the polypeptide consisting of the sequence X_1 - X_2 - X_3 - X_4 is LESD (SEQ ID NO:253).

[024] In various embodiments, the PP or the PP variant can be on the N-terminus end relative to the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant.

[025] In various embodiments, the PP or the PP variant serves as a masking domain.

[026] In various embodiments, the fusion protein further comprises one or more protease cleavage sites.

[027] In various embodiments, the one or more protease cleavage sites can be between the IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant and the first protein capable of translocating into an endoplasmic reticulum (ER) or fragment thereof, or within the PP, between PP or the PP variant and the IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant, or within the PP, between the PP or the PP variant and the first protein capable of translocating into an endoplasmic reticulum (ER) or fragment thereof, or within the IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant, or within the PP, or a combination thereof.

[028] In various embodiments, the fusion protein further comprises a second protein capable of translocating into the ER or a fragment thereof, wherein the second protein capable of translocating into the ER can be on the C-terminus end relative to the interleukin 18 (IL-18), the fragment of the IL-18, the IL-18 variant, or the fragment of the IL-18 variant.

[029] In various embodiments, the fusion protein further comprises a protease cleavage site between the IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant and the second protein capable of translocating into an endoplasmic reticulum (ER) or fragment thereof.

[030] In various embodiments, the interleukin 18 (IL-18), the fragment of the IL-18, the IL-18 variant, or the fragment of the IL-18 variant can be fused to the C-terminus of the first protein capable of translocating into the ER.

[031] In various embodiments, the second protein capable of translocating into the ER or a fragment thereof can be fused to the C-terminus of the interleukin 18 (IL-18), the fragment of the IL-18, the IL-18 variant, or the fragment of the IL-18 variant.

[032] In various embodiments, the IL-18 variant can have diminished binding to IL-18 binding protein (IL-18BP), as compared to a wild type (wt) IL-18. In various embodiments, the IL-18 variant having a binding affinity to the human IL-18 receptor (IL-18R) within 30-fold of the wild-type IL-18. In various embodiments, the ratio of binding affinity of the fusion protein comprising the IL-18 variant to IL-18BP : binding affinity of the fusion protein comprising the IL-18 variant to IL-18R can be no higher than 3:1.

[033] In various embodiments, the first protein capable of translocating into the ER or a fragment thereof can be a globular protein, immunoglobulin protein, or a fragment thereof, or can be a short polypeptide or protein engineered with a signal peptide for translocating into the ER, optionally the short polypeptide or protein being about 2kDa or no greater than 250 kDa.

[034] In various embodiments, the first protein capable of translocating into the ER or a fragment thereof can be selected from the group consisting of a fragment crystallizable (Fc) region, human serum albumin (HSA), beta2microglobulin, transferrin, fragment antigen-binding region (Fab region), VHH antibody, single-chain variable fragment (scFv), anticalin, designed ankyrin repeat protein (DARPin), a binding domain thereof, and a fragment thereof.

[035] In various embodiments, the first protein capable of translocating into the ER or a fragment thereof of the fusion protein can be a type I transmembrane protein or a fragment thereof or a type II transmembrane protein or a fragment thereof.

[036] In various embodiments, the second protein capable of translocating into the ER or a fragment thereof can be a globular protein, immunoglobulin protein, or a fragment thereof, or can be a short polypeptide or protein engineered with a signal peptide for translocating into the ER, optionally the short polypeptide or protein being about 2kDa or no greater than 250 kDa.

[037] In various embodiments, the second protein capable of translocating into the ER or a fragment thereof can be selected from the group consisting of a fragment crystallizable (Fc) region, human serum albumin (HSA), beta2microglobulin, transferrin, fragment antigen-binding region (Fab region), VHH antibody, single-chain variable fragment (scFv), anticalin, designed ankyrin repeat protein (DARPin), a binding domain thereof, and a fragment thereof.

[038] In various embodiments, the second protein capable of translocating into the ER or a fragment thereof of the fusion protein can be a type I transmembrane protein or a fragment thereof, or a type II transmembrane protein or a fragment thereof.

[039] In various embodiments, the Fc region can be an Fc region from IgA, IgM, IgG, or IgE. In various embodiments, the Fc region can be an Fc region from IgG4, KiH, or IgG1. In various embodiments, the Fc region can be an Fc region from Knob-in-hole, HA-TF, Xmab, ZW1, 7.8.60, Electrostatic Steering, DD-KK, EW-RVT, A107, or Duobody.

[040] In various embodiments, one or more cysteines in the fusion protein can be modified. In various embodiments, one or more cysteines in the fusion protein can be replaced with a natural or non-natural amino acid.

[041] In various embodiments, one or more cysteines in the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant of the fusion protein can be modified or can be replaced with a natural or non-natural amino acid.

[042] In various embodiments, the one or more cysteines in the PP or PP variant of the fusion protein can be modified or can be replaced with a natural or non-natural amino acid.

[043] In various embodiments, the natural amino acid can be charged, polar uncharged, or hydrophobic. In various embodiments, the natural amino acid can be each independently selected from serine and valine. In various embodiments, the natural amino acid can be each independently selected from threonine, asparagine, and glutamine.

[044] In various embodiments, the natural amino acid can be each independently selected from alanine, isoleucine, leucine methionine, phenylalanine, tyrosine, and tryptophan. In various embodiments, the natural amino acid the natural amino acid can be each independently selected from phenylalanine, alanine, aspartic acid, and asparagine. In various embodiments, the natural amino acid can be valine. In various embodiments, the natural amino acid can be each independently selected from threonine, glutamine, aspartic acid, phenylalanine, isoleucine and histidine.

[045] In various embodiments, the protease can be selected from the group consisting of EK, TEV, Adam17, cathepsin, MMP2, MMP9, MMP14, Granzyme A, Granzyme B, Granzyme M, Granzyme K, and combinations thereof.

[046] In various embodiments, the fusion protein can have one or more sequences as set forth in any one in Tables 1 and 4.

[047] In various embodiments, the fusion protein can have polypeptide 1 and polypeptide 2, and optionally polypeptide 3 selected from Table 1. In various embodiments, the fusion protein can have polypeptide 1 and polypeptide 2, and optionally polypeptide 3 selected from Table 1, wherein polypeptide 1 and polypeptide 2, and optionally polypeptide 3 can be selected from the same row of Table 1. In various embodiments, the fusion protein can have polypeptide 1 selected from Table 1, wherein polypeptide 1 comprises HSA.

[048] In various embodiments, the IL-18 variant can have an amino acid sequence selected from Mature IL-18 column in Table 1.

[049] In various embodiments, the IL-18 variant can have an amino acid sequence selected from Mature IL-18 column in Table 1, and the propeptide can have an amino acid sequence selected from Propeptide column in Table 1, optionally the same from the same row.

[050] Various embodiments provide for an IL-18 propeptide variant comprising a polypeptide having AAEPVEDNX₁INFVAMKFIDNTLYFIAEDDEN, wherein X₁ can be any amino acid except cysteine (SEQ ID NO:238).

[051] In various embodiments, X₁ can be alanine, valine, isoleucine, leucin, methionine, phenylalanine, tyrosine or tryptophan (SEQ ID NO:239). In various embodiments, X₁ can be valine (SEQ ID NO:78). In various

embodiments, X₁ can be serine, threonine, asparagine, or glutamine (SEQ ID NO:240). In various embodiments, X₁ can be serine (SEQ ID NO:76).

[052] Various embodiments provide for a polynucleotide encoding any one of the fusion protein of the invention described herein. In various embodiments, the first protein capable of translocating into the ER can be encoded by a polynucleotide having one or more sequences as set forth in Table 2. In various embodiments, the polynucleotide can have one or more sequences from the same row as set forth in Table 2.

[053] Various embodiments provide for an expression vector comprising any one of the polynucleotides of the invention described herein.

[054] Various embodiments provide for a cell transfected with any one of the expression vector of the invention described herein. In various embodiments, the cell can be a mammalian cell. In various embodiments, the cell can be a bacterial cell.

[055] Various embodiments provide for a method of producing a fusion protein, comprising: culturing a cell transfected with any one of the expression vectors of the invention as described herein, in cell culture medium to allow the fusion protein to be secreted into the cell culture medium.

[056] In various embodiments, the method further comprises isolating the fusion protein from the culture medium. In various embodiments, the method further comprises purifying the fusion protein. In various embodiments, the fusion protein can be produced at greater than 135 mg/L under transient transfection in CHO cells or HEK-293 cells.

[057] Various embodiments provide for a method of producing interleukin 18 (IL-18), a fragment thereof, an IL-18 variant, or a fragment of the IL-18 variant, comprising: culturing a cell transfected with any one of the expression vectors of the invention as described herein, in cell culture medium to allow a fusion protein to be produced and secreted into the extracellular space; and contacting a protease to the fusion protein to cleave the fusion protein to produce the IL-18, the fragment thereof, the IL-18 variant, or the fragment of the IL-18 variant.

[058] In various embodiments, the method further comprises isolating the fusion protein from the culture medium. In various embodiments, the method further comprises purifying the fusion protein. In various embodiments, contacting the protease to the fusion protein comprises including the protease in the cell culture medium.

[059] In various embodiments, the protease can be selected from the group consisting of EK, TEV, Adam17, cathepsin, MMP2, MMP9, MMP14, Granzyme A, Granzyme B, Granzyme M, and combinations thereof.

[060] In various embodiments, the IL-18, the fragment thereof, the IL-18 variant, or the fragment of the IL-18 variant can be produced at greater than 135mg/L.

[061] Other features and advantages of the invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, various features of embodiments of the invention.

BRIEF DESCRIPTION OF THE FIGURES

[062] Exemplary embodiments are illustrated in referenced figures. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

[063] Figure 1 (panels A-E) depicts exemplary fusion proteins in which the N-terminus of pro-IL-18 is fused to the C-terminus of the knob of a knob-into-hole heterodimeric IgG1 protein; which has a structure from N- to C-terminus comprising knobs-in-hole (KiH) Fc – propeptide (pp) – enterokinase-cleavable site (EK) – IL-18 wild type or its variants. This depicts exemplary fusion proteins such as IDs: FUSE-480, FUSE-481, and FUSE-442 in Table 1. Further modification was made to pro-IL-18 to reduce aggregation of the molecule, wherein each cysteine residue in both the pro-peptide and mature IL-18 was replaced with serine (as in FUSE-480, denoted as “IL-18AS”), with alanine (as in FUSE-481, denoted as “IL-18AA”), or with valine (as in FUSE-442, denoted as “IL-18AV”). Alternatively, the N-terminus of pro-IL-18 can be fused to the C-terminus of the hole chain of a KiH heterodimeric IgG1 proteins. The biological activity defined as the EC50-SEAP for each compound is shown in panel E.

[064] Figure 2 (panels A-E) depicts exemplary fusion proteins in which the N-terminal of pro IL-18 was fused to the C-terminal of an IgG1 CH3 domain (which is also a knob chain of a knob-into-hole heterodimeric IgG1 protein as in Figure 1), and the pro IL-18 incorporated four amino acid substitutions hypothesized to reduce binding to IL-18BP while maintaining wild type binding to the IL-18 receptor complex, denoted as “pro-IL-18mut2”. These fusion proteins have a structure from N- to C-terminus comprising knobs-in-hole (KiH) Fc – propeptide (PP) – enterokinase-cleavable site (EK) – IL-18mut2. Further modification was made to the pro-IL-18mut2 to reduce aggregation of the molecule, wherein each cysteine residue in both the pro-peptide and mature IL-18mut2 was substituted with serine (denoted as “IL-18mut2AS”, as in FUSE-422; panel B), with alanine (denoted as “IL-18mut2AA”, as in FUSE-423; panel C), or with valine (denoted as “IL-18mut2AV”, as in FUSE-424; panel D). The biological activity defined as the EC50-SEAP for each compound is shown in panel E.

[065] Figure 3 (panels A-D) depicts exemplary fusion proteins with (panel A) or without (panel B) the propeptide to examine the impact on masking of “IL-18AV” biological activity (panel C), wherein Fc fusion variants were generated incorporating “IL-18AV” with the propeptide (panel A; FUSE-442) or without (panel B; FUSE-505) the propeptide. The biological activity defined as the EC50-SEAP for each compound is shown in panel D.

[066] Figure 4 (panels A-D) depicts exemplary fusion proteins with (panel A) or without (panel B) the propeptide to examine the impact of propeptide on masking of “IL-18mut2AV” biological activity, wherein Fc

fusion variants were generated incorporating “IL-18mut2AV” without the propeptide (hence, a mature IL-18 with mutation, denoted as “matIL-18mut2-AV”, see panel B; FUSE-441) or with the propeptide (panel A; FUSE-424). For a fusion protein devoid of the propeptide, the EK cleavage site that replaced the Caspase 1 site was moved to a position directly in between the CH3 domain of the knob and the mature IL-18AV without the addition of a flexible linker. Panel C depicts the activation readout using the HEK-Blue IL-18AV reporter cell assay following exposure to a titration of FUSE-441 (Fc-EK-IL-18AV) or FUSE-424 (Fc-EKpp-IL-18AV) with or without treatment with EK. The biological activity defined as the EC50-SEAP for each compound is shown in panel D.

[067] Figure 5 (panels A-D) depicts exemplary fusion proteins in which the N-terminus of pro-IL-18 is fused to the C-terminus of IgG1 Fc protein or IgG4 Fc; which has a structure from N- to C-terminus comprising IgG1 Fc- propeptide (pp) - IL-18AV (FUSE-507; panel A) and IgG4 Fc- propeptide (PP) - IL-18AV (FUSE-509; panel B). Panel C depicts the activation readout using the HEK-Blue IL-18AV reporter cell assay of exposing the cells to a titration of FUSE-507 or FUSE-509 with or without treatment with EK. The biological activity defined as the EC50-SEAP for each compound is shown in panel D.

[068] Figure 6 (panels A-E) depicts exemplary fusion proteins in which the N-terminus of pro-IL-18 is fused to the C-terminus of HSA with or without the propeptide (pp); which has a structure from N- to C-terminus comprising HSA- propeptide (PP) - IL-18AV (FUSE-501; panel A) and HSA- IL-18AV (FUSE-503; panel B). Panels C and D depict the activation readout. The biological activity defined as the EC50-SEAP for each compound is shown in panel E.

[069] Figure 7 (panels A-E) depicts exemplary fusion proteins in which the N-terminus of pro-IL-18mut2 is fused to the C-terminus of HSA with or without the propeptide (PP); which has a structure from N- to C-terminus comprising HSA- propeptide (PP) - IL-18mut2AV (FUSE-502; panel A) and HSA- IL-18mut2AV (FUSE-504; panel B). Panels C and D depict the activation readout. The biological activity defined as the EC50-SEAP for each compound is shown in panel E.

[070] Figure 8 (panels A-D) depicts exemplary fusion proteins in which the C-terminus of pro-IL-18 is fused to the N-terminus of the knob of a knob-into-hole heterodimeric IgG1 protein with or without the propeptide (PP); which has a structure from N- to C-terminus comprising propeptide (PP) - IL-18AV - knobs-in-hole (KiH) Fc (FUSE-499; panel A) and IL-18AV - knobs-in-hole (KiH) Fc (FUSE-500; panel B). Panel C depicts the activation readout. The biological activity defined as the EC50-SEAP with or without exposure to Caspase 1 for each compound is shown in panel D.

[071] Figure 9A and 9D depicts exemplary fusion proteins with a structure from N- to C- terminus: Fc-ppMMP2/9-cleavage sites-IL-18-AV (FUSE-486), Fc-ppMMP9/2-cleavage sites-IL-18-AV (FUSE-487), in which the cleavage sites are specific for the metalloproteases, MMP2 and MMP9, with preferred enzyme to the left of the forward-slash, or FUSE-485 (Fc-GzmBpp-IL-18AV) and FUSE-462 (Fc-GzmBpp-IL-18mut2AV). Figure 9B depicts the activation readout relating to FUSE-486 and FUSE-487, with or without MMP2 treatment.

The biological activity defined as the EC50-SEAP for each of FUSE-486 and FUSE-487, with or without MMP2 treatment, is shown in figure 9B. FIG. 9C shows that FUSE587 was about 3,000-fold attenuated relative to recombinant human IL-18. Interestingly, we observed that cleavage of FUSE587 with MMP2 released an IL-18AV variant that was still about 100-fold attenuated relative to recombinant IL-18. In contrast, cleavage with Granzyme B released an IL-18AV variant with activity similar activity as recombinant IL-18. Cleavage with Granzyme B results in release of mature IL-18AV without any N-terminal residues constituting an overhang, whereas 11 and 15 amino acid N-terminal polypeptide overhangs remain after cleavage of FUSE486 and FUSE587, respectively, with MMP2. We speculated that these overhangs might be attenuating IL-18AV activity, albeit to a lesser degree than the full size variant propeptide. This phenomenon was further investigated in FIG. 11 and FIG. 13. Figures 9D and 9G also depicts exemplary fusion proteins with a structure from N- to C- terminus: Fc-ppGb-cleavage sites-IL-18-AV (FUSE-485; 9D) or Fc-ppGb-cleavage sites-IL-18mut2-AV (FUSE-462; 9D) or Fab-Cetuximab-Fc-ppGb-cleavage sites-IL-18-AV (FUSE-517; 9G), in which the cleavage site is specific for granzyme B (Gb). Figure 9E depicts the activation readout relating to FUSE-462 and FUSE-485, with or without granzyme B treatment. Figure 9F shows the biological activity defined as the EC50-SEAP for each of FUSE-462 and FUSE-485, with or without granzyme B treatment. Figure 9H depicts the activation readout relating to FUSE-517, with or without enzyme treatment. Figure 9I shows the biological activity defined as the EC50-SEAP for FUSE-517, with or without granzyme B treatment.

[072] Figure 10 (panels A-G) depicts the impact of IL-18BP on the biological activity of recombinant human IL-18 (rhIL-18) and the EK cleavage products of the exemplary fusion proteins, Fc-ppEK-IL-18-AV (FUSE-442) and Fc-ppEK-IL-18mut2AV (FUSE-424). The biological activity defined as the EC50-SEAP for each compound with and without the addition of IL-18BP (competition assay) is shown in panels B, D and F, with corresponding biological activity defined as the EC50-SEAP shown in panels C, E, and G, respectively.

[073] Figure 11 (panel A) depicts diagrams of exemplary fusion proteins in which the C-terminus of pro-IL-18 is fused to the N-terminus of the knob of a knob-into-hole heterodimeric IgG1 protein with different size polypeptides fused to the N-terminus of mature IL-18. Figure 11 (panel B) depicts the biological activity of each fusion protein using the IL-18 reporter cell line, HEK-Blue IL-18.

[074] Figure 12A, 12B(i), 12B(ii), 12C, 12D(i), 12D(ii) and 12E depict human IL-18 engineered mutant fusion proteins in accordance with various embodiments of the invention.

[075] Figure 13 shows the impact of the size of polypeptides fused to the N-terminus of mature IL-18 on the biological activity of a single IL-18AV fused to the N-terminus of IgG1 Fc.

[076] Figure 14A-14H shows the impact of the substituting the cysteine residue in the pro-peptide and cysteine residues in the mature IL18, which were fused together to form the pro-IL-18 variant cassette, on the biological activity of each variant using the HEK Blue IL18 assay system.

[077] Figure 15A-15B shows the impact of targeting pro-IL18 to within close proximity of its receptor complex (i.e., “cis activity”).

DESCRIPTION OF THE INVENTION

[078] All references cited herein are incorporated by reference in their entirety as though fully set forth. Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton *et al.*, *Dictionary of Microbiology and Molecular Biology 3rd ed., Revised*, J. Wiley & Sons (New York, NY 2006); March, *Advanced Organic Chemistry Reactions, Mechanisms and Structure 7th ed.*, J. Wiley & Sons (New York, NY 2013); and Sambrook and Russel, *Molecular Cloning: A Laboratory Manual 4th ed.*, Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY 2012), provide one skilled in the art with a general guide to many of the terms used in the present application. For references on how to prepare antibodies, see D. Lane, *Antibodies: A Laboratory Manual 2nd ed.* (Cold Spring Harbor Press, Cold Spring Harbor NY, 2013); Kohler and Milstein, (1976) Eur. J. Immunol. 6: 511; Queen *et al.* U. S. Patent No. 5,585,089; and Riechmann *et al.*, Nature 332: 323 (1988); U.S. Pat. No. 4,946,778; Bird, Science 242:423-42 (1988); Huston *et al.*, Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); Ward *et al.*, Nature 334:544-54 (1989); Tomlinson I. and Holliger P. (2000) Methods Enzymol. 326, 461-479; Holliger P. (2005) Nat. Biotechnol. Sep;23(9):1126-36).

[079] One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described. For purposes of the present invention, the following terms are defined below.

[080] As used herein the term “about” or “approximately” when used in connection with a referenced numeric indication means the referenced numeric indication plus or minus up to 5% of that referenced numeric indication, unless otherwise specifically provided for herein. For example, the language “about 50%” covers the range of 45% to 55%. In various embodiments, the term “about” when used in connection with a referenced numeric indication can mean the referenced numeric indication plus or minus up to 4%, 3%, 2%, 1%, 0.5%, or 0.25% of that referenced numeric indication, *if* specifically provided for in the claims.

[081] As used herein the term “immunoglobulin heavy chain constant region” is used interchangeably with the term “Fc region” and is understood to mean the carboxyl-terminal portion of an immunoglobulin heavy chain constant region, or an analog or portion thereof capable of binding an Fc receptor. Each immunoglobulin heavy chain constant region comprises four or five domains. The domains are named sequentially as follows: CH1-hinge-CH2-CH3(-CH4). CH4 is present in IgM, which has no hinge region. The immunoglobulin heavy chain constant region suitable for the invention preferably comprises an immunoglobulin hinge region, and preferably

also includes a CH3 domain. The immunoglobulin heavy chain constant region most preferably comprises an immunoglobulin hinge region, a CH2 domain and a CH3 domain.

[082] As used herein, the term immunoglobulin “hinge region” is understood to mean an entire immunoglobulin hinge region or at least a portion of the immunoglobulin hinge region sufficient to form one or more disulfide bonds with a second immunoglobulin hinge region.

[083] As used herein, the term “vector” is understood to mean any nucleic acid comprising a nucleotide sequence competent to be incorporated into a host cell and to be recombined with and integrated into the host cell genome, or to replicate autonomously as an episome. Such vectors include linear nucleic acids, plasmids, phagemids, cosmids, RNA vectors, viral vectors and the like. Non-limiting examples of a viral vector include a retrovirus, an adenovirus and an adeno-associated virus.

[084] As used herein, the term “gene expression” or “expression” of a fusion protein, is understood to mean the transcription of a DNA sequence, translation of the mRNA transcript, and secretion of a fusion protein product. In some embodiments, the expression process also includes or is followed by purification; for example, protein A affinity chromatography or other means such as size exclusion chromatography can be used for purification.

[085] As used herein, “IL-18 fusion protein” refers to a fusion protein that includes wild-type IL-18 or IL-18 variants, unless specifically noted as only including the wild-type IL-18, or only including the IL-18 variant. Thus, in particular embodiments, the “IL-18 fusion protein” only includes any one of the IL-18 variants as described herein.

[086] The term “linker” with respect to amino acid linker in a polypeptide can be a short peptide, such as a dimer of two amino acids, a tri-mer of three amino acids, or a peptide selected from the group consisting of T, PT, MPT, S, GS, GGS, GGGG (SEQ ID NO:235), and (GGGGX_n) (SEQ ID NO:236), wherein X_n is Q, A, E or S and n=1-5 or an integer larger than 5. In some embodiments, the amino acid linker has the amino acid sequence of (GGGGG (SEQ ID NO:237))_n where n is an integer between 1 and 5, thereby an amino acid linker of 25 amino acids or shorter in length. In some embodiments, the amino acid linker is an IL-18 propeptide or IL-18 propeptide variant. In some embodiments, the amino acid linker is a fragment of an IL-18 propeptide or IL-18 propeptide variant; for example, about 30-36 amino acids in length, about 5-10, 11-20, 21-30, or 31-40 amino acids in length.

Fusion proteins

[087] Various embodiments provide one or more fusion proteins, each comprising (i) an IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant, and (ii) a first protein capable of translocating into an endoplasmic reticulum (ER) including a cytosolic or nuclear protein engineered to translocate into an endoplasmic reticulum (ER) by means of addition of signal peptide/leader sequence onto the N-terminus of such an engineered protein, or a fragment of said proteins. Preferably, the protein capable of translocating into an

ER has an amino acid sequence which initiates transport of a protein (e.g., the IL-18 or its fragment, variant, or a fragment of its variant) across the membrane of the endoplasmic reticulum. In various embodiments, the fusion protein comprises further an amino acid linker. For example, the amino acid linker can be between (a) the protein capable of translocating into an endoplasmic reticulum (ER) and (b) the propeptide (or variant) or IL-18 (or variant).

[088] In some embodiments, the one or more fusion proteins do not comprise an IL-18 propeptide or its variant. An “IL-18 propeptide”, or “propeptide” or “PP” in this invention, may also be used interchangeably, which describes an amino acid sequence linked to IL-18 or IL-18 variant in an IL-18 precursor or IL-18 variant precursor, and which upon removal renders a mature IL-18 or its fragment, or IL-18 variant or its fragment thereof. For example, an IL-18 propeptide may have a sequence of amino acid residues 1-36 of Uniprot ID Q14116.

[089] In some embodiments, the one or more fusion proteins also include a propeptide (PP) or its variant. Examples of propeptide variants are provided herein, including those in Table 1. This can inactivate IL-18 or IL-18 variant, and so a propeptide directly or indirectly is linked to the IL-18 or IL-18 variant forms a precursor IL-18 or precursor IL-18 variant. Preferably, the PP or its variant is on the N-terminus end relative to IL-18 (or its fragment, variant, or a fragment of its variant) in the fusion protein.

[090] In some embodiments, the one or more fusion proteins also include a cleavage site, which is preferably based on a peptide substrate sensitive to enzymatic/protease cleavage. The cleavage site may be positioned within the PP, between the PP or its variant (if present) and the IL-18 (or its fragment, variant, or a fragment of its variant); or may be positioned between the protein capable of translocating into an ER and the PP (if present); or may be positioned between the protein capable of translocating into an ER and the IL-18 or its fragment, variant, or a fragment of its variant, especially in the absence of a PP. In some embodiments, when PP is present, the cleavage site is positioned within the PP. In further embodiments, the one or more fusion proteins include (i) an IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant, (ii), a propeptide (PP) or its variant, which inactivates IL-18, and a cleavage site.

[091] Examples of propeptide variants include a polypeptide having AAEPVEDNX₁INFVAMKFIDNTLYFIAEDDEN, wherein X₁ is any amino acid except cysteine (SEQ ID NO:238). In various embodiments, X₁ is alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine or tryptophan (SEQ ID NO:239). In various embodiments, X₁ is valine (SEQ ID NO:78). In various embodiments, X₁ is serine, threonine, asparagine, or glutamine (SEQ ID NO:240). In various embodiments, X₁ is serine (SEQ ID NO:76).

[092] In various embodiments, the fusion protein does not comprise a polypeptide consisting of the sequence X₁-X₂-X₃-X₄ between the (i) propeptide or propeptide variant, and (ii) the mature IL-18 or mature IL-18 variant, wherein X₁ is L or absent, X₂ is E or absent, X₃ is S or absent, and X₄ is D or absent, when X₁, X₂, X₃, and X₄ are all present the sequence being LESD (SEQ ID NO:253).

[093] In various aspects of the fusion proteins, the IL-18 (or its fragment, variant, or fragment of its variant) is linked by a polypeptide bond to the first protein capable of translocating into the ER. The fusion proteins may have a variety of configurations. Preferably, the N-terminus of the IL-18 (or its fragment, variant, or a fragment of its variant) is linked by a polypeptide bond directly or indirectly to the C-terminus of the first protein capable of translocating in the ER.

[094] Yet in other embodiments, the C-terminus of the IL-18 (or its fragment, variant, or a fragment of its variant) is linked by a polypeptide bond directly or indirectly to the N-terminus of the first protein capable of translocating in the ER. As a nonlimiting example, the IL-18-variant (or IL-18, a fragment of IL-18, a fragment of the IL-18 variant) is fused to the N-terminus of a knob of a knob-into-hole heterodimeric IgG1 protein with or without a propeptide (pp).

[095] In further embodiments, where the C-terminus of the IL-18 is linked to the N-terminus of the first protein capable of translocating in (or through) the ER, a second protein capable of translocating through the ER is often fused to the N-terminus of the IL-18 to mediate masking. It is contemplated that a fusion protein further comprises (iii) a second protein capable of translocating into/through an ER, or a "scaffold" such as heat shock proteins (HSPs) that may not translocate through the ER. In some embodiments, if HSP (nuclear protein) or a cytosolic protein is fused to the N-terminus of the IL-18 to mediate masking, it often requires a signal peptide fused to the N-terminus of the "scaffold" to mediate transport to the ER; and, if the scaffold is fused to the C-terminus of IL-18 to serve to stabilize the complex, then a second protein capable of translocating through the ER is often fused to the N-terminus of the IL-18 to mediate masking. Hence, in some embodiments, the IL-18 (or its fragment, variant, or a fragment of its variant) is at the C-terminus of the fusion protein; in some embodiments, the N-terminus of the IL-18 (or its fragment, variant, or a fragment of its variant) is on the C-terminus end relative to the first protein capable of translocating in the ER, and the C-terminus of the IL-18 (or its fragment, variant, or a fragment of its variant) is on the N-terminus end relative to the second protein capable of translocating in the ER. The "first" or "second" protein capable of translocating in an ER is used as a relative reference.

[096] One or more exemplary amino acid sequences of each component of the fusion protein are shown in Tables 1 and 4.

[097] Some embodiments provide that the first protein/polypeptide capable of translocating into an ER comprises an immunoglobulin heavy chain constant region. In some embodiments, the immunoglobulin heavy chain constant region comprises an immunoglobulin heavy chain constant region domain selected from the group consisting of a CH2 domain, a CH3 domain, and a CH4 domain, or a combination thereof. In some embodiments, wherein the immunoglobulin heavy chain constant region comprises a CH2 domain and a CH3 domain. In some embodiments, the immunoglobulin heavy chain constant region lacks at least a CH1 domain. In some embodiments, the immunoglobulin heavy chain constant region is a human immunoglobulin heavy chain constant region. In some embodiments, the immunoglobulin heavy chain constant region is an immunoglobulin heavy chain

constant region present in the same species as the IL-18. In other embodiments, the immunoglobulin heavy chain constant region is an immunoglobulin heavy chain constant region present in the same species as an organism with which a nucleic acid molecule encoding the fusion protein or a precursor of the fusion protein is transformed or transfected. Further embodiments provide that the fusion protein lacks an immunoglobulin variable domain (V_H).

[098] In various embodiments, the IL-18 (or its fragment, variant, or fragment of its variant) is identical (in sequence) to that of a human origin, and the immunoglobulin heavy chain constant region comprises a hinge region, and a CH2 domain or a CH3 domain, and more preferably comprises a hinge region and both a CH2 domain and a CH3 domain. In various embodiments, the IL-18 (or its fragment, variant, or fragment of its variant) is at least 95%, 90%, or 85% identical (in sequence) to that of a human origin, but with amino acid substitutions or other modifications that reduces affinity of the IL-18 (or its fragment, variant, or fragment of its variant) for IL-18BP. It is contemplated that immunoglobulin heavy chain constant regions suitable for the invention may be derived from immunoglobulins belonging to any of the five immunoglobulin classes referred to in the art as IgA (Ig α), IgD (Ig δ), IgE (Ig ϵ), IgG (Ig γ), and IgM (Ig μ). However, immunoglobulin heavy chain constant regions from the IgG class are preferred. Furthermore, the immunoglobulin heavy chain constant regions may be derived from any of the IgG antibody subclasses referred to in the art as IgG1, IgG2, IgG3, and IgG4. Immunoglobulin heavy chain constant region domains have cross-homology among the immunoglobulin classes. For example, the CH2 domain of IgG is homologous to the CH2 domain of IgA and IgD, and to the CH3 domain of IgM and IgE. Preferred immunoglobulin heavy chain constant regions include protein domains corresponding to a CH2 region and a CH3 region of IgG, or functional portions or derivatives thereof. Further description of immunoglobulin heavy chain constant regions is discussed in detail in U.S. Pat. No. 5,541,087, and U.S. Pat. No. 5,726,044, which are incorporated by reference herein.

[099] In multiple embodiments, the protein/polypeptide to be fused with the IL-18 (or its fragment, variant, or a fragment of its variant) is a dimer of two immunoglobulin heavy chain constant regions/chains, optionally cross-linked by a pair of disulfide bonds between cysteines on adjacent hinge regions. In some embodiments, a hinge region may have an upper hinge domain, a core hinge domain, and a lower hinge domain. In some embodiments, an upper portion of the hinge domain may include or remove the cysteine that is known to form a disulfide bond with the light chain or a fab, resulting in sequences such as EPKSC (SEQ ID NO:241) or EPKSS (SEQ ID NO:242) or EPKSA (SEQ ID NO:243). For example, fusion proteins including IgG1-based ER translocating protein, except FUSE-501, FUSE-503, and FUSE-509, may have removed cysteine from the hinge region, e.g., EPKSS (SEQ ID NO:242) in IgG1-based ER translocating protein, except for FUSE-507 (FUSE-507 has EPKSA (SEQ ID NO:243) in the hinge region). A hinge region may also contain a core hinge domain, such as comprising a sequence CPPCP (SEQ ID NO:244) or a variant where the cysteine is replaced. A hinge region may further include a lower hinge domain, such as comprising a sequence APELLGGP (SEQ ID NO:245) or APEAAGGP (SEQ ID NO:246). In another example, FUSE-509 has an IgG4-based ER-translocating protein,

using a hinge region as depicted in Chiu et al., *Antibodies* 2019, 8(4), 55, 2019. While constructs including immunoglobulin hinge regions are preferred, as depicted in the drawings, the invention contemplates that crosslinking at other positions may be chosen as desired. Furthermore, in some cases, two or more monomers may associate non-covalently to produce dimers or multimers. In various aspects wherein the protein/polypeptide is a dimer of two immunoglobulin heavy chain constant regions/chains, the IL-18 (or its fragment, variant, or a fragment of its variant) is linked to one, and only one, of the two (or more) immunoglobulin heavy chain constant regions/chains. In the case of a wild type IgG-Fc that forms a homodimer, in various instances, a IL-18 is placed on the C-terminus of each monomer of the Fc, thereby having two IL-18 placed on the C-terminus of the Fc. In some instances, a heterodimer may form (e.g., in purification step) when one wild-type Fc fused to one IL-18 is mixed with another wild-type Fc not fused to IL-18. In other aspects, an IL-18 (or its fragment, variant, or a fragment of its variant) is linked each of the two (or more) immunoglobulin heavy chain constant regions/chains in the fusion protein.

[0100] In some embodiments, two arms (or chains) of immunoglobulin heavy chain constant regions (e.g., Fc polypeptides) can be heterodimerized by creating “knobs-in-holes” (KiH) mutations in the CH3 domain. This structural feature in the polypeptide arms allows for assembly of two half antibodies (e.g., Fc heterodimer; and VH-CH and VL-CL domains). For example, a heteromultimer (including a heterodimer) may comprise a first polypeptide and a second polypeptide each comprising a CH3 domain, wherein the polypeptides meet at an engineered interface within the CH3 domain, and the first polypeptide contains an engineered protuberance (“knob”) in the interface with at least one contact residue replaced with an import residue having a larger side chain volume than the original residue, and the second polypeptide contains an engineered cavity (“hole”) in the interface with at least one contact residue replaced with an import residue having a smaller side chain volume than the original residue. In some embodiments, the engineered interface of a heteromultimer includes at least two protuberance-into-cavity mutant pairs. Volumes and accessible surface areas of each amino acid are described in A. A. Zamyatnin, *Prog. Biophys. Mol. Biol.* 24: 107-123, 1972 and C. Chothia, *J. Mol. Biol.* 105: 1-14, 1975. For example, import residues for the formation of a protuberance can be arginine (R), phenylalanine (F), tyrosine (Y) and tryptophan (W); and preferably the original residue for the formation of the protuberance has a small side chain volume, such as alanine, asparagine, aspartic acid, glycine, serine, threonine or valine. As another example, import residues for the formation of a cavity can be alanine (A), serine (S), threonine (T) and valine (V); and preferably the original residue for the formation of the cavity has a large side chain volume, such as tyrosine, arginine, phenylalanine or tryptophan. For example, a T366W mutation in CH3 domain for the “knob”/protuberance chain, and a T366S/L368A/Y407V mutation in CH3 domain for the “hole”/cavity chain. Additionally, the KiH configuration may be coupled further mutations to permit S-S disulfide linkage between the two chains. In various aspects wherein the protein/polypeptide is a heterodimer of a the KiH configuration, the IL-18 (or its fragment,

variant, or a fragment of its variant) is linked to one, and only one, of the two (or more) immunoglobulin heavy chain constant regions/chains (i.e. knob or hole).

[0101] In some embodiments, the two or more arms (or chains) of immunoglobulin heavy chain constant regions (e.g., Fc polypeptides) can contain another symmetric-to-asymmetric steric complementarity design (e.g., HA-TF, ZW1), a charge-to-charge swap interaction (DD-KK), a charge-to-steric complementarity swap plus additional long-range electrostatic interaction (e.g., EW-RVT), or an isotype strand swap design (e.g., strand-exchange engineered domain (SEED)), or Xmab, 7.8.60, Electrostatic Steering, A107, or Duobody, so as to form heterodimers/heteromultimers. Further description of these configurations and exemplary mutations/residues are seen in *Front Immunol.* 2016; 7: 394.

[0102] In additional embodiments, suitable proteins capable of translocating into the ER or a fragment thereof of the fusion protein is a globular protein, immunoglobulin protein, or a fragment thereof. In various embodiments, suitable proteins capable of translocating into the ER or a fragment thereof of the fusion protein is a short polypeptide or protein engineered with a signal peptide for translocating into the ER. For example, the short polypeptide or protein being about 2 kDa or no greater than 250 kDa. As additional examples, the short polypeptide or protein is about 2-5 kDa, about 6-10kDa, about 11-20 kDa, about 21-30 kDa, about 31-40 kDa, about 41-50 kDa, about 51-75 kDa, about 76-100 kDa, about 101-125 kDa, about 126-150 kDa, about 151-175 kDa, about 176-200 kDa, about 201-225 kDa, or about 256-250 kDa.

[0103] In additional embodiments, suitable proteins capable of translocating in an ER can be a globular protein, human serum albumin (HSA), beta2microglobulin, transferrin, fragment antigen-binding region (Fab region), VHH antibody, single-chain variable fragment (scFv), anticalin, designed ankyrin repeat protein (DARPin), a binding domain thereof, and a fragment thereof. Additional suitable proteins capable of translocating in an ER can include type I transmembrane proteins or a fragment thereof, or type II transmembrane proteins or a fragment thereof.

[0104] In various embodiments, the fusion protein comprising the short polypeptide or protein and the IL-18 or IL-18 variant, or fragments thereof, further comprises a second proteins capable of translocating into the ER or a fragment thereof. The second protein capable of translocating into the ER or a fragment thereof can be an Fc domain or HSA, beta2microglobulin, transferrin, fragment antigen-binding region (Fab region), VHH antibody, single-chain variable fragment (scFv), anticalin, designed ankyrin repeat protein (DARPin), a binding domain thereof, and a fragment thereof, or type I transmembrane proteins or a fragment thereof, or type II transmembrane proteins or a fragment thereof as described herein. Figures 8A and 11A (first three from left to right) are nonlimiting examples of such fusion proteins.

[0105] In yet other embodiments, the fusion protein further comprises a protein that cannot naturally translocate into the ER such as nuclear or cytosolic proteins fused to the N-terminus of IL-18. For said proteins, a signal peptide (which may be termed a leader sequence), such as Ig-kappa leader sequence (e.g.,

METDTILLWVLLLWVPGSTG (SEQ ID NO:247)) in FUSE-499, or one or more other signal peptides including but not limited to those derived from human albumin and human azurocidin, *see* Kober et al. *Biotechnol Bioeng.* 2013 Apr; 110(4):1164-73 is fused to the N-terminus of the non ER translocating protein. For example, the signal peptide may be on the N-terminus end of the propeptide or of the IL-18 (or its fragment, variant, or a variant of its fragment). A further example of a protein capable of translocating in/into/through ER may be a protein engineered with a signal peptide, e.g., on the N-terminus end. As an example, Hsp70 is a nuclear protein, but can be engineered to be an ER-translocating protein when fused or linked with a signal peptide on the N-terminus of Hsp70. In various embodiments, the addition of an N-terminal signal peptide, such as the Ig-kappa leader sequence, is in place of a Fc, globular protein, or HSS that'd otherwise be present in a fusion protein disclosed herein.

[0106] In some embodiments, the fusion protein (e.g., a masked IL-18) further comprises a tumor targeting fragment, e.g., a fragment that targets cell surface proteins including but not limited to a tumor associated antigen (TAA). For example, FUSE-517 as shown in FIG. 9G is a masked IL-18 fusion protein that also comprises an anti-EGFR antibody fragment, e.g., Fab of cetuximab. One or more antigen-targeting (preferably tumor antigen-targeting) fragments of known antibodies are conceived to be compatible with the fusion protein system disclosed herein.

[0107] In some embodiments, the fusion protein (e.g., a masked IL-18) comprises an activation receptor targeting fragment, e.g., a fragment that targets activation receptors on cell surface including but not limited to CD16 on natural killer cell surface. Activation receptors include immunoreceptor tyrosine-based activation motif (ITAM)-associated receptors, such as CD16 and NKp46. Activation receptors also include those participating in spontaneous NK cell activation, such as NKp46 (CD335), NKp30 (CD337), NKp44 (CD336), NKG2D (CD314), DNAM-1 (CD226), 2B4 (CD244), LFA-1 (CD11a-CD18), and CD2. In some embodiments, the fusion protein (e.g., a masked IL-18) comprises both an activation receptor targeting fragment and a tumor targeting fragment. Examples of anti-CD16 fragments include but are not limited to CH2 domains of IgG1, CH2 domain of IgG4. In some embodiments, the fusion protein (e.g., a masked IL-18) comprises a polypeptide fragment that targets an immune checkpoint, e.g., fragment that targets an immune checkpoint expressed on T cell. For example, FUSE-694 as shown in FIG. 4 is a masked IL-18 fusion protein that also comprises an anti-PD1 fragment. Example immune checkpoints include but are not limited to PD-1, PD-L1, CTLA-4, LAG-3. One or more immune checkpoint-targeting fragments of known antibodies are conceived to be compatible with the fusion protein system disclosed herein. Examples of anti-PD1 fragments include fragments (e.g., Fab, Fv) from pembrolizumab, nivolumab, pidilizumab, AMP-514, spartalizumab, cemiplimab, AK105, BCD-100, BI 754091, JS001, LJM009, MGA012, Sym021, TSR-042, MGD013, AK104, XmAb20717, tislelizumab, or PF-06801591.

[0108] In some embodiments, the fusion protein (e.g., a masked IL-18) comprises a targeting polypeptide, wherein the targeting polypeptide targets a protein on the same surface as the IL-18 RC. Examples of such proteins include but are not limited to CD16, $\gamma 9$ TCR, $\delta 2$ TCR or $\delta 1$ TCR, NKp46, CD137, CD40 or NKG2D.

In some embodiments, fusion protein (e.g., a masked IL-18) comprises a targeting polypeptide, wherein the targeting polypeptide targets a protein on a cell that does not contain an IL-18RC. In these embodiments, the IL-18 fusion protein will need to be delivered close to the IL-18R complex for a cis or density effect to result in the interaction between the IL-18 fusion protein and the IL-18R complex. For example, TAA targeted IL-18 fusion protein could get to interact with the IL-18R complex on T cells if (a) the fusion protein bridged T cells with TAA+ cells or (b) the fusion protein was combined with another protein that bridged T cells with TAA+ cells or (c) the fusion protein bound to a TAA+ cell that naturally interacted with T cell via a secondary means (e.g. TCR/MHC interaction). In other examples, the fusion protein could be delivered to fibroblasts or other accessory cells in the tumor microenvironment and released by proteases such that it can act on IL-18R+ T or NK cells at a distance.

[0109] Exemplary targeting polypeptides include those noted in Table 5 or fragments thereof. Of those listed as the antigen-binding antibodies, their VHH, Fab regions, or single-chain variable fragments (scFv) can be used as the antigen-binding site of the multispecific antibodies disclosed herein.

[0110] In some embodiments, enterokinase is used for site-specific cleavage of recombinant fusion proteins containing an accessible enterokinase recognition site. For example, enterokinase can specifically cleave after the C-terminal end of the lysine residue at its cleavage site, Asp-Asp-Asp-Asp-Lys (SEQ ID NO:87). Therefore, the fragment produced from this cleavage reaction does not inherit any residues from the DDDDK (SEQ ID NO:87) recognition sequence. Additionally, DDDDK (SEQ ID NO:87) is a part of the octapeptide FLAG tag (DYKDDDDK (SEQ ID NO:248)), which can be utilized as a fusion tag for recognition by antibody, and for detection of fusion protein with Western blot analysis, as well as for purification of the fusion protein by Anti-FLAG affinity chromatography.

[0111] Preferably, a cleavage site can be based on peptide substrates sensitive to other enzymes, especially proteases highly expressed in tumor microenvironment, such as granzyme B, granzyme A, granzyme M, granzyme K, matrix metalloproteinase (MMP) 1/2/9/14 or other MMPs. Of note, granzymes are usually only upregulated in inflamed tumors. For example, a substrate sequence for granzyme B can be Ile-Glu-Xaa-Asp↓Xaa-Gly (SEQ ID NO:249) with the cleavage at the Asp↓Xaa peptide bond. Alternatively, a substrate sequence for granzyme B can also be Ile-Glu-Xaa-Asp↓, with the cleavage at the C-terminus end of Asp, and Xaa can be Gln (SEQ ID NO:88) or another amino acid.

[0112] Several immune cells can release granzyme, such as T cells, NK cells, neutrophils, and mast cells. In several embodiments, a fusion protein comprising (a) a polypeptide fragment that targets an immune checkpoint expressed on an immune cell and/or a polypeptide fragment that targets an activation receptor on NK cell, and (b) a tumor targeting fragment, is effective for bringing the immune cell (e.g., T cell, NK cell) to the tumor, which can result in the release of granzymes that release IL-18. For example, an IL-18 fusion protein comprising a polypeptide

fragment targeting an immune checkpoint protein can reverse exhaustion of NK and/or T cells that then are capable of releasing more granzymes.

[0113] In additional embodiments, the fusion protein comprises a cleavage site recognized by a serine protease, a cysteine protease, an aspartate protease, a threonine protease, a glutamic acid protease, a metalloproteinase, a gelatinase, or an asparagine peptide lyase. In some embodiments, the protease cleavage site is recognized by a Cathepsin B, a Cathepsin C, a Cathepsin D, a Cathepsin E, a Cathepsin K, a Cathepsin L, a kallikrein, a hK1, a hK10, a hK15, a plasmin, a collagenase, a Type IV collagenase, a stromelysin, a Factor Xa, a chymotrypsin-like protease, a trypsin-like protease, an elastase-like protease, a subtilisinlike protease, an actinidain, a bromelain, a calpain, a caspase, a caspase-3, a Mir 1-CP, a papain, a HIV-1 protease, a HSV protease, a CMV protease, a chymosin, a renin, a pepsin, a matriptase, a legumain, a plasmepsin, a nepenthesin, a metalloexopeptidase, a metalloendopeptidase, a matrix metalloprotease (MMP), a MMP1, a MMP2, a MMP3, a MMP8, a MMP9, a MMP10, a MMP11, a MMP12, a MMP13, a MMP14, an ADAM10, an ADAM17, an ADAM12, an urokinase plasminogen activator (uPA), an enterokinase, a prostate-specific target (PSA, hK3), an interleukin-1 β converting enzyme, a thrombin, a FAP (FAP- α), a dipeptidyl peptidase, or dipeptidyl peptidase IV (DPP/IV/CD26), a type II transmembrane serine protease (TTSP), a neutrophil elastase, a cathepsin G, a proteinase 3, a neutrophil serine protease 4, a mast cell chymase, a mast cell tryptase, a dipeptidyl peptidase, and a dipeptidyl peptidase IV (DPP/IV/CD26). Nonlimiting examples of cleavage sites are included in Table I. As a particular example, IEQD (SEQ ID NO:88) can be used.

[0114] It is contemplated that a variant, fragment, or a fragment of a variant of the IL-18 is suitable, and in some embodiments preferred, for the composition of the fusion protein. For example, a variant of mature IL-18 can have one, two, three, four, five, or more amino acid substitutions compared to the wild type mature IL-18. For example, one or more cysteines in the IL-18 or its propeptide are replaced with a natural or non-natural amino acid, such as from Cys to Ser, Ala, or Val, so as to reduce aggregation of the molecule in the fusion protein. Additional examples include cysteine to threonine, asparagine, or glutamine; cysteine to alanine, isoleucine, leucine, methionine, phenylalanine, tyrosine, or tryptophan; cysteine to phenylalanine, alanine, aspartic acid, or asparagine; or cysteine to threonine, glutamine, aspartic acid, phenylalanine, isoleucine or histidine.

[0115] A variant of IL-18 may have a 95%, 90%, 85%, 83%, 80%, 75%, 70%, 65% or at least 60% sequence identity to wild type IL-18. In some embodiments, a variant of IL-18 may have at least 60% and at most 83% sequence identity to wild type IL-18. In some embodiments, the variant of IL-18 in the fusion protein is released as an about 15 kDa functional fragment (e.g., on the electrophoresis gels as tested) when cleaved at a cleavage site of the fusion protein. (It is conceived that the released protein may be mature IL-18 which would normally run at 18 kDa but may appear as about 15 kDa due to the ladder being used or the specific polyacrylamide percentage in a gel.) A fragment of IL-18 may have a 95%, 90%, 85%, 83%, 80%, 75%, 70%, 65%, or at least 60% sequence identity (and/or length) to wild type IL-18. In some embodiments, an IL-18 fragment produced by

the fusion protein disclosed herein, especially after protease cleavage of the fusion protein, is less than 85% (e.g., about 83%, about 83%-80%, about 80%-75%, about 75%-70%, or about 70%-65%) in size compared to natural/wild-type mature IL-18; for example, an IL-18 fragment of about 15 kDa in size, preferably having comparable binding affinity for IL-18Ra/b as the wild type mature IL-18, is fused to a propeptide (or PP variant) and an ER translocating protein (with or without mutations), and the fusion protein also includes a protease cleavage site, such that upon protease cleavage, a small IL-18 fragment (e.g., about 15 kDa in size), is released. Preferably, this small IL-18 fragment maintains the natural binding affinity for IL-18Ra/b and an equal or lower binding affinity relative to IL-18Ra/b for IL-18BP. Preferably a variant, fragment, or a fragment of a variant of the IL-18 is capable of binding IL-18R and forming complex, so as to activate proinflammatory programs and/or NF- κ B pathway. In some embodiments, the variant, fragment, or a fragment of a variant of the IL-18 is capable of having an increased binding affinity (e.g., 150%, 140%, 130%, 120%, 110%, or at least 100% relative to wild type IL-18) and/or inducing the biological activity of at least 150%, 140%, 130%, 120%, 110%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10%, compared to wild type IL-18. In some embodiments, the variant, fragment, or a fragment of a variant of the IL-18 is capable of having an increased binding affinity at 120%, 110%, or at least 100% relative to wild type IL-18, and/or inducing the biological activity of at 120%, 110%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10%, compared to wild type IL-18. In additional embodiments, a variant, fragment, or a fragment of a variant of the IL-18 has diminished binding to IL-18 binding protein (IL-18BP), as compared to a wild type IL-18.

[0116] In some embodiments, the IL-18 or its fragment or variant cleaved from the fusion protein has at least 1,000, 2,000, 3,000, 5,000, 10,000, 30,000, 50,000, 70,000, 80,000, 90,000, or 100,000-fold increase in biological activity (e.g., binding with IL-18R to form IL-18/IL-18R α/β complex and induce downstream signaling), compared to an uncleaved form in the fusion protein especially with propeptide. In further embodiments, the IL-18 or its fragment or variant cleaved from the fusion protein has a comparable biological activity, or within about 10, 20, 30, 40, or 50-fold difference in the biological activity, compared to recombinant human mature IL-18.

[0117] In some embodiments, the IL-18 or its fragment or variant cleaved from the fusion protein has a binding affinity for its IL-18R complex with an equilibrium dissociation constant (KD) of about 18 nM, (e.g., 18 nM $\pm$ 0.3 nM, 18 nM $\pm$ 0.5 nM, 18 nM $\pm$ 1.0 nM). In some embodiments, the IL-18 or its fragment or variant cleaved from the fusion protein has a binding affinity for its IL-18R complex which is about the same, or at least 100%, 95%, or 90%, compared to that of the wild type IL-18. In some embodiments, the IL-18 or its fragment or variant cleaved from the fusion protein has a binding affinity for its IL-18R complex which is greater than that of the wild type IL-18, e.g., a binding affinity that is at least 105%, 110% compared to that of the wild type IL-18, or having a KD value at least 10% or 20% smaller than that of wild type IL-18. Preferably, the IL-18 or its fragment or variant cleaved from the fusion protein has a reduced binding affinity for IL-18BP, compared to that of the wild

type IL-18. For example, in some instances, the IL-18 or its fragment or variant cleaved from the fusion protein has a K_D with IL-18BP of 18 nM or greater, such that it has a lower binding affinity to IL-18BP than to IL-18R. In some instances, the IL-18 or its fragment or variant cleaved from the fusion protein has a K_D with IL-18BP of 18 nM or greater, whereas the wild type IL-18 has a K_D with IL-18BP of about 0.4 nM. It is also conceived that K_D may vary depending on instrument and protocol setup.

[0118] In various embodiments, the fusion protein comprises a first polypeptide or protein capable of translocating into an endoplasmic reticulum (ER) or a fragment thereof; and an interleukin 18 (IL-18), a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant, wherein the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant is on the C-terminus end of the fusion protein relative to the first polypeptide or protein capable of translocating into the ER. In various embodiments, the first polypeptide is not the wild-type IL-18 propeptide. In various embodiments, the protein capable of translocating into an endoplasmic reticulum (ER) or a fragment thereof is not the wild-type IL-18 propeptide. In addition to these features, additional features of the fusion protein are discussed herein.

[0119] In some embodiments, the fusion protein comprises an IL-18 variant. In various embodiments, the IL-18 variant has an amino acid sequence comprising or consisting of amino acid positions 37-193 of SEQ ID NO:250 with one to five amino acid substitutions at positions E42, M87, K89, M96, and M149 of MAAEPVEDNCINFMKFDNTLYFIAEDDENIEQDYFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDVRDNAPRTIFIIISMYKDSQPRGMAVTISVKVEKISTLSVENKIIISFKEMNPPDNIKDTKSDIIFQ RSVPGHDNKMQFESSYEGYFLAVEKERDLFKLILKKEDELGDRSIMFTVQNED (SEQ ID NO:250). In various embodiments, the one to five amino acid substitutions is one amino acid substitution. In other embodiments, the one to five amino acid substitutions are two amino acid substitutions. In other embodiments, the one to five amino acid substitutions are three amino acid substitutions. In other embodiments, the one to five amino acid substitutions are four amino acid substitutions. In other embodiments, the one to five amino acid substitutions are five amino acid substitutions. In various embodiments, the IL-18 variant comprises no more than five amino acid substitutions, with the exception of substituting cysteines.

[0120] In various embodiments, the IL-18 variant has an amino acid sequence comprising or consisting of amino acid positions 37-193 of SEQ ID NO:251 with one to five amino acid substitutions at positions E42, M87, K89, M96, and M149 of MAAEPVEDNCINFMKFDNTLYFIAEDDENIEQDYFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRDNAPRTIFIIISMYKDSQPRGMAVTISVKCEKISTLSCENKIIISFKEMNPPDNIKDTKSDIIFQ RSVPGHDNKMQFESSYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNED (SEQ ID NO:251).

[0121] In various embodiments, the IL-18 variant has an amino acid sequence comprising or consisting of amino acid positions 37-193 of SEQ ID NO:251 with one or more amino acid substitutions at positions C74, C104, C112, and C164, and one to five amino acid substitutions at positions E42, M87, K89, M96, and M149, of

SEQ ID NO:251. In various embodiments, the amino acid substitutions at one or more of C74, C104, C112, and C164 are each independently substituted to valine, alanine or serine. In various embodiments, the amino acid substitutions at one or more of C74, C104, C112, and C164 are each substituted to alanine. In various embodiments, the amino acid substitutions at one or more of C74, C104, C112, and C164 are each substituted to serine.

[0122] In various embodiments, the one to five amino acid substitutions are one or more of: E42K, E42R, E42A, E42H, or E42Q; M87K, or M87H; K89G, K89A, or K89E; M96L, or M96I; or M149V or M149I. In various embodiments, the one to five amino acid substitutions are E42K, E42R, E42A, E42H, or E42Q; M87K, or M87H; K89G, K89A, or K89E; M96L, or M96I; and M149V or M149I.

[0123] In various embodiments, the fusion protein comprises an IL-18 variant selected from Table 1. In various embodiments, the fusion protein comprising the IL-18 variant selected from Table 1, further comprises a propeptide having an amino acid sequence selected from Propeptide column in Table 1, and optionally from the same row as the IL-18 variant. In various embodiments, the fusion protein comprising the IL-18 variant selected from Table 1 and propeptide selected from Table 1, further comprises a cleavage peptide selected from Table 1, and optionally from the same row as the IL-18 variant and propeptide. As a particular example, IEQD (SEQ ID NO:88) can be used.

[0124] In various embodiments, IL-18 variant is an IL-18 variant disclosed in U.S. Patent 7,524,488, U.S. Patent Publication No. 2019/0070262, U.S. Patent Publication No. 2021/0015891, or PCT Publication No. WO 2022/038417, the IL-18 variants and sequences of each of these patent or publications of which are hereby incorporated by reference as though fully set forth.

[0125] In various embodiments, the fusion protein further comprises a targeting polypeptide. In some embodiments, the targeting polypeptide targets a protein on a cell surface, wherein the cell surface also has an IL-18 RC or the cell is capable of expressing the IL-18 RC. In various embodiments, the fusion protein binds to a cell having an IL-18 RC or capable of expressing the IL-18 RC upon activation of the cell, and activates the IL-18 RC signal.

[0126] In other embodiments, the targeting polypeptide targets a protein on a cell surface that does not have an IL-18 RC or the cell is not capable of expressing the IL-18 RC. The cell not having the IL-18 RC on its surface or not capable of expressing the IL-18 RC is in close proximity to a cell expressing the IL-18 RC or is capable of expressing the IL-18 RC. In other instances, the fusion protein can bring the cell not having the IL-18 RC on its surface or not capable of expressing the IL-18 RC into close proximity to a cell expressing the IL-18 RC or is capable of expressing the IL-18 RC.

[0127] In various embodiments, the targeting polypeptide comprises a tumor associated antigen binding domain.

[0128] In various embodiments, the fusion protein further comprises a binding domain for a protein expressed on immune cells. In various embodiments, the fusion protein further comprises a binding domain for a

protein expressed on immune cells that express IL-18 receptor complex or on immune cells that upon activation express the IL-18 receptor complex.

[0129] In various embodiments, the fusion protein further comprises an antibody or antibody fragment, and the fusion protein binds to a tumor cell, or to an immune cell or stromal cell in a tumor tissue. Examples of antibody fragments include Fc fragment, Fab fragment, Fv fragment as well as others discussed herein.

[0130] In various embodiments, the fusion protein further comprises a masking domain. In these embodiments, a mature IL-18 or mature IL-18 variant can be released from a masking domain by a protease. In various embodiments, the protease is granzyme, which can be released from an immune cell. Examples of immune cells include but are not limited to an NK cell, a T cell, a neutrophil, or a mast cell. In various embodiments, the protease is a metalloprotease, which the metalloprotease can be expressed in a tumor microenvironment. Further examples of protease and types of granzymes are described herein. In various embodiments, the mature IL-18 increases the activity of NK cells or T cells, and optionally the activity being one or more of proliferation, survival, and cytotoxicity.

[0131] In various embodiments, the fusion protein further comprises half-life extending molecule. A nonlimiting example of a half-life extending molecule is a half-life extending polypeptide; for example, human serum albumin (HSA) or an HSA-binding fragment. In various embodiments, the fusion protein has reduced activity as compared to wild-type IL-18 when not bound to a cell having the IL-18 RC. In various embodiments, the reduced activity is at least a 75% reduction in activity as compared to wild-type IL-18.

[0132] In various embodiments, the fusion protein comprises polypeptide 1 and polypeptide 2 selected from Table 1. In various embodiments, the fusion protein further comprises polypeptide 3 selected from Table 1. In various embodiments, polypeptide 1 and polypeptide 2, and optionally polypeptide 3 is selected from the same row of Table 1.

[0133] In various embodiments, the fusion protein comprises polypeptide 1 selected from Table 1, wherein polypeptide 1 comprises HSA.

[0134] In various embodiments, the fusion protein does not comprise an IL-18 variant disclosed in U.S. Patent 7,524,488, U.S. Patent Publication No. 2019/0070262, U.S. Patent Publication No. 2021/0015891, or PCT Publication No. WO 2022/038417, the IL-18 variants and sequences of each of these patent or publications of which are hereby incorporated by reference as though fully set forth.

Propeptide Variants

[0135] Various embodiments of the invention provide for propeptide variants. In various embodiments, the propeptide variant has the following amino acid sequence: AAEPVEDNX₁INFVAMKFIDNTLYFIAEDDEN, wherein X₁ is any amino acid except cysteine (SEQ ID NO:238). In various embodiments, X₁ is alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine

or tryptophan (SEQ ID NO:239). In various embodiments, X₁ is valine (SEQ ID NO:78). In various embodiments, X₁ is serine, threonine, asparagine, or glutamine (SEQ ID NO:240). In various embodiments, X₁ is serine (SEQ ID NO:76).

IL-18 Variants

[0136] Various embodiments provide for IL-18 variants.

[0137] In various embodiments, the IL-18 variant has an amino acid sequence comprising or consisting of amino acid positions 37-193 of SEQ ID NO:250 with one to five amino acid substitutions at positions E42, M87, K89, M96, and M149 of
 MAAEPVEDNCIN FVAMKFIDNTLYFIAEDDENIEQDYFGKLESKLSVIRNLNDQVLFIDQGNRPLFED
 MTDSDVRDNAPRTIFIISMYKDSQPRGMAVTISVKVEKISTLSVENKHSFKEMNPPDNIKDTKSDIIFQ
 RSVPGHDNKMQFESSYEGYFLAVEKERDLFKLILKKEDELGDRSIMFTVQNE (SEQ ID NO:250). In various embodiments, the one to five amino acid substitutions is one amino acid substitution. In other embodiments, the one to five amino acid substitutions are two amino acid substitutions. In other embodiments, the one to five amino acid substitutions are three amino acid substitutions. In other embodiments, the one to five amino acid substitutions are four amino acid substitutions. In other embodiments, the one to five amino acid substitutions are five amino acid substitutions. In various embodiments, the IL-18 variant comprises no more than five amino acid substitutions, with the exception of substituting cysteines.

[0138] In various embodiments, the IL-18 variant has an amino acid sequence comprising or consisting of amino acid positions 37-193 of SEQ ID NO:251 with one to five amino acid substitutions at positions E42, M87, K89, M96, and M149 of
 MAAEPVEDNCIN FVAMKFIDNTLYFIAEDDENIEQDYFGKLESKLSVIRNLNDQVLFIDQGNRPLFED
 MTDSDCRDNAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKHSFKEMNPPDNIKDTKSDIIFQ
 RSVPGHDNKMQFESSYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNE (SEQ ID NO:251).

[0139] In various embodiments, the IL-18 variant has an amino acid sequence comprising or consisting of amino acid positions 37-193 of SEQ ID NO:251 with one or more amino acid substitutions at positions C74, C104, C112, and C164, and one to five amino acid substitutions at positions E42, M87, K89, M96, and M149, of SEQ ID NO:251. In various embodiments, the amino acid substitutions at one or more of C74, C104, C112, and C164 are each independently substituted to valine, alanine or serine.

[0140] In various embodiments, the one to five amino acid substitutions are one or more of: E42K, E42R, E42A, E42H, or E42Q; M87K, or M87H; K89G, K89A, or K89E; M96L, or M96I; or M149V or M149I. In various embodiments, the one to five amino acid substitutions are E42K, E42R, E42A, E42H, or E42Q; M87K, or M87H; K89G, K89A, or K89E; M96L, or M96I; and M149V or M149I.

[0141] In various embodiments, the IL-18 variant is selected from the “Mature IL18 variant” column in Table 1.

[0142] In various embodiments, the IL-18 variant further comprises an IL-18 propeptide or IL-18 propeptide variant.

[0143] In various embodiments, the IL-18 variant further comprises an IL-18 propeptide variant having the following amino acid sequence: AAEPVEDNX₁INFVAMKFIDNTLYFIAEDDEN, wherein X₁ is any amino acid except cysteine (SEQ ID NO:238). In various embodiments, X₁ is alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine or tryptophan (SEQ ID NO:239). In various embodiments, X₁ is valine (SEQ ID NO:78). In various embodiments, X₁ is serine, threonine, asparagine, or glutamine (SEQ ID NO:240). In various embodiments, X₁ is serine (SEQ ID NO:76). In various embodiments, the IL-18 variant is selected from the “Mature IL18 variant” column of Table 1, and further comprises a propeptide having an amino acid sequence selected from “Propeptide” column in Table 1, and optionally from the same row as the IL-18 variant.

[0144] In various embodiments, the IL-18 variant further comprises an IL-18 propeptide variant, and a cleavage peptide. In various embodiments, the cleavage peptide selected from Table 1. As a particular example, IEQD (SEQ ID NO:88) can be used.

[0145] In various embodiments, a fusion protein comprising an IL-18 variant selected from Table 1, a propeptide selected from Table 1, and a cleavage peptide selected from Table 1, and optionally from the same row as the IL-18 variant and propeptide.

[0146] In various embodiments, the IL-18 variant is not an IL-18 variant disclosed in U.S. Patent 7,524,488, U.S. Patent Publication No. 2019/0070262, U.S. Patent Publication No. 2021/0015891, or PCT Publication No. WO 2022/038417, the IL-18 variants and sequences of each of these patent or publications of which are hereby incorporated by reference as though fully set forth.

Polynucleotides, vectors and cells

[0147] Various embodiments provide polynucleotides encoding the fusion proteins disclosed herein. For example, the polynucleotides may encode in a 5' to 3' direction, a first protein or polypeptide capable of translocating in an ER and an IL-18 (or its fragment, variant, or a fragment of its variant). Nonlimiting examples of such polynucleotides are in Table 2.

[0148] Furthermore, the polynucleotides optionally may also include a “leader” or “signal” sequence based upon, for example, (1) a propeptide (PP) linked directly to IL-18 (or IL-18 variant) as in FUSE499 or (2) an immunoglobulin light chain sequence fused directly to a hinge region of the immunoglobulin heavy chain constant region. In some embodiments, when the protein/polypeptide capable of translocating in an ER is based upon IgG sequences, the nucleic acid encodes in a 5' to 3' direction, at least an immunoglobulin hinge region (i.e., a hinge

region containing at least one cysteine amino acid capable of forming a disulfide bond with a second immunoglobulin hinge region sequence), an immunoglobulin CH2 domain and a CH3 domain, and an IL-18 (or its fragment, variant, or a fragment of its variant).

[0149] In various embodiments, a polynucleotide encoding the fusion proteins may also be integrated within a replicable expression vector. Hence, a vector encoding the fusion protein is also provided, which may express the fusion protein in, for example, a bacterial host, an intended recipient, or both.

[0150] Additional embodiments provide cells transformed or transfected with one or more nucleic acid molecules (polynucleotides) encoding the fusion protein. The cell can be a prokaryotic cell. Or the cell is a eukaryotic cell, preferably a mammalian cell, and more preferably a human cell. Examples of mammalian cells include Chinese hamster ovary (CHO) cells, NS0 cells (a mouse myeloma cell line), PER.C6® cells, and human embryonic kidney cells (HEK cells).

[0151] In some embodiments, a non-human organism transformed or transfected with one or more nucleic acid molecules encoding the fusion protein is also provided.

Compositions

[0152] Further embodiments provide a composition comprising combinations of two or more different fusion proteins, or combinations of the nucleic acid sequences encoding the fusion proteins. For example, a pharmaceutical composition is provided, wherein the fusion protein or a nucleic acid molecule encoding the fusion protein is an active agent.

[0153] The pharmaceutical compositions according to the invention can also contain any pharmaceutically acceptable carrier. "Pharmaceutically acceptable carrier" as used herein refers to a pharmaceutically acceptable material, composition, or vehicle that is involved in carrying or transporting a compound of interest from one tissue, organ, or portion of the body to another tissue, organ, or portion of the body. For example, the carrier may be a liquid or solid filler, diluent, excipient, solvent, or encapsulating material, or a combination thereof. Each component of the carrier must be "pharmaceutically acceptable" in that it must be compatible with the other ingredients of the formulation. It must also be suitable for use in contact with any tissues or organs with which it may come in contact, meaning that it must not carry a risk of toxicity, irritation, allergic response, immunogenicity, or any other complication that excessively outweighs its therapeutic benefits. The pharmaceutical compositions according to the invention can also be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, alcohols and water. Solid carriers include starch, lactose, calcium sulfate, dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling,

mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule...The pharmaceutical compositions according to the invention may be delivered in a therapeutically effective amount. The precise therapeutically effective amount is that amount of the composition that will yield the most effective results in terms of efficacy of treatment in a given subject. This amount will vary depending upon a variety of factors, including but not limited to the characteristics of the therapeutic compound (including activity, pharmacokinetics, pharmacodynamics, and bioavailability), the physiological condition of the subject (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage, and type of medication), the nature of the pharmaceutically acceptable carrier or carriers in the formulation, and the route of administration. One skilled in the clinical and pharmacological arts will be able to determine a therapeutically effective amount through routine experimentation, for instance, by monitoring a subject's response to administration of a compound and adjusting the dosage accordingly. For additional guidance, see Remington: The Science and Practice of Pharmacy (Gennaro ed. 20th edition, Williams & Wilkins PA, USA) (2000).

Methods of producing

[0154] Methods for making the fusion proteins, or nucleic acids encoding the fusion proteins, are also provided. Some embodiments provide that conventional recombinant DNA methodologies are utilized for generating the fusion proteins. The fusion constructs preferably are generated at the DNA level, and the resulting DNAs integrated into expression vectors, and expressed to produce the fusion proteins of the invention. Subsequently, the vector is expressed in a host cell to obtain the fusion protein; and optionally the method further includes a step of recovering the fusion protein from the host cell culture. In some embodiments, a method of producing interleukin 18 (IL-18), a fragment thereof, an IL-18 variant, or a fragment of the IL-18 variant, comprises culturing a cell transfected with an expression vector comprising a nucleic acid encoding a fusion protein, in cell culture medium to allow a fusion protein to be produced and secreted into the extracellular space for purification; said protein, when contacting a protease to the fusion protein to cleave the fusion protein to produce the IL-18, the fragment thereof, the IL-18 variant, or the fragment of the IL-18 variant. Exemplary nucleic acid molecules encoding a fusion protein are seen in Table 2 Other embodiments provide that chemical conjugation using conventional chemical cross-linkers may be used to fuse protein moieties.

[0155] In some embodiments, the nucleic acid molecules encoding the fusion proteins is expressed in CHO cells or HEK-293. Preferably, expressing the fusion proteins in the host cells results in a recoverable secreted fusion protein of at least 135 mg/L from supernatant of the host cells. In some embodiments, a yield of the fusion protein of at least 135 mg/L is obtained via transient transfection. In some embodiments, an even higher yield of the fusion protein, e.g., at least 150, 200, 250, or 300 mg/L is obtained via stable producer cell clones, or pools of

clones. In some embodiments, from a transient transfection, a yield of the fusion protein is about 130-400 mg/L. In some embodiments, a fusion protein, or the IL-18, the fragment thereof, the IL-18 variant, or the fragment of the IL-18 variant cleaved from the fusion protein, is recovered in more than about 400 mg/L, between 350-400 mg/L, 300-350 mg/L, 200-300 mg/L, 100-200 mg/L, or at least 50 mg/L from supernatant of the host cells.

[0156] In some embodiments, using a Chinese hamster ovary (CHO) expression system, the fusion protein is produced via a process including the steps of: (1) cell recovery, which may be to recover frozen CHO cells via water bath at 37°C; (2) cell subculturing, which may be to sub-culture the cells and adjust the cell density to 6×10^6 /ml for transfection; (3) transfection and expression, using a solution 1 (in which a plasmid is diluted with a diluting agent), a solution 2 (in which a transfection reagent is diluted with a/the diluting agent), and then mixing the solution 1, the solution 2 and the CHO cells, followed by incubating the mixture at a shaker for expression for 12-14 days at 32°C to collect the supernatant of the culture after centrifuge.

[0157] In some embodiments, a purification process is performed after the expression of the fusion protein. In some embodiments, a purification process includes the steps of: (1) washing a column with a binding buffer (10 times volume) at a flow rate of 1 mL/min; (2) loading a fusion-protein-containing sample into the column at a flow rate of 1 mL/min; (3) washing the column with 10x volumes of PBS buffer with a flow rate of 1 mL/min; (4) eluting the protein from the column with 40 mM sodium citrate (pH3.4); optionally the elution sample may be collected into tubes (1ml/min) and measured for optical density (OD) using NanoDrop at 280 nm; and (5) performing dialysis, e.g., against PBS buffer in a dialysis bag overnight.

Table 1. Amino acid sequences of respective components in exemplary fusion proteins ("FUSE"). (Most identical sequences are labeled with a same numerical number next to the component. For example, "Polypeptide 1" sequences, i.e., first polypeptide arm sequences, are identical in FUSE-422, FUSE-423, FUSE-424, FUSE-441, FUSE-442, FUSE-462, FUSE-480, FUSE-481, FUSE-484, FUSE-485, FUSE-486, FUSE-487, FUSE-499, FUSE-500, FUSE-505, FUSE-516, FUSE-517, FUSE-545, FUSE-546, FUSE-556, FUSE-583-587, FUSE-588, FUSE-599-602, FUSE-645, FUSE-686, FUSE-756-758, FUSE-775, FUSE-874-876, and FUSE-878-892 – all labeled with "0" next to respective component.) Residues represented by a lower-case letter are amino acid locations with potential mutations.

	<u>Polypeptide 1</u>	<u>Polypeptide 2</u>	<u>Polypeptide 3</u>	<u>Propeptide</u>	<u>Cleavage</u>	<u>Mature IL18 variant</u>
F	EPKSSDKTHTCPPCPAPPELLG	0 EPKSSDKTHTCPPCPAPPELLGGPSVFLF		AAEPVEDNSI	3 DDDD	YFGKLESKLS
U	GPSVFLFPKPKDTILMISRTF	PPKPKDTILMISRTTEVTCVVVDVSHEDP		NEVAMKFIDN	K	VIRNLNDQVL
S	EVTCTVVVDVSHEDPEVKFNWY	EVKFNWYVDGVEVHNAKTKPREEQYNST		TLYFIAEDDE	(SEQ	FIDQGNRELF
E	VDGVEVHNAKTKPREEQYNST	YRVVSVLTIVLHQDWLNGKEYKCKVSNKA		N (SEQ ID	ID	EDMTDSDSRD
-	YRVVSVLTIVLHQDWLNGKEYK	LPAPTEKTIISKAKGQPREPQVYTLPPSR		NO: 76)	NO: 8	NAPRTIFIIS
4	CKVSNKALPAPIEKTIISKAKG	EEMTKNQVSLWCLVKGYFPSDIAVEWES			7)	KYGDSPQRGL
2	QPREPQVYTLPPSREEMTKNQ	NGQPENNYKTTTPVLDSDGSFFLYSKLT				AVTISVKSEK
2	VSLSCAVKGYFPSDIAVEWES	VDKSRWQQGNVFCSSVMHEALHNHYTQK				ISTLSSENKI
	NGQPENNYKTTTPVLDSDGSF	SLSLSPGKAAEPVEDNS INFVAMKFIDN				ISFKEMNFPD
	FLVSKITFVDKSRWQQGNVFC	TLYFTAEDDENDDDKYFGKLESKLSVT				NIKDTKSDII
	SVMHEALHNRTQKSLSLSPG	RNLNDQVLFIDQGNREPLFEDMTDSDSRD				FFQRSVPFGHD
	K (SEQ ID NO:1)	NAPRTIFIISKYGDSPQRGLAVTISVKS				NKVQFESSY
		EKISTLSSENKIISFKEMNPPDNKDTK				EGYFLASEKE
		SDIIFFQRSVPGHENKVQFESSYEGYF				RDLEFKLILKK
		LASEKERDLFKLILKKEDELGORSIMFT				EDELGORSIM
		VQNEED (SEQ ID NO:20)				FTVQNEED
						(SEQ ID
						NO: 97)
F	EPKSSDKTHTCPPCPAPPELLG	0 EPKSSDKTHTCPPCPAPPELLGGPSVFLF		AAEPVEDNAI	4 DDDD	YFGKLESKLS
U	GPSVFLFPKPKDTILMISRTF	PPKPKDTILMISRTTEVTCVVVDVSHEDP		NEVAMKFIDN	K	VIRNLNDQVL
S	EVTCTVVVDVSHEDPEVKFNWY	EVKFNWYVDGVEVHNAKTKPREEQYNST		TLYFIAEDDE	(SEQ	FIDQGNRELF
E	VDGVEVHNAKTKPREEQYNST	YRVVSVLTIVLHQDWLNGKEYKCKVSNKA		N (SEQ ID	ID	EDMTDSARD
-	YRVVSVLTIVLHQDWLNGKEYK	LPAPTEKTIISKAKGQPREPQVYTLPPSR		NO: 77)	NO: 8	NAPRTIFIIS
4	CKVSNKALPAPIEKTIISKAKG	EEMTKNQVSLWCLVKGYFPSDIAVEWES			7)	KYGDSPQRGL
2	QPREPQVYTLPPSREEMTKNQ	NGQPENNYKTTTPVLDSDGSFFLYSKLT				AVTISVKAEK
3	VSLSCAVKGYFPSDIAVEWES	VDKSRWQQGNVFCSSVMHEALHNHYTQK				ISTLSAENKI

	NGQPENNYKTTTPVLDSDGSF FLVSKLTVDKSRWQGNVFS SVMHEALHNRTQKSLSPG K (SEQ ID NO:1)	SLSPGKAAEPVEDNAINFVAMKFTDN TLTYFLAEDDDDDKYFGKLESLSVI RNLDQVLFIDQGNRPLFEDMTSDARD NAPRTIFIISKYGSQPRGLAVTISVKA EKISTLSAENKIISFKEMNPPDNIKDTK SDIIFQRSVPGHNKVQFESSSYEGYF LAAKERDLFKLILKKEDELGDRSIMFT VQNEQ (SEQ ID NO:21)			AAEPVEDNVI NFVAMKFIDN TLTYFLAEDDE N (SEQ ID NO:78)	5 DDDD K (SEQ ID NO:8 7)	ISFKEMNPPD NIKDTKSDII FFQRSVPBGHD NKVQFESSY EGYFLAAEKE RDLFKLILKK EDELGDRSIM FTVQNEQ (SEQ ID NO:98)	9
F U S E - 4 2 4	EPKSSDKTHTCPPCPAPELLG GPSVFLFPKPKDTLMISRT EVTGVVVDVSHEDPEVKFNWY VDGVEVHNKTKPREEQYNST YRVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKG QPREEQVYTLPPSREEMTKNQ VLSCAVKGFPYPSDIAVEWES NGQPENNYKTTTPVLDSDGSF FLVSKLTVDKSRWQGNVFS SVMHEALHNRTQKSLSPG K (SEQ ID NO:1)	EPKSSDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVDVSHEDP EVKFNWYVDGVEVHNKTKPREEQYNST YRVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGPREPQVYTLPPSR EEMTKNQVSLWCLVKGYFSPDIAVEWES NGQPENNYKTTTPVLDSDGSFFLYSKLT VDKSRWQGNVFSVSMHEALHNHYTQK SLSPGKAAEPVEDNVIINFVAMKFIDN TLTYFLAEDDDDDKYFGKLESLSVI RNLDQVLFIDQGNRPLFEDMTSDVDRD NAPRTIFIISKYGSQPRGLAVTISVKV EKISTLSVENKIISFKEMNPPDNIKDTK SDIIFQRSVPGHNKVQFESSSYEGYF LAVEKERDLFKLILKKEDELGDRSIMFT VQNEQ (SEQ ID NO:22)					YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTSDVDRD NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDTKSDII FFQRSVPBGHD NKVQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNEQ (SEQ ID NO:99)	9
F U S E - 4 4 1	EPKSSDKTHTCPPCPAPELLG GPSVFLFPKPKDTLMISRT EVTGVVVDVSHEDPEVKFNWY VDGVEVHNKTKPREEQYNST YRVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKG QPREEQVYTLPPSREEMTKNQ VLSCAVKGFPYPSDIAVEWES NGQPENNYKTTTPVLDSDGSF	EPKSSDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVDVSHEDP EVKFNWYVDGVEVHNKTKPREEQYNST YRVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGPREPQVYTLPPSR EEMTKNQVSLWCLVKGYFSPDIAVEWES NGQPENNYKTTTPVLDSDGSFFLYSKLT VDKSRWQGNVFSVSMHEALHNHYTQK SLSPGKGGDDDDKYFGKLESKLSVIRN					YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTSDVDRD NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD	9

FLVSKLTVDKSRWQGNVFC SVMHEALHNRFTQKSLSPG K (SEQ ID NO:1)	LNDQVLFDQGNRFLFEDMTDSVDRNA PRTIIFIISKYGDSPQRLAVTISVKVEK ISTLSVENKIISEKEMNPPDNIKDIXSD IIFQRSVPGHDKVQFESSSYEGYFLA VEKERDLFKLILKKEDELGDRSIMFTVQ NED (SEQ ID NO:23)			AAEPVEDNVI NFVAMKFIDN TLYFIAEDDE N (SEQ ID NO:78)	5 DDDD K (SEQ ID NO:8 7)	DDDD K (SEQ ID NO:8 7)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSVDRD NAPRTIFIIS MYKDSQPRGM AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDKSDII FFQRSVPGHD NKMQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNE (SEQ ID NO:99)	NIKDKSDII FFQRSVPGHD NKVQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNE (SEQ ID NO:99)
F EPKSSDKHTHTCPCPAPELLG U GPSVFLFPPKPKDTLMISRT S EVTCVVVDVSHEDDEVKFNWY E VDGVEVHNAKTKPREEQYNST - YRVVSVLTVLHQDWLNGKEYK 4 CKVSNKALPAPIEKTISKAGG 4 QPREPQVYTLPPSREEMTKNQ 2 VLSLCAVKGFPYSDIAVEWES NGQPENNYKTTPPVLDSDGSF FLVSKLTVDKSRWQGNVFC SVMHEALHNRFTQKSLSPG K (SEQ ID NO:1)	0 EPKSSDKHTHTCPCPAPELLGSPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDP EVKENWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLWCLVKGYFSPDSIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQGNVFCSSVMHEALHNYTQK SLSLSPGKAAEPVEDNVI NFVAMKFIDN TLYFIAEDDENDDDKYFGKLESKLSVI RNLDQVLFDQGNRPLFEDMTDSVDRD NAPRTIFIISMYKDSQPRGMVTTISVKV EKISTLSVENKIISEKEMNPPDNIKDTK SDIIFQRSVPGHDKVQFESSSYEGYF LAVEKERDLFKLILKKEDELGDRSIMFT VQNE (SEQ ID NO:24)			AAEPVEDNVI NFVAMKFIDN TLYFIAEDDE N (SEQ ID NO:78)	5 IEQD (SEQ ID NO:8 8)	IEQD (SEQ ID NO:8 8)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSVDRD NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDKSDII	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSVDRD NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDKSDII
F EPKSSDKHTHTCPCPAPELLG U GPSVFLFPPKPKDTLMISRT S EVTCVVVDVSHEDDEVKFNWY E VDGVEVHNAKTKPREEQYNST - YRVVSVLTVLHQDWLNGKEYK 4 CKVSNKALPAPIEKTISKAGG 6 QPREPQVYTLPPSREEMTKNQ 2 VLSLCAVKGFPYSDIAVEWES NGQPENNYKTTPPVLDSDGSF FLVSKLTVDKSRWQGNVFC	0 EPKSSDKHTHTCPCPAPELLGSPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDP EVKENWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLWCLVKGYFSPDSIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQGNVFCSSVMHEALHNYTQK SLSLSPGKAAEPVEDNVI NFVAMKFIDN TLYFIAEDDENIEQYFGKLESKLSVIR			AAEPVEDNVI NFVAMKFIDN TLYFIAEDDE N (SEQ ID NO:78)	5 IEQD (SEQ ID NO:8 8)	IEQD (SEQ ID NO:8 8)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSVDRD NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDKSDII	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSVDRD NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDKSDII

	SVMHEALHNRFTQKSLSLSPG K (SEQ ID NO:1)	NLNDQVLFIDQGNRPLFEDMTDSDVRN APRTIFIISKYQDSQPRGLAVTISVKVE KISTLSVENKIISFKEMNPPDNIKDTKS DIIFFQRSVPGHDNKNVQFESSYEGYFL AVEKERDLFKLILKKEDELGDRSIMFTV QNEED (SEQ ID NO:25)				FFQRSVPFGHD NKVQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNEED (SEQ ID NO:99)	
F	EPKSSDKTHTCPCPAPPELLG	0	EPKSSDKTHTCPCPAPPELLGPGSVFLF PPKPKDTIMISRTPEVTCVVVDVSHEDP EVKENWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNVSLWCLVKGFYPSDIAVEWES NGQENNYKTFPPVLDSGSFFLYSKLT VDKSRWQQGNVFSVCSVMHEALHNHYTQK SLSLSPGKAAEPVEDNSINFVAMKFIDN TLYFIAEDDENDDDKYFGKLESKLSVI RNLDQVLFIDQGNRPLFEDMTDSDSRD NAPRTIFIISMYKDSQPRGMATISVKS EKISTLSSENKIISFKEMNPPDNIKDTK SDIIFQRSVPGHDNKNQFESSYEGYF LASEKERDLFKLILKKEDELGDRSIMFT VQNEED (SEQ ID NO:26)	3	AAEPVEDNSI NFVAMKFIDN TLYFIAEDDE N (SEQ ID NO:76)	DDDD K (SEQ ID NO:8 7)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDSRD NAPRTIFIIS MYKDSQPRGM AVTISVKSEK ISTLSSENKI ISFKEMNPPD NIKTKSDII FFQRSVPFGHD NKVQFESSY EGYFLASEKE RDLFKLILKK EDELGDRSIM FTVQNEED (SEQ ID NO:101)
F	EPKSSDKTHTCPCPAPPELLG	0	EPKSSDKTHTCPCPAPPELLGPGSVFLF PPKPKDTIMISRTPEVTCVVVDVSHEDP EVKENWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNVSLWCLVKGFYPSDIAVEWES NGQENNYKTFPPVLDSGSFFLYSKLT VDKSRWQQGNVFSVCSVMHEALHNHYTQK SLSLSPGKAAEPVEDNAINFVAMKFIDN TLYFIAEDDENDDDKYFGKLESKLSVI RNLDQVLFIDQGNRPLFEDMTDSDARD	4	AAEPVEDNAI NFVAMKFIDN TLYFIAEDDE N (SEQ ID NO:77)	DDDD K (SEQ ID NO:8 7)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDARD NAPRTIFIIS MYKDSQPRGM AVTISVKA EK ISTLSAENKI ISFKEMNPPD NIKTKSDII FFQRSVPFGHD
U	GPSVFLFPPKPKDTIMISRT						
S	EYTCVVVDVSHEDPEVKFNWY						
E	VDGVEVHNAKTKPREEQYNST						
-	YRVVSVLTVLHQDWLNGKEYK						
4	CKVSNKALPAPIEKTISKAKG						
8	QPREPQVYTLPPSREEMTKNQ						
0	VSLSCAVKGFYPSDIAVEWES						
	NGQENNYKTFPPVLDSGSF						
	FLVSKLTVDKSRWQQGNVFSC						
	SVMHEALHNRFTQKSLSLSPG						
	K (SEQ ID NO:1)						
F	EPKSSDKTHTCPCPAPPELLG						
U	GPSVFLFPPKPKDTIMISRT						
S	EYTCVVVDVSHEDPEVKFNWY						
E	VDGVEVHNAKTKPREEQYNST						
-	YRVVSVLTVLHQDWLNGKEYK						
4	CKVSNKALPAPIEKTISKAKG						
8	QPREPQVYTLPPSREEMTKNQ						
1	VSLSCAVKGFYPSDIAVEWES						
	NGQENNYKTFPPVLDSGSF						
	FLVSKLTVDKSRWQQGNVFSC						

[illegible]

		KISTLSVENKIISFKEMNPPDNIKTKS DIIFFQRSVPGHDKMQFESSYEGYFL AVEKERDLFKLILKKEDELGDRSIMFTV QNEID (SEQ ID NO:29)				AAEPVEDNVI NEVAMKFIDN TLYFTAEDDE N (SEQ ID NO:78)	5 GPLG VR (SEQ ID NO:8 9)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTSDVRD NAPRTIFIIS MYKDSQPRGM AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKTKSDII FFQRSVPGHD NMQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNEID (SEQ ID NO:100)	EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNEID (SEQ ID NO:100)	
F	EPKSSDKTHTCPPCPAPELLG	0	EPKSSDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDP EVKENWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYCKVSNKA LPAPIEKTISAKAQPREPQVYTLPPSR EEMTKNQVSLWCLVKGYFSPDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFCSSVMHEALHNHYTQK SLSLSPGKAAEPVEDNVI NEVAMKFIDN TLYFIAEDDENGLVRCGYFGKLESKL SVIRNLNDQVLFIDQGNRPLFEEMTDS VRDNAPRTIFTISMYKDSQPRGMATIS VKVEKISTLSVENKIISFKEMNPPDNIK DTKSDIIFQRSVPGHDKMQFESSYE GYFLAVEKERDLFKLILKKEDELGDRSI MFTVQNEID (SEQ ID NO:30)				AAEPVEDNVI NEVAMKFIDN TLYFTAEDDE N (SEQ ID NO:78)	5 VHMP LGFL GP (SEQ ID NO:9 0)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTSDVRD NAPRTIFIIS MYKDSQPRGM AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKTKSDII FFQRSVPGHD NMQFESSY EGYFLAVEKE	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTSDVRD NAPRTIFIIS MYKDSQPRGM AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKTKSDII FFQRSVPGHD NMQFESSY EGYFLAVEKE
U	GPSVFLFPKPKDTLMISRT									
S	EVTCTVVVDVSHEDPEVKFNWY									
E	VDGVEVHNAKTKPREEQYNST									
-	YRVVSVLTVLHQDWLNGKEYK									
4	CKVSNKALPAPIEKTISKAG									
8	QPREPQVYTLPPSREEMTNQ									
6	VLSLCAVKGYFSPDIAVEWES									
8	NGQPENNYKTTPPVLDSDGSF									
6	FLVSKLTVDKSRWQQGNVFC									
8	SVMHEALHNRTFTQKSLSLSPG									
K	(SEQ ID NO:1)									
F	EPKSSDKTHTCPPCPAPELLG	0	EPKSSDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDP EVKENWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISAKAQPREPQVYTLPPSR EEMTKNQVSLWCLVKGYFSPDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFCSSVMHEALHNHYTQK SLSLSPGKAAEPVEDNVI NEVAMKFIDN TLYFIAEDDENVHMFGLFGCGYFGKL ESKLSVIRNLNDQVLFIDQGNRPLFEDM TDSVDRDNAPRTIFTIISMYKDSQPRGMA VTISVKVEKISTLSVENKIISFKEMNPP				AAEPVEDNVI NEVAMKFIDN TLYFTAEDDE N (SEQ ID NO:78)	5 VHMP LGFL GP (SEQ ID NO:9 0)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTSDVRD NAPRTIFIIS MYKDSQPRGM AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKTKSDII FFQRSVPGHD NMQFESSY EGYFLAVEKE	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTSDVRD NAPRTIFIIS MYKDSQPRGM AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKTKSDII FFQRSVPGHD NMQFESSY EGYFLAVEKE
U	GPSVFLFPKPKDTLMISRT									
S	EVTCTVVVDVSHEDPEVKFNWY									
E	VDGVEVHNAKTKPREEQYNST									
-	YRVVSVLTVLHQDWLNGKEYK									
4	CKVSNKALPAPIEKTISKAG									
8	QPREPQVYTLPPSREEMTNQ									
7	VLSLCAVKGYFSPDIAVEWES									
8	NGQPENNYKTTPPVLDSDGSF									
6	FLVSKLTVDKSRWQQGNVFC									
K	(SEQ ID NO:1)									

[illegible]

	FSCSVMEALHNHYTQKSLSLSPGK (SEQ ID NO:33)					EDELGDRSIM FTVQNE (SEQ ID NO:100)	1
F	DAKSEVAHRFKDLGEENFKA					YFGKLESKLS	1
U	LVLIAFAQYLQCCPEFDHVKL					VIRNLNDQVL	0
S	VNEVTEFAKTCVADESAENCD					FIDQGNRELE	
E	KSLHTLFGDKLCIVATLRETY					EDMTDSDVRD	
-	GEMADCCAKQEPERNECFLOH					NAPRTIFIIS	
5	KDNPENLPRLVPEVDWMTA					MYKDSQPRGM	
0	FHDNEETFLKKYLYEIARRHP					AVTISVKVEK	
1	YFYAPELLEFFAKRYKAAFTEC					ISTLSVENKI	
	QOADAACAILLPKLDELDEG					ISFKEMNPPD	
	KASSAKQRLKASLQKFGERA					NIKDTKSDII	
	EKAWAVARLSQREFPKAEFAEV					FFQRSVPGH	
	SKLVDTLTKVHTECHGDILLE					NKMQFESSY	
	CADBRADLAKY ICENQDSISS					EGYFLAVEKE	
	KLKECCEKPLLEKSHCIAEVE					RDLFKLIIKK	
	NDEMFADLPSLAADFVESKDV					EDELGDRSIM	
	CKNYAEAKDVFLGMFLYIYAR					FTVQNE (SEQ ID NO:100)	
	RHPDYSVVLRLRLAKTYETTL						
	EKCCAAADPHECYAKVFDEFK						
	PLVEEPQNLIKQNCLEFEQLG						
	EYKFQNALLVRYTRKVPQVST						
	PTLVEVSRNLGKVGSKCKHP						
	EAKMPCAEDYLSVVLNQLCV						
	LHEKTPVSDRVTKCTESLVN						
	RRPCFSALEVDETVVPKEFNA						
	ETFTFHADICTLSEKERQIKK						
	QTALVELLVKHKPKATKEQLKA						
	VMDDFAAFVEKCKKADDDKETC						
	FAEEGKKLVAASQAALGLAAE						
	PVEDNVINVFAMKFIINTLYF						
	IAEDDENDDDKYGKLESKL						
	SVIRNLNDQVLFIQGNRPLF						
	EDMTDSDVRDNAPRTIFIISM						
	YKDSQPRGMVTVISVKVEKIS						

	TLSVENKIISFKEMNPPDNIK DTKSDILFFQRSVFGHDNMQ FESSYEGYFLAVEKERDLFK LILKKEDELGDRSIMFTVQNE D (SEQ ID NO:2)					AAEPVEDNVI NEVAMKFIDN TLYFIAEDDE N (SEQ ID NO:78)	5 DDDD K (SEQ ID NO:8 7)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDVRD NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDTKSDII FFQRSVPCHD NKVQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNE (SEQ ID NO:99)	9
F	DAHSEVAHRFKDLGENFKA								
U	LVLIAFAQYLQCFEDHVKL								
S	VNEVTEFAKTCVADESAENCD								
E	KSLHTLFGDKLCTVATIRETY								
-	GEMADOCAKQEPERNECFLOH								
5	KDDNENLPRLVRPEVDMCTA								
O	FHDNEETFLKKYLYELARRHP								
2	YFYAPELILFFAKRYKAAFTEC								
	CQAADKAAACILPKLDELDEG								
	KASSAKQRLKASLQKEGERA								
	FKAWAVARLSQRFKAFAEV								
	SKLVTDLTKVHTECCHGDLLE								
	CADDRADIACY ICENQDSISS								
	KLKECCEKPLLEKSHCIAEVE								
	NDEMPADLPSLAADVESKDV								
	CKNYAEAKDVFLGMELYEYAR								
	RHPDYSVVLRLRLAKTYETTL								
	EKCCAAADPHECYAKVDEFK								
	PLVEEPQNLIKQNCLEFEQLG								
	EYKFQNALLVRYTKKVPQVST								
	PTLVEVSRNLGKVGSKCKHP								
	EAKMPCAEDYLSVLNQLCV								
	LHEKTEVSDRVTKCTESLVN								
	RRPCFSALEVDETYVPKEFNA								
	ETTFHADICTLSEKERQIKK								
	QTALVELVKHKFKATKEQLKA								
	VMDDFAAFVEKCCKADDKETC								
	FAEEGKKIQAASQAALGLAAE								
	PVEDNVINFVAMKFIDNTLYF								
	IAEDDNDDDKYFGKLESKL								
	SVIRNLNDQVL FIDQGNRPLF								
	EDMTDSDVRDNAPRTIIFIISK								

YGDSPRGLAVTISVKVEKIS TSLSVENKIISFKEMNPPDNIIK DTKSDIIFQRSVPCHDNKVQ FESSYEGYFLAVEKERDLFK LILKREDELGDRSIMFTVQNE D (SEQ ID NO:3)							YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDVRD NAPRTIFIIS MYKDSQPRGM AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDTKSDII FFQRSVPCHD NKMQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNE (SEQ ID NO:100)	1 0
F DAHSEVAHREKDLGEENFKA U LVLIAFAQYLQCCPEFDHVKL S VNEVTEFAKTCVADESAENCD E KSLHTLFGDKLCTVATLRETY - GEMADCCAKQEPERNECFLOH 5 KDDNENLPRLVRPEVDVMCTA O FHDNEETFLKKYLYELIARRHP 3 YFYAPELLEFFAKRYKAAFTEC COADKAAACLLPKLDELRDEG KASAKQRLKCAQLQKFCGERA FKAWAVARLSQRFPKAEFAEV SKLVTDLTKVHTECHGDILLE CADDRADIACYICENQDSISS KLKCCCKPLLEKSHCIAEVE NDENFADLPSLAADFVESKDV CKNYAEAKDVFLGMFLYEYAR RHPDYSVVLLRLAKTYETTL EKCCAAADPHECVAKVFEFK PLVEEPQNLIKQNCSELFQLG EYKFQNALLVRYTKKVPQVST PTLVEVSRNLGKGSCKCKHP EAKMPCAEDYLSVVLNQLCV LHEKTPVSDRVTKCTESLVN RRPCFSALEVDEITYVPKEFNA ETTFTHADICTLSEKERQIKK QVALVELVKHKPKATKEQLKA VMDDFAAFVEKCKKADDKETC FAEGKKLVAASQAALGLGDD DDKYFGKLESKLSVIRNLNDQ VLFIDQGNRPLFEDMTDSDVR DNAPRTIFIISMYKDSQPRGM							DDDD K (SEQ ID NO:8 7)	

AVTISVKVEKISTLSVENKII SEKEMNPENIKDTKSDIIF QRSVPGHDKMQFESSYEGY FLAVEKERDLFKLILKREDEL GDRSIMFTVQNEO (SEQ ID NO: 4)						DDDD K (SEQ ID NO: 8 7)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDVRD NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDTKSDII FFQRSVPGH NKVQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNEO (SEQ ID NO: 99)
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AVTISVKVEKISTLSVENKII SFKEMNPDNIKDKSDIIFF QRSVPFGHDKVQFESSSYEGY FLAVEKERDLFKLILKEDEL GDRSIMFTVQNE (SEQ ID NO: 5)	EPKSSDKTHCTPCPPAPELLG GPSVFLFPKPKDTIMISRTIP EVTGVVDVSHEDPEVKFNWY VDGVEVHNNAKTPREEQNST YRVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAG QPREPQVYTLPPSREEMTKNQ VSLSCAVGFGYPSDIAVEWES NGQFENNXYKTPPVLDSDGSF FLVSKLTVDKSRWQGNVFS SYMHEALHNRTQKSLSPG K (SEQ ID NO: 1)	0	EPKSSDKTHCTPCPPAPELLGGPSVFLF PPKPKDTIMISRTPEVTCVVVDVSHEDP EVKENWYVDGVEVHNNAKTPREEQNST YRVSVLTVLHQDWLNGKEYCKVSNKA LPAPIEKTISKAGQPREPQVYTLPPSR EEMTKNQVSLWCLVKGYFSPDIAVEWES NGQFENNXYKTPPVLDSDGSFFLYSKLT VDKSRWQGNVFSQSYMHEALHNHYTQK SLSLSPGKDDDDKYFGKLESKLSVIRNL NDQVLFDQGNRPLFEDMTDSVDRNAP RTIFILSMYKDSQPRGMATISVKVEKI STLSVENKIIISFKEMNPDNIKDKSDI IFFQRSVPFGHDKVQFESSSYEGYFLAV EKERDLFKLILKEDELGDRSIMFTVQNE ED (SEQ ID NO: 34)					YFGKLESKLS 1 VIRNLNDQVL 0 FIDQGNRPLF (SEQ ID NO: 8 7) MYKDSQPRGM AVTISVKVEK ISTLSVENKI ISFKEMNPD NIKDKSDII FFQRSVPFGH DKVQFESSSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNE (SEQ ID NO: 100)
EPKSADKTHCTPCPPAPELLG GPSVFLFPKPKDTIMISRTIP EVTGVVDVSHEDPEVKFNWY VDGVEVHNNAKTPREEQNST YRVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAG QPREPQVYTLPPSREEMTKNQ VSLTCLVKGFGYPSDIAVEWES NGQFENNXYKTPPVLDSDGSF FLYSKLTVDKSRWQGNVFS SYMHEALHNHYTQKSLSPG KAAEPVEDNVINVFAMKFDN TLYFIAEDDENDDDKYFGKL	EPKSADKTHCTPCPPAPELLG GPSVFLFPKPKDTIMISRTIP EVTGVVDVSHEDPEVKFNWY VDGVEVHNNAKTPREEQNST YRVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAG QPREPQVYTLPPSREEMTKNQ VSLTCLVKGFGYPSDIAVEWES NGQFENNXYKTPPVLDSDGSF FLYSKLTVDKSRWQGNVFS SYMHEALHNHYTQKSLSPG KAAEPVEDNVINVFAMKFDN TLYFIAEDDENDDDKYFGKL	5	AAEPVEDNVI NEVAMKFDN TLYFIAEDDE N (SEQ ID NO: 78)					YFGKLESKLS 1 VIRNLNDQVL 0 FIDQGNRPLF (SEQ ID NO: 8 7) MYKDSQPRGM AVTISVKVEK ISTLSVENKI ISFKEMNPD NIKDKSDII FFQRSVPFGH DKVQFESSSY EGYFLAVEKE

ESKLSVIRNLNDQVLFIDQGN RPLFEIMTDSVDRDNAPRTIIF IISMYKDSQPRGMAVTISVKV EKISTLSVENKIISFKEMNPP DNIKDKSDIIFFORSVPGHD NKMOFESSSYEGYFLAVEKER DLFKLILKKEDELGDRSIMFT VQNEID (SEQ ID NO:6)						RDLFKLILKK EDELGDRSIM FTVQNEID (SEQ ID NO:100)	1 0
F EPKSADKTHTCPPCPAPELLG U GPSVLFPPPKPKDTIMISRTF S EVTCVVVDVSHEDPEVKFNWY E VDGVEVHNAKTKPREEQYNST - YRVSVITVLHQDWLNGKEYK 5 CKVSNKALPAPIERTISKAKG 0 QPREFQVITLPPSRREEMTKNQ 8 VSLTCLVKGFPYPSDIAVEWES NGQFENNYKTTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVESC SYMHEALHNHYTQKSLSLSPG KDDDKYFGKLESKLSVIRNL NDQVLFIDQGNRPLEFEDMTDS DVRDNAPRTIFIISMYKDSQP RGMATVISVKVEKISTLSVEN KIISFKEMNPPDNIDKTKSDI IFFQRSVPGHDNKMQFESSY EGYFLAVEKERDLFKLILKE DELGDRSIMFTVQNEID (SEQ ID NO:7)						DDDD K (SEQ ID NO:8 7)	1 0
F ESKYGPCCPCPCPAPEFLGGPS U VFLEPPKPKDTIMISRTPEVT S CVVVDVSDQEDPEVFQFNWYVDG E VEVHNAKTKPREEQENSTYRV - VSVLTVLHQDWLNGKEYKCKV 5 SNKGLPSSIEKTIISKAKGQPR 0 EPQVYITLPPSQEEMTKNQVSL 9 TCVLKGFPYPSDIAVEWESNGQ PENNYKTTTPPVLDSDGSFFLY					AAEPVEDNVI NEVAMKFIDN TLYFIAEDDE N (SEQ ID NO:78)	5 DDDD K (SEQ ID NO:8 7)	1 0

SRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLGKAA EPVEDNVINFAVMKFIDNTLY FTAEDDENDDDDKYFGKLESK LSVIRNLNDQVLFIQQGNRPL FEDMTSDVRDNAPRTIFIIS MYKDSQPRGMVATISVKVEKI STLSVENKLIISFKEMNPPDNI KDTKSDIIFQORSVPFGHDKM QFESSSYEGYFLAVEKERDLF KLILKKEDELGDRSIMETVQN ED (SEQ ID NO:8)					NIKDTKSDII FFQORSVPBGHD NKMQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNE (SEQ ID NO:100)
F ESKYPPPCPCPAPEFLGGPS U VFLPEPKPKDTLMISRTPEVT S CVVDVDSQEDPEVQFNWYVDG E VEVHNAKTKPREEQFNSTYRV - VSVLTVLHQDWLNGKEYKCKV 5 SNKGLPSSIEKTIISKAKQPR 1 EPQVYTLPPSQEEMTKNQVSL 0 TCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLGKDD DDKYFGKLESKLSVIRNLNDQ VLFIDQGNRPLFEDMTSDVR DNAPRTIFIISMYKDSQPRGM AVTISVKVEKISTLSVENKII SFKEMNPPDNIKDTKSDIIF QRSVPFGHDNKMQFESSSYEGY FLAVEKERDLFKLILKKEDEL GDRSIMFTVQNEO (SEQ ID NO:9)				DDDD K (SEQ ID NO:8 7)	YFGKLESKLS 1 VIRNLNDQVL 0 FIDQGNRPLF EDMTSDVRD NAPRTIFIIS MYKDSQPRGM AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDTKSDII FFQORSVPBGHD NKMQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNE (SEQ ID NO:100)
F EPKSSDKTHTCPCPAPEILG U GPSVFLFPPKPKDTLMISRTPE S EVTCVVVDVSHEDPEVKFNWY E VDGVEVHNAKTKPREEQYNST - YRVVSVLTVLHQDWLNGKEYK	0 EVQLVESGGGLVQAGGSLRLSCAASGRT FSSVAMGWFRQAPGKEREFVVAINWSSG STYYADSVKGRFTISRDNAKNTMYLQMN SLKPEDTAVYYCAAGYQINSGYNFKDY EYDWGQGTQVTVSSEPKSSDKTHTCPE	AAEPVEDNVI NEVAMKFIDN TLIFYIAEDDE N (SEQ ID NO:78)	5 IEQD (SEQ ID NO:8 8)	YFGKLESKLS 9 VIRNLNDQVL FIDQGNRPLF EDMTSDVRD NAPRTIFIIS	

5	CKVSNKALPAPIEKTISKAKG	CPAPELLGGPSVTFEPFKPKDTLMISRT				KYGDSQPRGL
1	QPREQVYTLPPSREEMTKNQ	FEVTCVVVDVSHEDPEVKFNWYVDGVEV				AVTISVKVEK
6	VSLSCAVKGFYPSDIAVEWES	HNAKTKPREEQYNSTYRVVSVLTVLHQD				ISTLSVENKI
	NGQPENNYKTTTPVLDSDGSF	WLANGREYKCKVSNKALPAPIEKTISKAK				ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC	GQRFEPQVYTLPPSREEMTKNQSLWCL				NIKDTKSDII
	SVMHEALHNRFTQKSLSLSPG	VKGFPYSDIAVEWESNQGNVNYKTTPP				FFQRSVPGH
	K (SEQ ID NO:1)	VLDSDGSFFLYSKLTVDKSRWQQGNVFS				NKVQFESSY
		CSVMHEALHNHYTQKSLSLSPGKAAPV				EGYFLAVEKE
		EDNVINFVAMKFIDNTLYFIAEDDENIE				RDLFKLILKK
		QDYFGKLESKLSVIRNLNDQVLFIDQGN				EDELGDRSIM
		RPLFEDMTDSVDRNAPRTIIFTISKYGD				FTVQNE
		SQPRGLAVTISVKVEKISTLSVENKIIIS				(SEQ ID
		EKEMNPPDNIKDKSDIIFQRSVPGH				NO:99)
		NKVQFESSYEGYFLAVEKERDLFKLIL				
		KKDELGDRSIMFTVQNE (SEQ ID				
		NO:35)				
F	EPKSDKTHTCPPCPAPELLG	QVQLKQSGGGLVQPSQSLSTICIVSGFS	DILLTQSPVIL	AAEPVEDNVI	5	YFGKLESKLS
U	GPSVFLFPPKPKDTLMISRT	LTNYGVHWVRQSPGKGLWLGVIWSSGN	SVSPGERVSFS	NEVAMKFIDN	IEQD	VIRNLNDQVL
S	EVTCCVVVDVSHEDPEVKFNWY	TDYNTPTFTSRLSINKDNKSQVFTKMS	CRASQSIGTNI	TLYFIAEDDE	(SEQ	FIDQGNRPLF
E	VDGVEVHNAKTKPREEQYNST	LQSDNTAIYCARALTYDYEFAYWGQ	HWYQRTNGSP	N (SEQ ID	ID	EDMTDSDVRD
-	YRVVSVLTVLHQDWLNGKEYK	TLTVSAASTKGPSVTFPLAPSSKSTSGG	RLLIKYASESI	NO:78)	NO:8	NAPRTIFTIS
5	CKVSNKALPAPIEKTISKAKG	TAALGCLVKDYFPEPTVSWNSGALTSG	SGIPSRFSGSG		8)	KYGDSQPRGL
1	QPREQVYTLPPSREEMTKNQ	VHTFPAVLQSSGLYSLSSVTVPSSSLG	SGTDFTLISNS			AVTISVKVEK
7	VSLSCAVKGFYPSDIAVEWES	TQTYICNVNHKPSNTKVDKKVEPKSCDK	VESEDIADYYC			ISTLSVENKI
	NGQPENNYKTTTPVLDSDGSF	THTCPPCPAPELLGGPSVFLFPPKPKDT	QQNNNWPTTFG			ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC	LMISRTPEVTCVVVDVSHEDPEVKFNWY	AGTKLELKRTV			NIKDTKSDII
	SVMHEALHNRFTQKSLSLSPG	VDGVEVHNAKTKPREEQYNSTYRVVSVL	AAPSVFIFFPS			FFQRSVPGH
	K (SEQ ID NO:1)	TVLHQDWLNGKEYKCKVSNKALPAPIEK	DEQLKSGTASV			NKVQFESSY
		TISKAKGQPREPQVYTLPPSREEMTKNQ	VCLLNNFYPRE			EGYFLAVEKE
		VSLMCLVKGFYPSDIAVEWESNGQPENN	AKVQWKVDNAL			RDLFKLILKK
		YKTTTPVLDSDGSFFLYSKLTVDKSRWQ	QSGNSQESVTE			EDELGDRSIM
		QGNVFSCSVMHEALHNHYTQKSLSLSPG	QDSKSDSTYLS			FTVQNE
		KAAEPVEDNVINFVAMKFIDNTLYFIAE	STLTLSKADYE			(SEQ ID
		DDENIEQDYGKLESKLSVIRNLNDQVL	KHKVYACEVTH			NO:99)
		FIDQGNRPLFEDMTDSVDRNAPRTIFTI	QGLSSPVTKSF			
		ISKYGDSQPRGLAVTISVKVEKISTLSV	NRGEC (SEQ			
		ENKIISFKEMNPPDNIKDKSDIIFQR	ID NO:73)			

[illegible]

						(SEQ ID NO:104)
F	EPKSDKTHTCPPCPAPELIG	0	YFGKLSKLSVIRNLNDQVL	FIDQGNRP		YFGKLSKLS
U	GPSVFLPPKPKDILMISRT		LFEDMTDSDVRDNAPTIF	IISM9DSQ		VIRNLNDQVL
S	EVTGVVVDVSHEDPEVKFNW		PRGMAVTISVKEKISTLSVENKI	ISFK		FIDQGNRPLE
E	VDGVEVHNAKTPREEQNST		EMPPDNITKTSKDI	FFQRSVP		EDMTDSDVRD
-	YRVSVLTVLHQDLNGKEYK		MQFESSYEGYFLAVEKERDL	FKLILKK		NAPRTIFIIS
5	CKVSNKALPAPIEKTISKAG		EDELGDRSIMFTVQNEDEPK	SSDKTHTC		MY9DSQPRGM
4	QPREQVYTLPPSREEMTKNQ		PPCPAPELIGGPSVFLPPKPKDILMIS			AVTISVKVEK
7	VSLCAVKGFPDIAVEWES		RTPEVTCWVDVSHEDPEVKFNWYDGV			ISTLSVENKI
	NGQPENNYKTPPVLDSDGSF		EVHNAKTPREEQNSTYRVVSVLTVLH			ISFKEMNPPD
	FLVSKLTVDKSRWQGNVFSC		QDWLNGKEYKCKVSNKALPAPIEKTISK			NIKDKSDII
	SVMHEALHNRFTQKSLSLSPG		AKGQPREPQVYTLPPSREEMTKNQVSLW			FFQRSVP
	K (SEQ ID NO:1)		CLVKGFPESDIAVEWESNGQPENNYKT			NKMQFESSY
			PFVLDSDGSFFLYSKLTVDKSRWQGNV			EGYFLAVEKE
			FSCVMHEALHNYTQKSLSLSPGK			RDLEFKLILKK
			(SEQ ID NO:39)			EDELGDRSIM
						ETVQNEDE
						(SEQ ID NO:105)
F	QVQLKQSGPGLVQPSQSLIT		QVQLKQSGPGLVQPSQSLITCTVSGFS		IEQD	YFGKLSKLS
U	CTVSGFSLTNYGVHWVRQSPG		LTNYGVHWVRQSPGKLEWLGVTWSSGN		(SEQ ID NO:8)	VIRNLNDQVL
S	KGLEWLGVIWSSGNTDNTPF		TDYNTPTISRLSINKDNKSQVFFKMNS		ID NO:8)	FIDQGNRPLE
E	TSRLSINKDNKSQVFFKMNS		LQSNDAIYYCARALTYDYEEFAYWGQG			EDMTDSDVRD
-	LQSNDAIYYCARALTYDYEE		TLVTVAASTKGPSVFELAPSSKSTSGG			NAPRTIFIIS
5	FAYWGQGLTVTVSAASTKGPS		TAALGCLVKDYFPEPVTVSWNSGALTSG			KYGDSQPRGL
5	VFLAPSSKSTSGGTAALGCL		VHTFPAVLQSSGLYSLSSVTVPSSSLG			AVTISVKVEK
5	VKDYFPEPVTVSWNSGALTSG		TQTYICNVNHKPSNTKVDKKVEPKSCDK			ISTLSVENKI
	VHTFPAVLQSSGLYSLSSVTV		THTCPCPAPPELLGGPSVFLFPPKPKDT			ISFKEMNPPD
	VPSSSLGTQTYICNVNHKPSN		LMISETPEVTCVVDVSHEDPEVKFNWY			NIKDKSDII
	TKVDKKVEPKSCDKTHTCPPC		VDGVEVHNAKTPREEQNSTYRVVSVL			FFQRSVP
	PAPELLGGPSVFLFPPKPKDT		TVLHQDLNGKEYKCKVSNKALPAPIEK			NKMQFESSY
	LMISRTPEVTCVVDVSHEDP		TISKAKGQPREPQVYTLPPSREEMTKNQ			EGYFLAVEKE
	EVKENWYVDGVEVHNAKTKPR		VSLWCLVKGFPDIAVEWESNGQFENN			RDLEFKLILKK
	EEQYNSTYRVVSVLTVLHQDW		YKTTPEVLDSDGSFFLYSKLTVDKSRWQ			EDELGDRSIM
	INGREYKCKVSNKALPAPIEK		QGNVFSCVMHEALHNYTQKSLSLSPG			ETVQNEDE
	TISKAKGQPREPQVYTLPPSR		KGGGSGGGSGGGSGGGGGAAPVED			

EEMTKNQVLSLSCAVKGFYPSD IAVWESNGQPENNYKTPPV LSDSGSFFLVSKLTVDKSRWQ QCNVFCSSVMHEALHNRFTQK SLSLSPGK (SEQ ID NO:10)	NVINFMVKFIDNTLYFIAEDDENIEQD YFGKLESKLSVIRNLNDQVLFIDQGNRP LFEDMTDSDVRDNAPRTIFIISKYGDSQ PRGLAVTISVKVEKISTLSVENKIIISFK EMNPDNIKDKTSDIFFQRSVPGHDK VQFESSYEGYFLAVEKERDLFKLILKK EDELGDRSIMFTVQNEQ (SEQ ID NO:40)	KHKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:73)	(SEQ ID NO:99)
F EPKSSDKTHTCPPCPAPELLG U GPSVFLFPPKPKDTLMISRTF S EVTCVVVDVSHEDPEVKFNWY E VDGVEVHNAKTKPREEQYNST - YRVSVLTVLHQDWLNGKEYK 5 CKVSNKALPAPIETISKAGK 5 QPREPQVYITLPPSRREMTKNQ 6 VLSLCAVKGFPYPSDIAVWES NGQPENNYKTTTPVLDSDGSF FLVSKLTVDKSRWQGNVFSC SVMHEALHNRFTQKSLSPG K (SEQ ID NO:1)	0 EVQLVESGGGLVQAGCSLRLSCAASRT FSSYAMGWFRQAPGEREFVVAINWSSG STYYADSVKGRFTISRDNAKNTMYLQMN SLKPEDTAVYYCAAGYQINSNGYNFKDY EYDYGQGTQVTVSSEPKSSDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEV HNATKPREEQYNSTYRVVSVLTVLHQD WLNKEYCKVSNKALPAPIETISKAK GQPREPQVYITLPPSRREMTKNQVSLWCL VKGFYPSDIAVWESNGQPENNYKTTTP VLDSDGSFFLYSKLTVDKSRWQGNVFS CSVMHEALHNYTQKSLSLSPGK (SEQ ID NO:41)		
F EPKSSDKTHTCPPCPAPELLG U GPSVFLFPPKPKDTLMISRTF S EVTCVVVDVSHEDPEVKFNWY E VDGVEVHNAKTKPREEQYNST - YRVSVLTVLHQDWLNGKEYK 5 CKVSNKALPAPIETISKAGK 8 QPREPQVYITLPPSRREMTKNQ 3 VLSLCAVKGFPYPSDIAVWES NGQPENNYKTTTPVLDSDGSF FLVSKLTVDKSRWQGNVFSC SVMHEALHNRFTQKSLSPG K (SEQ ID NO:1)	0 YFGKLaSKLSVIRNLNDQVLFIDQGNRP LFEDMTDSDVRDNAPRTIFIISMYaDSQ PRGMAVTISVKVEKISTLSVENKIIISFK EMNPDNIKDKTSDIFFQRSVPGHDK MQFESSYEGYFLAVEKERDLFKLILKK EDELGDRSIMFTVQNEDEPKSSDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNATKPREEQYNSTYRVVSVLTVLH QDWLNKEYCKVSNKALPAPIETISK AKGQPREPQVYITLPPSRREMTKNQVSLW CLVKGFYPSDIAVWESNGQPENNYKTT PFVLDSDGSFFLYSKLTVDKSRWQGNV FSCVMHEALHNYTQKSLSLSPGK (SEQ ID NO:42)		YFGKLaSKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDVRD NAPRTIFIIS MYaDSQPRGM AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDKTSDI FFQRSVPGH NKMQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM

[illegible]

F	EPKSSDKTHTCPPCPAPELLG	0	YFGKLqSKLSVIRNLNDQVLFIDQNRPLFEDMTDSDVRDNAPRTIFIISMVADSQPRGMATISVKVEKISTLSVENKIIISFKEMPPDNIKTKSDIIFQRSVPGHDKMQFESSYEGYFLAVEKERDLFKLILKK					(SEQ ID NO:108)
U	GPSVFLPPKPKDTLMISRTIP							YFGKLqSKLSVIRNLNDQVLFIDQNRPLF
S	EVTGVVDVSHEDPEVKFNWY							VIRNLNDQVLFIDQNRPLF
E	VDGVEVHNAKTKPREEQYNST							EDMTDSDVRDNAPRTIFIIS
-	YRVSVLTVLHQDLWLNKEYK							NAPRTIFIIS
5	CKVSNKALPAPIEKTISKAKG							MYADSQPRGM
8	QPREQVYTLPPSREEMTKNQ							AVTISVKVEK
6	VSLSCAVKGFYPSDIAVEWES							ISTLSVENKI
	NGQPENNYKTTPPVLDSDGSF							ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC							NIKDKSDII
	SVMHEALHNRFTQKSLSLSPG							FFQRSVPGH
	K (SEQ ID NO:1)							NKMQFESSY
								EGYFLAVEKE
								RDLFKLILKK
								EDELGDRSIM
								FTVQNE
								(SEQ ID NO:109)
F	EPKSSDKTHTCPPCPAPELLG	0	EPKSSDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKENWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDLWLNKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLVCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNYTQKSLSLSPGK (SEQ ID NO:45)					IEQD (SEQ ID NO:8)
U	GPSVFLPPKPKDTLMISRTIP							YFGKLESKLS
S	EVTGVVDVSHEDPEVKFNWY							VIRNLNDQVLFIDQNRPLF
E	VDGVEVHNAKTKPREEQYNST							EDMTDSDVRDNAPRTIFIIS
-	YRVSVLTVLHQDLWLNKEYK							NAPRTIFIIS
5	CKVSNKALPAPIEKTISKAKG							MYKDSQPRGM
8	QPREQVYTLPPSREEMTKNQ							AVTISVKVEK
7	VSLSCAVKGFYPSDIAVEWES							ISTLSVENKI
	NGQPENNYKTTPPVLDSDGSF							ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC							NIKDKSDII
	SVMHEALHNRFTQKSLSLSPG							FFQRSVPGH
	K (SEQ ID NO:1)							NKMQFESSY
								EGYFLAVEKE
								RDLFKLILKK
								EDELGDRSIM
								FTVQNE

						(SEQ ID NO:100)
F	EPKSSDKTHTCPPCPAPELLG	0	YFGKLKSKLSVIRNLNDQVLFIDQGNRP			YFGKLKSKLS
U	GPSVFLPPKPKDILMISRTIP		LFEDMTDSDVRDNAPRTIFIISYgDSQ			VIRNLNDQVL
S	EVTGVVVDVSHEDPEVKFNWY		PRGMATISVKVEKISTLSVENKIIISFK			FIDQGNRPLE
E	VDGVEVHNAKTPREEQYNST		EMNPPDNIKDKSDIIFQRSVPGHDK			EDMTDSDVRD
-	YRVSVLTVLHQDLNGKEYK		MQFESSYEGYFLAVEKERDLFKLILKK			NAPRTIFIIS
5	CKVSNKALPAPIEKTISKAG		EDELGDRSIMFTVQNEDEPKSSDKTHTC			hYgDSQPRGM
9	QPREQVYTLPPSREEMTKNQ		PPCPAPELLGGPSVFLFPPKPKDILMIS			AVTISVKVEK
9	VSLCAVKGFPSPDIAREWES		RTPEVTCVWVDVSHEDPEVKFNWYDGV			ISTLSVENKI
	NGQPENNYKTPPVLDSDGSF		EVHNAKTPREEQYNSTYRVVSVLTVLH			ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC		QDWLNGKEYKCKVSNKALPAPIEKTISK			NIKDKSDII
	SVMHEALHNRFTQKSLSLSPG		AKGQPREPQVYTLPPSREEMTKNQVSLW			FFQRSVPGH
	K (SEQ ID NO:1)		CLVKGFPSPDIAREWESNGQPENNYKTT			NKMQFESSY
			PFVLDSDGSFFLYSKLTVDKSRWQQGNV			EGYFLAVEKE
			FSCSVMEALHNYTQKSLSLSPGK			RDLFKLILKK
			(SEQ ID NO:47)			EDELGDRSIM
						ETVQNE
						(SEQ ID NO:110)
F	EPKSSDKTHTCPPCPAPELLG	0	YFGKLKSKLSVIRNLNDQVLFIDQGNRP			YFGKLKSKLS
U	GPSVFLPPKPKDILMISRTIP		LFEDMTDSDVRDNAPRTIFIISYgDSQ			VIRNLNDQVL
S	EVTGVVVDVSHEDPEVKFNWY		PRGMATISVKVEKISTLSVENKIIISFK			FIDQGNRPLE
E	VDGVEVHNAKTPREEQYNST		EMNPPDNIKDKSDIIFQRSVPGHDK			EDMTDSDVRD
-	YRVSVLTVLHQDLNGKEYK		MQFESSYEGYFLAVEKERDLFKLILKK			NAPRTIFIIS
6	CKVSNKALPAPIEKTISKAG		EDELGDRSIMFTVQNEDEPKSSDKTHTC			KYgDSQPRGM
0	QPREQVYTLPPSREEMTKNQ		PPCPAPELLGGPSVFLFPPKPKDILMIS			AVTISVKVEK
0	VSLCAVKGFPSPDIAREWES		RTPEVTCVWVDVSHEDPEVKFNWYDGV			ISTLSVENKI
	NGQPENNYKTPPVLDSDGSF		EVHNAKTPREEQYNSTYRVVSVLTVLH			ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC		QDWLNGKEYKCKVSNKALPAPIEKTISK			NIKDKSDII
	SVMHEALHNRFTQKSLSLSPG		AKGQPREPQVYTLPPSREEMTKNQVSLW			FFQRSVPGH
	K (SEQ ID NO:1)		CLVKGFPSPDIAREWESNGQPENNYKTT			NKMQFESSY
			PFVLDSDGSFFLYSKLTVDKSRWQQGNV			EGYFLAVEKE
			FSCSVMEALHNYTQKSLSLSPGK			RDLFKLILKK
			(SEQ ID NO:48)			EDELGDRSIM
						ETVQNE

						(SEQ ID NO:111)
F	EPKSDKTHTCPPCPAPELLG	0	YFGKLESKLSVIRNLNDQVLFIDQGNRP			YFGKLESKLS
U	GPSVFLPPKPKDILMISRTIP		LFEDMTDSDVRDNAPRTIFIISHYADSQ			VIRNLNDQVLF
S	EVTGVVVDVSHEDPEVKFNWY		PRGIAVTISVKVEKISTLSVENKIIISFK			FIDQGNRPLE
E	VDGVEVHNAKTPREEQYNST		EMNPPDNIKDKSDIIFQRSVPGHDK			EDMTDSDVRD
-	YRVSVLTVLHQDLNGKEYK		IQFESSYEGYFLAVEKERDLFKLILKK			NAPRTIFIIS
6	CKVSNKALPAPIEKTISKAG		EDELGDRSIMFTVQNEDEPKSSDKTHTC			hYadsQPRGI
0	QPREQVYTLPPSREEMTKNQ		PPCPAPELLGGPSVFLFPPKPKDILMIS			AVTISVKVEK
1	VSLSCAVKGFYPSDIAVEWES		RTPEVTCVWVDVSHEDPEVKFNWYDGV			ISTLSVENKI
	NGQPENNYKTTPPVLDSDGSF		EVHNAKTPREEQYNSTYRVVSVLTVLH			ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC		QDWLNGKEYKCKVSNKALPAPIEKTISK			NIKDKSDII
	SVMHEALHNRFTQKSLSLSPG		AKGQPREPQVYTLPPSREEMTKNQVSLW			FFQRSVPGH
	K (SEQ ID NO:1)		CLVKGFPESDIAVEWESNGQPENNYKTT			NKiQFESSY
			PFVLDSDGSFFLYSKLTVDKSRWQQGNV			EGYFLAVEKE
			FSCSVMEALHNYTQKSLSLSPGK			RDLFKLILKK
			(SEQ ID NO:49)			EDELGDRSIM
						ETVQNE
						(SEQ ID NO:112)
F	EPKSDKTHTCPPCPAPELLG	0	YFGKLESKLSVIRNLNDQVLFIDQGNRP			YFGKLESKLS
U	GPSVFLPPKPKDILMISRTIP		LFEDMTDSDVRDNAPRTIFIISHYADSQ			VIRNLNDQVLF
S	EVTGVVVDVSHEDPEVKFNWY		PRGIAVTISVKVEKISTLSVENKIIISFK			FIDQGNRPLE
E	VDGVEVHNAKTPREEQYNST		EMNPPDNIKDKSDIIFQRSVPGHDK			EDMTDSDVRD
-	YRVSVLTVLHQDLNGKEYK		IQFESSYEGYFLAVEKERDLFKLILKK			NAPRTIFIIS
6	CKVSNKALPAPIEKTISKAG		EDELGDRSIMFTVQNEDEPKSSDKTHTC			KYadsQPRGI
0	QPREQVYTLPPSREEMTKNQ		PPCPAPELLGGPSVFLFPPKPKDILMIS			AVTISVKVEK
2	VSLSCAVKGFYPSDIAVEWES		RTPEVTCVWVDVSHEDPEVKFNWYDGV			ISTLSVENKI
	NGQPENNYKTTPPVLDSDGSF		EVHNAKTPREEQYNSTYRVVSVLTVLH			ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC		QDWLNGKEYKCKVSNKALPAPIEKTISK			NIKDKSDII
	SVMHEALHNRFTQKSLSLSPG		AKGQPREPQVYTLPPSREEMTKNQVSLW			FFQRSVPGH
	K (SEQ ID NO:1)		CLVKGFPESDIAVEWESNGQPENNYKTT			NKiQFESSY
			PFVLDSDGSFFLYSKLTVDKSRWQQGNV			EGYFLAVEKE
			FSCSVMEALHNYTQKSLSLSPGK			RDLFKLILKK
			(SEQ ID NO:50)			EDELGDRSIM
						ETVQNE

F	QVQLKQSGPGLVQPSSQSLST	QVQLKQSGPGLVQPSSQSLSTCTVSGFS	DILLTQSPVIL	AAEPVEDNVI	KPLG	(SEQ ID NO:113)
U	CTVSGFSLTNVGVHWRQSPG	LTNYGVHWRQSPGKLEWLGVIWSGGN	VSPGERSVS	NFVAMKFIDN	LQAR	YFGKLESKLS
S	KGLEWLGVIWSGGENTDYNTP	TDYNTFTSRLSINKDNKSQVFFKMS	CRASQSIGTNI	TLIFYIAEDDE	VWGG	VIRNLNDQVL
E	TSRLSINKDNKSQVFFKMS	LQNDTAIYYCARALTYDYEFAYWGQ	HWYQORTNGSP	N (SEQ ID NO:78)	GGTI	FIDQGNRPLF
-	LQNDTAIYYCARALTYDYEF	TLVTVSAASTKGSVFYFLAPSSKTS	RLLIKYASESI		EQD	EDMTDSVDRD
6	FAYWGQGLTVVSAASTKGPS	TAALGCLVKDYFPEPTVSWNSGALTSG	SGIPSRFSGS	(SEQ ID NO:9)	EQD	NAPRTIFIIS
2	VFPLAPSSKTSCTAALGCL	VHTFPAVLQSSGLYSLSSVTVPSSSLG	SGTDFTLTINS		(SEQ ID NO:9)	KYDGSQPRGL
4	VKDYFPEPTVSWNSGALTSG	TQTYICNVNHPKSTKVDKKVEPKSCDK	VESEDIADYVC		ID	AVTISVKVEK
	VHTFPAVLQSSGLYSLSSVTV	THTCPPCPAPELLGGPSVFLFPKPKDT	QONNNWPTTFG		NO: 9	ISTLSVENKI
	VPSSSLGTQTYICNVNHPKPSN	LMISRTPEVTCVVVDVSHEDPEVKENWY	AGTKLELKRTV		2)	ISFKEMNPPD
	TKVDKKVEPKSCDKTHTCPPC	VDGVEVHNAKTKPREEQYNSTYRVVSVL	AAPSVEIFPPS			NIKDKSDII
	PAPELLGGPSVFLFPKPKDT	TVLHQDWLNGKEYKCKVSNKALPAPIEK	DEQLKSGTASV			FFQRSVPCHD
	LMISRTPEVTCVVVDVSHEDP	TISKARGQPREPQVYTLPPSREEMTKNQ	VCLINNIFYPRE			NKVQFESSY
	EVKENWYVDGVEVHNAKTKPR	VSLWCLVKGYPSDIAVEWESNGQPENN	AKVQWKVDNAL			EGYFLAVEKE
	EEQYNSTYRVVSVLTVLHQDW	YKTTTPEVLDSDGSSEFLYSKLTVDKSRWQ	QSGNSQESVTE			RDLEKLIHK
	INGREYKCKVSNKALPAPIEK	QGNVFSCSVMHAEALHNHYTQKSLSPG	QDSKDSYSLS			EDELGDRSIM
	TISKARGQPREPQVYTLPPSR	KGGGSGGGSGGGSGGGGSAAPVED	STLTLSKADYE			FTVQNE
	EEMTKNQVSLSCAVKGYP	NVINFAVAMKFIIDNTLYFIAEDDENGGG	KHKVIACEVTH			(SEQ ID NO:99)
	IAVEWESNGQPENNYKTTFPV	KPLGLQARVVGQGTIEQDYFGKLESKL	QGLSSPVTKSF			
	LDSDGSFELVSKLTVDKSRWQ	SVIRNLNDQVLFIDQGNRPLFEDMTDSD	NRGEC (SEQ ID NO:73)			
	QGNVFSCSVMHAEALHNFTQK	VRDNAPRTIFIISKYDGSQPRGLAVTIS				
	SLSLSPGK (SEQ ID NO:10)	VKVEKISTLSVENKIISFKEMNPPDNIK				
		DTKSDIIFQRSVPGHDKVKQFESSYE				
		GYFLAVEKERDLFKLILKNEDELGDRSI				
		MFTVQNE (SEQ ID NO:51)				
F	EVQLVESGGGLVQPGGSLRLS	EVQLVESGGGLVQPGGSLRLSCAASGFN	DIQMTQSPSSL	AAEPVEDNVI	KPLG	YFGKLESKLS
U	CAASGFNIKDTYIHWRQAPG	IKDTYIHWRQAPGKLEWVARIYPTNG	SASVGDRTVIT	NFVAMKFIDN	LQAR	VIRNLNDQVL
S	KGLEWVARIYPTNGTRYADS	YTRYADSVKGRFTISADTSKNTAYLQMN	CRASQDVNTAV	TLIFYIAEDDE	VWGG	FIDQGNRPLF
E	VKGRTISADTSKNTAYLQMN	SLRAEDTAVIYCSRWGGDFYAMDYWGQ	AWYQQKPGKAP	N (SEQ ID NO:78)	GGTI	EDMTDSVDRD
-	SLRAEDTAVIYCSRWGGDFY	GTLIVTVSSASTKGSVFYFLAPSSKTS	KLLIYASFLY		EQD	NAPRTIFIIS
6	AMDYWGQGLTVTVSSASTKGP	GTAALGCLVKDYFPEPTVSWNSGALT	SGVPSRFSGSR		(SEQ ID NO:9)	KYDGSQPRGL
2	SVFPLAPSSKTSCTAALGCL	GVHTFPAVLQSSGLYSLSSVTVPSSSL	SGTDFTLTIS		ID	AVTISVKVEK
5	LVKDYFPEPTVSWNSGALT	GTQTYICNVNHPKSTKVDKKVEPKSCD	LQPEDFATYVC		NO: 9	ISTLSVENKI
	GVHTFPAVLQSSGLYSLSSV	KTHTCPPCPAPELLGGPSVFLFPKPKD	QQHYTTPPTFG		2)	ISFKEMNPPD
	TVPSSSLGTQTYICNVNHPKS	TLNISRTPEVTCVVVDVSHEDPEVKENW	QCTKVEIKRTV			NIKDKSDII

NTKVDKKVEPKSCDKTHTCPP CPAPELLGGPVSVEFPKPKD TLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKP REEQNSTYRVVSVLTVLHQD WLNKEYKCKVSNKALPAPIE KTIISKAGQPPREPQVYTLPPS REEMTKNQVSLSCAVKGFPYS DIAVWESNGQPENNYKTTPP VLDSDGSFFLVSKLTVDKSRW QQGNVFSCSVMHEALHNFTQ KSLSLSPGK (SEQ ID NO:11)	YVDGVEVHNAKTPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIE KTIISKAGQPPREPQVYTLPPSREEMTKN QVSLWCLVKGFYPSDIAVWESNGQFEN NYKTTFFVLDSDGSFFLVSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSP GKGGGGGGGGGGGGGGGSAAPVE DNVINEVAMKFIDNTLYFLAEDDNGGG GKFLGLQARVVGGGTIEQDYFGKLESK LSVTNINLNDQVLFIDQGNRPLFEDMFD DVRDNAPRTIFIIISKYGDSPRGLAVTI SVKVEKISTLSVENKIIISFKEMNPPDNI KDTKSDIIFFQRSVPCHDNKVQFESSY EGYFLAVEKERDLFKLILKKEDELGDRS IMFTVQNEQ (SEQ ID NO:52)	AAPSVFIFPPS DEQLKSGTASV VCLINNFYPRE AKVQWKVDNAL QSGNSQESVTE (SEQ ID NO:74)	AAEPVEDNVI NEVAMKFIDN TLYFIAEDDE N (SEQ ID NO:78)	IEQD (SEQ ID NO:8 8)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLE EDMTSDSDVRD NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDTKSDII FFQRSVPCHD NKVQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNEQ (SEQ ID NO:99)
EPKSSDKTHTCPPCPAPEaag GPSVLEFPKPKDTLMISRT EVTCTVVVDVSHEDDEVKENWY VDGVEVHNAKTPREEQYNST YRVVSVLTVLHQDWLNGKEYK CKVSNKALGAPIEKTISKANG QPREPQVYTLPPSREEMTKNQ VSLSCAVKGFPYPSDIAVWES NGQPENNYKTTPPEVLDSGSE FLVSKLTVDKSRWQQGNVFSC SVMHEALHNFTQKSLSLSPG K (SEQ ID NO:12)	EVQLVESGGGLVQAGGSLRLSCAASGRT FSSYAMGWFRQAPGKEREFVVALNWSSG STYYADSVKGRFTISRDNAKNTMYLQM SLKPEDTAVYYCAAGYQINSNGYNPKDY EYDWGQGTQVTVSEPKSSDKTHTCPP CPAPEaaggpsvtfppkpkdtlmisrt PEVTCVVVDVSHEDDEVKENWYVDGVEV HNAKTPREEQYNSTYRVVSVLTVLHQD WLNKEYKCKVSNKALGAPIEKTISKAK GQPRFPQVYTLPPSREEMTKNQVSLWCL VKGYFSPDIAVWESNGQFENNYKTTPP VLDSDGSFFLVSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGAAEPV EDNVINFVAMKFIDNTLYFLAEDDENIE QDYFGKLESKLSVTNINLNDQVLFIDQGN RPLELMDTSDVRDNAPRTIFIIISKYGD SQPRGLAVTISVKVEKISTLSVENKIIIS FKEMNPPDNIKDTKSDIIFFQRSVPCHD NKVQFESSYEGYFLAVEKERDLFKLIL KKEDELGDRSIMFTVQNEQ (SEQ ID NO:53)				YFGKLESKLS VIRNLNDQVL FIDQGNRPLE EDMTSDSDVRD NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDTKSDII FFQRSVPCHD NKVQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNEQ (SEQ ID NO:99)

F	EPKSSDKTHTCPPCPAPELLG	EVQLVESGGGLVQAGGSLRLSCAASGRT	AAEPVEDNSI	IEQD	YFGKLESKLS
U	GPSVFLFPPKPKDTLMISRTF	FSSYAMGWFRQAPGKEREFVVAINWSSG	NFVAMKFIDN	(SEQ	VIRNLNDQVL
S	EVTCTVVVDVSHEDPEVKFNWY	STYYADSVKGRFTISRDNAKNTIMYLQMN	TLYFIAEDDE	ID	FIDQGNRPLF
E	VDGVEVHNAKTKPREEQYNST	SLKPEDTAVYYCAAGYQINSGNYPKDY	N (SEQ ID	NO: 8	EDMTDSDSRD
-	YRVSVLTVLHQDWLNGKEYK	EYDYGQGTQVTVSSEPKSDDKTHTCPP	NO: 76)	8)	NAPRTIFIIS
6	CKVSNKALPAPIEKTIISKAG	CPAPELLGGPSVTFLEPPKPKDTLMISRT			KYGDSQPRGL
4	QPREQVYITLPPSREEMTKNQ	PEVTCVVVDVSHEDPEVKFNWYVDGVEV			AVTISVKSEK
5	VSLSCAVKGFYPSDIAVEWES	HNAKTKPREEQYNSTYRVVSVLTVLHQD			ISTLSSENKI
	NGQPENNYKTTTPVLDSDGSF	WLANGKEYCKCKVSNKALPAPIEKTIISKAK			ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC	GQPREPQVYITLPPSREEMTKNQVSLWCL			NIKDTKSDII
	SVMHEALHNRFTQKSLSLSPG	VKGFEYPSDIAVEWESNGQPENNYKTTTP			FFQRSVPGHD
	K (SEQ ID NO: 1)	VLDSDGSFFLYSKLTVDKSRWQQGNVFS			NKVQFESSY
		CSVMHEALHNYTQKSLSLSPGKAEPV			EGYFLASEKE
		EDNSINFVAMKFIDNTLYFIAEDDENIE			RDLFKLILKK
		QDYFGKLESKLSVIRNLNDQVLFIDQGN			EDELGDRSIM
		RPLFEDMTDSDSRDNAPRTIFIISKYGD			FTVQNE
		SQPRGLAVTISVKSEKISTLSSENKLIIS			(SEQ ID
		FKEMNPPDNIKDTKSDIIFQRSVPGHD			NO: 97)
		NKVQFESSYEGYFLASEKERDLFKLIL			
		KKEDELGDRSIMFTVQNE (SEQ ID			
		NO: 54)			
F	EPKSSDKTHTCPPCPAPELLG	EVQLVESGGGLVQAGGSLRLSCAASGRT	AAEPVEDNVI	IGNR	YFGKLESKLS
U	GPSVFLFPPKPKDTLMISRTF	FSSYAMGWFRQAPGKEREFVVAINWSSG	NFVAMKFIDN	S	VIRNLNDQVL
S	EVTCTVVVDVSHEDPEVKFNWY	STYYADSVKGRFTISRDNAKNTIMYLQMN	TLYFIAEDDE	(SEQ	FIDQGNRPLF
E	VDGVEVHNAKTKPREEQYNST	SLKPEDTAVYYCAAGYQINSGNYPKDY	N (SEQ ID	ID	EDMTDSDVRD
-	YRVSVLTVLHQDWLNGKEYK	EYDYGQGTQVTVSSEPKSDDKTHTCPP	NO: 78)	NO: 9	NAPRTIFIIS
6	CKVSNKALPAPIEKTIISKAG	CPAPELLGGPSVTFLEPPKPKDTLMISRT		3)	KYGDSQPRGL
5	QPREQVYITLPPSREEMTKNQ	PEVTCVVVDVSHEDPEVKFNWYVDGVEV			AVTISVKVEK
8	VSLSCAVKGFYPSDIAVEWES	HNAKTKPREEQYNSTYRVVSVLTVLHQD			ISTLSVENKI
	NGQPENNYKTTTPVLDSDGSF	WLANGKEYCKCKVSNKALPAPIEKTIISKAK			ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC	GQPREPQVYITLPPSREEMTKNQVSLWCL			NIKDTKSDII
	SVMHEALHNRFTQKSLSLSPG	VKGFEYPSDIAVEWESNGQPENNYKTTTP			FFQRSVPGHD
	KAAEPVEDNVIINFVAMKFIDN	VLDSDGSFFLYSKLTVDKSRWQQGNVFS			NKVQFESSY
	TLYFIAEDDENIGNRSYFGKL	CSVMHEALHNYTQKSLSLSPGK (SEQ			EGYFLAVEKE
	ESKLSVIRNLNDQVLFIDQGN	ID NO: 41)			RDLFKLILKK
	RPLFEDMTDSDVRDNAPRTIF				EDELGDRSIM
	IISKYGDSPQPRGLAVTISVKV				FTVQNE

	EKISTLSVENKIISFEKEMNPP DNIKDKSDIIFQORSVPBGHD NKVQFESSSEYEGYFLAVEKER DLFKLILKKEDELGDRSIMFT VQNEDE (SEQ ID NO:13)	EVQLVESGGGLVQAGGSLRLSCAASGRT FSSYAMGWFRQAPGKEREFVVAINWSSG STYYADSVKGRFTISRDNAKNTMYLQMN SLKPEDTAVYYCAAGYQINSGYNPKDY EYDYGQGTQVTVSSEPKSSDKTHTCPP CPAPELLGGPSVFTLPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQD WLANGKEYCKVSNKALPAPIEKTISKAK GQPREPQVYITLPPSEEMTKNQVSLWCL VKGYFSPDIAVEWESNGQPENNYKTTTP VLDSGSEFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:41)		AAEPVEDNVI NEVAMKFIDN TLYFIAEDDE N (SEQ ID NO:78)	KPLG LQAR VV (SEQ ID NO:9 4)	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSQPRGL NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDKSDII FFQRSVPBGHD NKVQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNEDE (SEQ ID NO:99)
F U S E - 6 5 9	EPKSSDKTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRT EVTGVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKG QPREPQVYITLPPSEEMTKNQ VSLSCAVKGFYPSDIAVEWES NGQPENNYKTTTPVLDSDGSF FLVSKLTVDKSRWQQGNVFSC SVMHEALHNRTQKSLSLSPG KAAEVEDNVINFAVMKFDN TLYFIAEDDENGGGKPLGLQ ARVVGGGTYFGKLESKLSVI RNLDQVLFIDQGNRPLFEDM TDSVDNAPRTIFIISKYGD SQPRGLAVTISVKVEKISTLS VENKIISFKEMNPPDNKDK SDIIFQORSVPBGHDNKVQFES SSYEGYFLAVEKERDLFKLIL KKEDELGDRSIMFTVQNEDE (SEQ ID NO:14)	EVQLVESGGGLVQAGGSLRLSCAASGRT FSSYAMGWFRQAPGKEREFVVAINWSSG STYYADSVKGRFTISRDNAKNTMYLQMN SLKPEDTAVYYCAAGYQINSGYNPKDY EYDYGQGTQVTVSSEPKSSDKTHTCPP CPAPELLGGPSVFTLPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQD WLANGKEYCKVSNKALPAPIEKTISKAK GQPREPQVYITLPPSEEMTKNQVSLWCL		AAEPVEDNVI NEVAMKFIDN TLYFIAEDDE N (SEQ ID NO:78)	IEQD GGS I GNRS GGGG KPLG LQAR VVG GGT I EQD (SEQ	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSQPRGL NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDKSDII
F U S E - 6 6 0	EPKSSDKTHTCPPCPAPELLG GPSVFLFPPKPKDTLMISRT EVTGVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKG QPREPQVYITLPPSEEMTKNQ VSLSCAVKGFYPSDIAVEWES NGQPENNYKTTTPVLDSDGSF FLVSKLTVDKSRWQQGNVFSC	EVQLVESGGGLVQAGGSLRLSCAASGRT FSSYAMGWFRQAPGKEREFVVAINWSSG STYYADSVKGRFTISRDNAKNTMYLQMN SLKPEDTAVYYCAAGYQINSGYNPKDY EYDYGQGTQVTVSSEPKSSDKTHTCPP CPAPELLGGPSVFTLPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQD WLANGKEYCKVSNKALPAPIEKTISKAK GQPREPQVYITLPPSEEMTKNQVSLWCL		AAEPVEDNVI NEVAMKFIDN TLYFIAEDDE N (SEQ ID NO:78)	IEQD GGS I GNRS GGGG KPLG LQAR VVG GGT I EQD (SEQ	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSQPRGL NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDKSDII

	SVMHEALHNRFTQKSLSLSPG KAAEPVEDNVINFVAMKFIDN TLYFLAEDDENIEQDGGSIGN RSGGCKPLGLQARVVGGGT IEQDYFGKLESKLSVIRNLND QVLFIDQGNRPLFEDMTDSDV RDNAPRTIFIISKYGDSPQPRG LAVTISVKVEKISTLSVENKI ISFERMPPDNKDKTSDIIF FQSVFPGHDNKVQFESSYEG YFLAVEKERDLFKLILKKEDE LGDRSIMFTVQNEID (SEQ ID NO:15)	VKGFYPSDIAVWESNGQPENNYKTTPF VLDSGSGFFLYSKLTVDKSRWQGNVFS CSVMHEALHNRHTQKSLSLSPGK (SEQ ID NO:41)			ID NO:9 5) EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNEID (SEQ ID NO:99)	FFQRSVPBGHD NKVQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNEID (SEQ ID NO:97)
F U S E - 6 8 6	EPKSSDKTHTCPCPAPELLG GPSVFLFPKPKDTMISRTP EVTGVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNST YRVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQ VLSCAVKGFYPSDIAVWES NGQPENNYKTTPFVLDSGSGF FLVSKLTVDKSRWQGNVFC SVMHEALHNRFTQKSLSLSPG K (SEQ ID NO:1)	0 EVQLVESGGGLVQAGGSLRLSCAASGRT FSSYAMGWFRQAPGREFERFVAINWSSG STYYADSVKGRFTISRDNAKNTMYLQMN SLKPEDTAVYYCAAGYQINSGNINPKDY EYDYGQGTQVTVSSEPKSSDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQD WLNKEYCKKVSNAKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLWCL VKGFYPSDIAVWESNGQPENNYKTTPP VLDSGSGFFLYSKLTVDKSRWQGNVFS CSVMHEALHNRHTQKSLSLSPGKAAEPV EDNsINFVAMKFIDNTLYFLAEDENQD IEYFGKLESKLSVIRNLNDQVLFIDQGN RPLFEDMTDSsRDNAPRTIFIISKYGD SQPRGLAVTISVKSEKISTLSSENKLIIS FKEMNPPDNKDKTSDIIFQRSVPBGHD NKVQFESSYEGYFLAVEKERDLFKLIL KKEDELGDRSIMFTVQNEID (SEQ ID NO:55)		AAEPVEDNsI NFVAMKFIDN TLYFLAENDE N (SEQ ID NO:79)	QDIE (SEQ ID NO:9 6) NAPRTIFIIS KYGDSQPRGL AVTISVKSEK ISTLSSENKI ISFKEMNPPD NIKDKSDII FFQRSVPBGHD NKVQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNEID (SEQ ID NO:97)	
F U S	QVQLVESGGGVVQPGKSLRLD CKASGITFSNCGMHWRQAPG KGLEWAVIVYDGSKRYYADS		EIVLTQSPATL SLSPGERATLS CPASQSVSSYL	2		

E	-	VKGRFTISRDN SKNTLELQMN SLRAEDTAVIYCATNDDYWGQ GTLVTVSSASTKGPSEVPLAP SSKSTSGGTAALGCLVKDYFF EPVTVSWNSGALISGVHTFPA VLQSSGLYSLSSVTVFPSSSL GTQYICNVNHNKPSNTKVDKK VEPKCDKTHTCPCPAPeaa GGPSVFLFPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNS TYRVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKN QVSLTCLVKGFPYPSDIAVEWE SNGQENNYKTTTPVLDSDGS FFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSP GK (SEQ ID NO:16)		AWYQQKPGQAP RLLIYDASRA TGIPARFSGSG SGTDFTLTISS LEPEDFAVYIC QQSSNWPRTFG QGTKVEIKRTV AAPSVFIFFPS DEQLKSGTASV VCLLNFPYPRE AKVQWKVDNAL QSGNSQESVTE QDSKDSYSTLS STLTLSKADYE KHKVYACEVTH QGLSPVTKSF NRGEC (SEQ ID NO:75)	2	AAEPVEDNsI NFVAMKFIDN TLYFTAEDDE N (SEQ ID NO:76)	3	IEQD (SEQ ID NO:8 8)	8	YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDsRD NAPRTIFIIIS KYGDSQPGRGL AVTISVKSEK ISTLSsENKI ISTKEMNPPD NIKDTKSDII FFQRSVPBGHD NKVQFESSSY EGYFLAsEKE RDLFKLILKK EDELGDRSIM FTVQNEID (SEQ ID NO:97)	
F	U	QVQLVESGGGVVQPGSRSLRLD CKASGITFSNGMHWVRQAPG KGLEWAVIYDGSKRYIADS VKGRFTISRDN SKNTLELQMN SLRAEDTAVIYCATNDDYWGQ GTLVTVSSASTKGPSEVPLAP SSKSTSGGTAALGCLVKDYFF EPVTVSWNSGALISGVHTFPA VLQSSGLYSLSSVTVFPSSSL GTQYICNVNHNKPSNTKVDKK VEPKCDKTHTCPCPAPeaa GGPSVFLFPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNS TYRVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKN QVSLSCAVKGFYPSDIAVEWE	QVQLVESGGGVVQPGSRSLRLDCKASGIT FSNGMHWVRQAPGKLEWAVIYDGS KRYIADSVKGRFTISRDN SKNTLELQMN SLRAEDTAVIYCATNDDYWGQGLTVTVS SASTKGPSEVFLAPSSKSTSGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVTVFPSSSLGTQYIC NVNHNKPSNTKVDKVEPKSCDKTHTCFF CPAPEaaGGPSVFLFPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVSVLTVLHQD WLNAGEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLWCL VKGYFSPDIAVEWESNGQPENNYKTTTP VLDSGDSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:56)		EIVLTQSPATL SLSPGERATLS CRASQSVSSYL AWYQQKPGQAP RLLIYDASRA TGIPARFSGSG SGTDFTLTISS LEPEDFAVYIC QQSSNWPRTFG QGTKVEIKRTV AAPSVFIFFPS DEQLKSGTASV VCLLNFPYPRE AKVQWKVDNAL QSGNSQESVTE QDSKDSYSTLS STLTLSKADYE KHKVYACEVTH						

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
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1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
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[illegible]

7	CKVSNKALPAPIEKTISKAKG	CPAPELLGGPSVTFEPFKPKDTLMISRT				KYGDSPRGL AVTISVKSEK ISTLSVENKI ISFKEMNPPD NIKDTKSDII FFQRSVPBGHD NKVQFESSY EGYFLAVEKE RDLFKLILKK EDELGDRSIM FTVQNE (SEQ ID NO: 99)
7	QPREPQVYTLPPSREEMTKNQ	FEVTCVVVDVSHEDPEVKFNWYVDGVEV				
5	VSLSCAVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSF FLVSKLTVDKSRWQQGNVFC SVMHEALHNRFTQKSLSLSPG K (SEQ ID NO: 1)	HNAKTKPREEQYNSTYRVVSVLTVLHQD WLANGREYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQSLWCL VKGFYPSDIAVEWESNGQPENNYKTTPP VLDSGSEFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGKAAPV EDNVINFAVMKFIDNTLYFIAENDEGG GSYFGKLESKLSVTRNLNDQVLFIDQGN RPLFEDMTDSVDRENAPRTIIFIISKYGD SQPRGLAVTISVKVEKISTLSVENKLIIS FKEMNPPDNIKDTKSDIIFQRSVPBGHD NKVQFESSYEGYFLAVEKERDLFKLIL KKEDELGDRSIMFTVQNE (SEQ ID NO: 60)				
F	QVQLVESGGGVQPGKSLRLD	1 QVQLVESGGGVQPGKSLRLDCKASGIT	EIVLTQSPATL	2 AAEPVEDNsI	7	YFGKLESKLS
U	CKASGITFSNCGMHWRQAPG	FSNSCGMHWRQAPGKGLEWAVAVIWDGS	SLSPGERATLS			VIRNLNDQVL
S	KGLEWAVAVIWDGSKRYADS	KRYADSVKGRFTISRDNKNTLFLQMS	CRASQSVSSYL			FIDQGNRPLF
E	VKGRFTISRDNKNTLFLQMS	SLRAEDTAVYICATDDYWGQGITVTS	AWYQKPGQAP			EDMTDSsRD
-	SLRAEDTAVYICATDDYWGQ	SASTKGPSVFPLAESSKSTSGGTAALGC	RLLIYDASNA			NAPRTIIFIS
7	GTLVTVSSASTKGPSVFPIAP	LVKDYFPEPTVTSWNSGALTSGVHTFPA	TCIPARFSGSG			KYGDSPRGL
8	SSKSTSGGTAALGCLVKDYFP	VLQSSGLYSLSSVTVPSSSLGTQTYIC	SGTDFTLTISS			AVTISVKSEK
2	EPVTVSWNSGALTSGVHTFPA	NVNHKPSNTKVDKKVEPKSCDKTHCTCPP	LEPEDFAVYVC			ISTLSSENKI
	GTQYICNVNHKPSNTKVDKK	CPAPEaaGGPSVTFEPFKPKDTLMISRT	QOSSNWPRTFG			ISFKEMNPPD
	VEPKSCDKTHCTCPPCPAPEaa	FEVTCVVVDVSHEDPEVKFNWYVDGVEV	QGTKVEIKRTV			NIKDTKSDII
	GGPSVTFEPFKPKDTLMISRT	HNAKTKPREEQYNSTYRVVSVLTVLHQD	AAPSVEIFPPS			FFQRSVPBGHD
	PEVTCVVVDVSHEDPEVKFNW	WLANGREYKCKVSNKALPAPIEKTISKAK	DEQLKSGTASV			NKVQFESSY
	YVDGVEVHNAKTKREEQYNS	GQPREPQVYTLPPSREEMTKNQVSLWCL	VCLLNNFYPRE			EGYFLaseKE
	TYRVVSVLTVLHQDWLNGKEY	VKGFYPSDIAVEWESNGQPENNYKTTPP	AKVQWKVDNAL			RDLFKLILKK
	KCKVSNKALPAPIEKTISKAK	VLDSGSEFFLYSKLTVDKSRWQQGNVFS	QSGNSQESVTE			EDELGDRSIM
	GQPREPQVYTLPPSREEMTKN	CSVMHEALHNHYTQKSLSLSPGSGGSG	QDSKDSYLSL			FTVQNE
	QVSLSCAVKGFYPSDIAVEWE	GGSGGGSGGGGSAAPVEDNsINFVA	STLTLSKADYE			(SEQ ID
	SNGQPENNYKTTPPVLDSDGS	MKFIDNTLYFIAENDEGGGsyFGKLES	KHKVYACEVTH			NO: 97)
	FFLVSKLTVDKSRWQQGNVFS	KLSTVIRNLNDQVLFIDQGNRFLFEDMTD	QGLSSPVTKSF			
		SDsRDNAPRTIIFIISKYGDSPRGLAVT	NRGEC (SEQ			
		ISVKSEKISTLSSENKLIISFKEMNPPDN	ID NO: 75)			

	C5VMHEALHNRFTQKSLSLSP GK (SEQ ID NO:18)	IKDTKSDIIFQRSVFGHDNKKVQFESS YEGYFLASEKERDLFKLLKKEDELGDR SIMFTVQNE (SEQ ID NO:61)	EIVLTQSPATL SLSPGERATLS CRASQSVSSYL AWYQQKPGQAP RLLIYDASNRA TGIPARFSGSG SGTDFTLTIS LEPEDEFAVYIC QQSSNWPRTEFG QGTKEVIEIKRTV AAPSVFIEPPPS DEQLKSGTASV VCLLNKNFYPRE AKVQWKVDNAL QSGNSQESVTE QDSKDSYSL STLTLSKADYE KHKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:75)	2	AAEPVEDNVI NFVAMKFIDN TLTYFAE ⁿ DE N (SEQ ID NO:80)	6	YFGKLESKLS VIRNLNDQVL FIDQGNRPFL EDMTDS ⁿ VRD NAPRTIFIIS KYGDSQPRGL AVTISVKVEK ISTLSVENKI ISFKEMNPPD NIKDTKSDII	9
F U S E - 7 8 3	QVQLVESGGGVQPGSRSLRD CKASGITFSNGMHWVRQAPG KGLEWAVAVIWDGSKRIYADS VKGRFTISRDNSKNTLFLQMS SLRAEDTAVYCATNDYWGQ GTLVTSSASTKGPSVFPLAP SSKTSGGTAALGLVKDYFP EPVTVSWNSGALTS ⁿ GVHTFPA VLQSSGLYSLSVVTVFPSSSL GTQTYICNVNHNKPSNTRVDKK VEPKSDKTHTCPPCPAPEaa GGPSVLEFPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNW YVDGEVHNAKTKPREEQYNS TYRVSIVTLVHQDLWGKEY KCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKN QVLSCAVKGFPYSDIAVEWE SNGQPENNYKTTTPPVLDSDGS FFLVSKLTVDKSRWQQGNVFS C5VMHEALHNRFTQKSLSLSP GK (SEQ ID NO:18)	1 QVQLVESGGGVQPGSRSLRDCKASGIT FSNSGMHWVRQAPGKLEWAVAVIWDGS KRIYADSVKGRFTISRDNKNTLFLQMS SLRAEDTAVYCATNDYWGQGLTVTVS SASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTIVSNWNSGALTSGVHTFPA VLQSSGLYSLSVVTVFPSSSLGTQTYIC NVNHNKPSNTRVDKVEPKSCDKTHTCPP CPAPEaaGGPSVLEFPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSKYRVSIVTLVHQD WLNKKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLWCL VKGFYPSDIAVEWESNGQPENNYKTTPE VLDSGSEFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNYTKQSLSPGGGGGGSG GGSGGGGGGSAAPFEDNINFA MKFDNTLYFIAEDENGGsYFGKLES KLSVIRNLNDQVLFIIDQGNRPLFEIDMTD SDVRDAPRTIFIIISKYGDSPRGLAVT ISVKVEKISTLSVENKIISFKEMNPPDN IKDTKSDIIFQRSVFGHDNKKVQFESS YEGYFLAVEKERDLFKLLKKEDELGDR SIMFTVQNE (SEQ ID NO:62)		AAEPVEDN <i>s</i> I NFVAMKFIDN TLTYFAE ⁿ DE N (SEQ ID NO:79)	7	YFGKLESKLS VIRNLNDQVL FIDQGNRPFL EDMTDS ⁿ RD NAPRTIFIIS KYGDSQPRGL AVTISVKSEK ISTLSSENKI ISFKEMNPPD NIKDTKSDII	8	
F U S E - 8 2 7	EPKSSDKTHTCPPCPAPEAAG GPSVLEFPKPKDTLMISRT EVTGVVDVSHEDPEVKFNWY VDGEVHNAKTKPREEQYNS YRVSIVTLVHQDLWGKEY KCKVSNKALPAPIEKTISKAG QPREPQVYTLPPSREEMTKNQ VLSCAVKGFPYSDIAVEWES NGQPENNYKTTTPPVLDSDGSF FLVSKLTVDKSRWQQGNVFSC	EPKSSDKTHTCPPCPAPEaaGGPSVFLF PKPKDTLMISRTPEVTCVVVDVSHEDP EVKENWYVDGEVHNAKTKPREEQYNS YRVSIVTLVHQDLWGKEYKCKVSNKA LPAPIEKTISKAKQPREPQVYTLPPSR EEMTKNQVSLWCLVKGFYPSDIAVEWES NGQPENNYKTTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMEALHNHYTQK SLSLSPGSGGGAAEPVEDNsINFAMK FIDNTLYFIAEDENGGsYFGKLESKL						

	SVMHEALHNRFTQKSLSLSPG K (SEQ ID NO:19)	SVIRNLNDQVLFDQGNRPLFEDMTDSD SRDNAPRTIFIISKYQDSQPRGLAVTIS VKSEKISTLSSENKISFKEMNPPENIK DTKSDIIFQRSVPGHDKVQFESSYE GYFLASEKERDLFKLILKKEDELGDRSI MFTVQNEDE (SEQ ID NO:63)				FFQRSVPGHD NKVQFESSY EGYFLASEKE RDLFKLILKK EDELGDRSIM FTVQNEDE (SEQ ID NO:97)
F	EPKSSDKTHTCPCPAPPELLG	0 sYFGKLESKLSVIRNLNDQVLFDQGNR				YFGKLESKLS 1
U	GPSVFLFPPKPKDTLMISRTF	PLFEDMTDSDVRDNAPRTIFIISKYKDS				VIRNLNDQVL 0
S	EVTGVVVDVSHEDPEVKFNWY	QPRGMATISVKVEKISTLSVENKIISF				FIDQGNRPLF
E	VDGVEVHNAKTKPREEQYNST	KEMNPPDNIKDTKSDIIFQRSVPGHDN				EDMTDSDVRD
-	YRVSVLTVLHQDWLNGKEYK	KMQFESSSYEGYFLAVEKERDLFKLILK				NAPRTIFIIS
8	CKVSNKALPAPIETISKAG	KEDELGDRSIMFTVQNEDEPKSSDKTHT				MYKDSQPRGM
7	QPREFQVYTLPPSREEMTKNQ	CPFCEAPELLGGPSVFLFPPKPKDTIMI				AVTISVKVEK
4	VSLSCAVKGFYPSDIAVEWES	SRTPEVTCVVVDVSHEDPEVKFNWYVDG				ISTLSVENKI
	NGQPENNYKTTTPVLDSDGSF	VEVHNAKTKPREEQYNSTYRVVSVLTVL				ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVESC	HQDWLNGKEYKCKVSNKALPAPIETIS				NIKDTKSDII
	SVMHEALHNRFTQKSLSLSPG	KAKGQPREFQVYTLPPSREEMTKNQVSL				FFQRSVPGHD
	K (SEQ ID NO:1)	WCLVKGFPYSDIAVEWESNGQPENNYKI				NKMQFESSY
		TPFVLDSDGSFFLYSKLTVDKSRWQQGN				EGYFLAVEKE
		VFSCSVMEALHNVYTKSLSLSPCK				RDLFKLILKK
		(SEQ ID NO:64)				EDELGDRSIM
						FTVQNEDE (SEQ ID NO:100)
F	EPKSSDKTHTCPCPAPPELLG	0 ggggsYFGKLESKLSVIRNLNDQVLFD				YFGKLESKLS 1
U	GPSVFLFPPKPKDTLMISRTF	QGNRPLFEDMTDSDVRDNAPRTIFIISM				VIRNLNDQVL 0
S	EVTGVVVDVSHEDPEVKFNWY	YKDSQPRGMATISVKVEKISTLSVENK				FIDQGNRPLF
E	VDGVEVHNAKTKPREEQYNST	IISFKEMNPPDNIKDTKSDIIFQRSVP				EDMTDSDVRD
-	YRVSVLTVLHQDWLNGKEYK	GHDNMQFESSSYEGYFLAVEKERDLFK				NAPRTIFIIS
8	CKVSNKALPAPIETISKAG	LILKKEDELGDRSIMFTVQNEDEPKSSD				MYKDSQPRGM
7	QPREFQVYTLPPSREEMTKNQ	KTHTOPPCPAPELLGGPSVFLFPPKPKD				AVTISVKVEK
5	VSLSCAVKGFYPSDIAVEWES	TLMSRTPEVTCVVVDVSHEDPEVKFNW				ISTLSVENKI
	NGQPENNYKTTTPVLDSDGSF	YVDGVEVHNAKTKPREEQYNSTYRVVSV				ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVESC	LTVLHQDWLNGKEYKCKVSNKALPAPIE				NIKDTKSDII
		KTISKAKGQPREPQVYTLPPSREEMTKN				FFQRSVPGHD

	SVMHEALHNRFTQKSLSLSPG K (SEQ ID NO:1)		QVSLWCLVKGFYPSDIAVEWESNGQFEN NYKTPPVLDSDGSFELYSKLTVDKSRW QQGNVFSCSVMHEALHNYTQKSLSLSP GK (SEQ ID NO:65)				NKMQFESSY EGYFLAVEKE RDLFKLIKK EDELGDRSIM FTVQNE (SEQ ID NO:100)
F	EPKSSDKTHTCPPCPAPELLG	0	gggsgggggyfgklesklsvirnlndq				YFGKLESKLS 1
U	GPSVLFPPKPKDTLMISRT		VLFIQGNRPLFEDMTDSVDRDAPRTI				VIRNLNDQVL 0
S	EVTGVVDVSHEDDEVKFNWY		FIISMYSKDSQPRGMVATISVKVEKISTL				FIDQGNRPLF
E	VDGVEVHNAKTKPREEQYNST		SVENKIISFKEMNPPDNIKDKSDIIF				EDMTDSVDRD
-	YRVSVLTVLHQDWLNGKEYK		QRSVPGHDNMQFESSSYEGYFLAVEKE				NAPRTIFIIS
8	CKVSNKALPAPIEKTISKAG		RDLFKLIKKDELDGDRSIMFTVQNEDE				MYKDSQPRGM
7	QPREQVYTLPPSREEMTKNQ		PKSSDKTHTCPPCPAPELLGGPSVFLFP				AVTISVKVEK
6	VLSCAVKGFYPSDIAVEWES		PKPKDTLMISRTPEVTCVVDVSHEDPE				ISTLSVENKI
	NGQPENNYKTTTPVLDSDGSF		VKENWYVDGVEVHNAKTKPREEQYNSTY				ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC		RVVSVLTVLHQDWLNGKEYKCKVSNKAL				NIKDKSDII
	SVMHEALHNRFTQKSLSLSPG		PAPIEKTISKAGQPREPQVYTLPPSRE				FFQRSVPCHD
K	(SEQ ID NO:1)		EMTKNQVSLWCLVKGYFSPDIAVEWESN				NKMQFESSY
			GQPENNYKTTTPVLDSDGSFFLYSKLTV				EGYFLAVEKE
			DKSRWQQGNVFSCSVMHEALHNYTQKS				RDLFKLIKK
			LSLSPGK (SEQ ID NO:66)				EDELGDRSIM
							FTVQNE (SEQ ID NO:100)
F	EPKSSDKTHTCPPCPAPELLG	0	EPKSSDKTHTCPPCPAPELLGGPSVFLF		AAEPVEDNtI		YFGKLESKLS 1
U	GPSVLFPPKPKDTLMISRT		PPKPKDTLMISRTPEVTCVVDVSHEDP		NFVAMKFIDN		VIRNLNDQVL 1
S	EVTGVVDVSHEDDEVKFNWY		EVKENWYVDGVEVHNAKTKPREEQYNST		TLYFIAEDDE		FIDQGNRPLF
E	VDGVEVHNAKTKPREEQYNST		YRVVSVLTVLHQDWLNGKEYKCKVSNKA		NLESD (SEQ		EDMTDSsRD
-	YRVSVLTVLHQDWLNGKEYK		LPAPIEKTISKAGQPREPQVYTLPPESR		ID NO:81)		NAPRTIFIIS
8	CKVSNKALPAPIEKTISKAG		EEMTKNQVSLWCLVKGYFSPDIAVEWES				MYKDSQPRGM
8	QPREQVYTLPPSREEMTKNQ		NGQPENNYKTTTPVLDSDGSFFLYSKLIT				AVTISVKSEK
7	VLSCAVKGFYPSDIAVEWES		VDKSRWQQGNVFSCSVMHEALHNYTQK				ISTLSsENKI
	NGQPENNYKTTTPVLDSDGSF		SLSLSPGKAAPVEDNtINFVAMKFIDN				ISFKEMNPPD
	FLVSKLTVDKSRWQQGNVFSC		TLYFIAEDDENLESDFGKLESKLSVIR				NIKDKSDII
	SVMHEALHNRFTQKSLSLSPG		NLNDQVLFIQGNRPLFEDMTDSsRDN				FFQRSVPCHD
K	(SEQ ID NO:1)		APRTIFIISMYSKDSQPRGMVATISVKSE				NKMQFESSY

		KISTLSsENKIISFKEMNPPDNIKDTKS DIIFFQRSVPGHDNKMQFESSSYEGYFL ASEKERDLFKLILKKEDELGDRSIMFTV QNEID (SEQ ID NO:67)				EGYFLAsEKE RDLEKLIKK EDELGDRSIM FTVQNEID (SEQ ID NO:101)
F	EPKSSDKTHTCPPCPAPELLG	0	EPKSSDKTHTCPPCPAPELLGGPSVFLF	AAEPVEDNqI	YFGKLESKLS	1
U	GPSVFLFPKPKDTILMISRTF		PPKPKDTILMISRTFETVCVVVDVSHEDP	NFVAMKFIDN	VIRNLNDQVL	1
S	EVTVCVVVDVSHEDPEVKENWY		EVKENWYVDGVEVHNAKTKPREEQYNST	TLTYFIAEDDE	FIDQGNRPLF	
E	VDGVEVHNAKTKPREEQYNST		YRVVSVLTVLHQDWLNGKEYCKVYSNKA	NLESD (SEQ	EDMTDSdSRD	
-	YRVVSVLTVLHQDWLNGKEYK		LPAPIEKTISKAKGQPREPQVYTLPPSR	ID NO:82)	NAPRTIFIIS	
8	CKVSNKALPAPIEKTISKAKG		EEMTKNQVSLWCLVKGYFSPDIAVEWES		MYKDSQPRGM	
8	QPREPQVYTLPPSREEMTNQ		NGQPENNYKTTPPVLDSDGSFFLYSKLT		AVTISVKsEK	
8	VSLSCAVKGYFSPDIAVEWES		VDKSRWQQGNVFSCSVMHEALHNHYTQK		ISTLSsENKI	
	NGQPENNYKTTPPVLDSDGSF		SLSLSPGKAAEPVEDNqINFVAMKFIDN		ISFKEMNPPD	
	FLVSKLTVDKSRWQQGNVFSC		TLTYFTAEDDENLESDFGKLESKLSVIR		NIKDTKSDII	
	SVMHEALHNRTQKSLSLSPG		NLNDQVLEFIDQGNRPLEFEDMTDSDsRDN		FFQRSVPFGHD	
	K (SEQ ID NO:1)		APRTIFIISMYKDSQPRGMATVISVKsE		NKMQFESSSY	
			KISTLSsENKIISFKEMNPPDNIKDTKS		EGYFLAsEKE	
			DIIFFQRSVPGHDNKMQFESSSYEGYFL		RDLEKLIKK	
			ASEKERDLFKLILKKEDELGDRSIMFTV		EDELGDRSIM	
			QNEID (SEQ ID NO:68)		FTVQNEID (SEQ ID NO:101)	
F	EPKSSDKTHTCPPCPAPELLG	0	EPKSSDKTHTCPPCPAPELLGGPSVFLF	AAEPVEDNqI	YFGKLESKLS	1
U	GPSVFLFPKPKDTILMISRTF		PPKPKDTILMISRTFETVCVVVDVSHEDP	NFVAMKFIDN	VIRNLNDQVL	2
S	EVTVCVVVDVSHEDPEVKENWY		EVKENWYVDGVEVHNAKTKPREEQYNST	TLTYFIAEDDE	FIDQGNRPLF	
E	VDGVEVHNAKTKPREEQYNST		YRVVSVLTVLHQDWLNGKEYCKVYSNKA	NLESD (SEQ	EDMTDSdARD	
-	YRVVSVLTVLHQDWLNGKEYK		LPAPIEKTISKAKGQPREPQVYTLPPSR	ID NO:83)	NAPRTIFIIS	
8	CKVSNKALPAPIEKTISKAKG		EEMTKNQVSLWCLVKGYFSPDIAVEWES		MYKDSQPRGM	
8	QPREPQVYTLPPSREEMTNQ		NGQPENNYKTTPPVLDSDGSFFLYSKLT		AVTISVKaEK	
9	VSLSCAVKGYFSPDIAVEWES		VDKSRWQQGNVFSCSVMHEALHNHYTQK		ISTLSaENKI	
	NGQPENNYKTTPPVLDSDGSF		SLSLSPGKAAEPVEDNqINFVAMKFIDN		ISFKEMNPPD	
	FLVSKLTVDKSRWQQGNVFSC		TLTYFTAEDDENLESDFGKLESKLSVIR		NIKDTKSDII	
	SVMHEALHNRTQKSLSLSPG		NLNDQVLEFIDQGNRPLEFEDMTDSDARDN		FFQRSVPFGHD	
	K (SEQ ID NO:1)		APRTIFIISMYKDSQPRGMATVISVKaE		NKMQFESSSY	
			KISTLSaENKIISFKEMNPPDNIKDTKS		EGYFLAaEKE	

			DIIFQRSVFGHDNMKQFESSYEGYFL AaeKerDLfKLILKKEDELGDRSIMFTV QNEd (SEQ ID NO:69)				RDLfKLILKK EDELGDRSIM FTVQNEd (SEQ ID NO:102)
F	EPKSSDKTHTCPPCPAPELLG	0	EPKSSDKTHTCPPCPAPELLGSPSVFLF	AAEPVEDNfI			YFGKLESKLS
U	GPSVFLFPKPKDTLMISRTF		PPKPKDTLMISRTPEVTCVVVDVSHEDP	NfVAMKFIDN			VIRNLNDQVL
S	EVTcVVVDVSHEDPEVKFNWY		EVKFNWYVDGVEVHNAKTKPREEQYNST	TLyFIAEDDE			FIDQGNRPLF
E	VDGVEVHNAKTKPREEQYNST		YRVVSVLTfVLHQDMLNGKEYKCKVSNKA	NLESD (SEQ			EDMTDSdARD
-	YRVVSVLTfVLHQDMLNGKEYK		LPAPIEKTIISKAKGQPREPQVYTLPPSR	ID NO:84)			NAPRTIfIIS
8	CKVSNKALPAPIEKTIISKAG		EEMTKNQVSLWCLVKGFYPSDIAVEWES				MYKDSQPRGM
9	QPREPQVYTLPPSREEMTKNQ		NGQPENNYKTTPPVLDSDGSFFLYSKLT				AVTISVKaEK
0	VSLSCAVKGfYPSDIAVEWES		VDKSRWQQGNVFSCSVMEALHNHYTQK				ISTLSaENKI
	NGQPENNYKTTPPVLDSDGSF		SLSLSPGKAAPVEDNfINFVAMKFIDN				ISFKEMNPPD
	FLVSKLTfVDKSRWQQGNVFSC		TLyFIAEDDENLESDFGKLESKLSVIR				NIKDTKSDII
	SVMHEALHNRTQKSLSLSPG		NLNDQVLfIDQGNRPLfEDMTDSdARDN				FFQRSVPGHd
	K (SEQ ID NO:1)		APRTIfIISMYKDSQPRGMATfISVKaE				NKMQFESSY
			KISTLSaENKIISFKEMNPPDNIKDTKS				EGYFLaAEKE
			DIIFQRSVFGHDNMKQFESSYEGYFL				RDLfKLILKK
			AaeKerDLfKLILKKEDELGDRSIMFTV				EDELGDRSIM
			QNEd (SEQ ID NO:70)				FTVQNEd (SEQ ID NO:102)
F	EPKSSDKTHTCPPCPAPELLG	0	EPKSSDKTHTCPPCPAPELLGSPSVFLF	AAEPVEDNfI			YFGKLESKLS
U	GPSVFLFPKPKDTLMISRTF		PPKPKDTLMISRTPEVTCVVVDVSHEDP	NfVAMKFIDN			VIRNLNDQVL
S	EVTcVVVDVSHEDPEVKFNWY		EVKFNWYVDGVEVHNAKTKPREEQYNST	TLyFIAEDDE			FIDQGNRPLF
E	VDGVEVHNAKTKPREEQYNST		YRVVSVLTfVLHQDMLNGKEYKCKVSNKA	NLESD (SEQ			EDMTDSdVRd
-	YRVVSVLTfVLHQDMLNGKEYK		LPAPIEKTIISKAKGQPREPQVYTLPPSR	ID NO:85)			NAPRTIfIIS
8	CKVSNKALPAPIEKTIISKAG		EEMTKNQVSLWCLVKGFYPSDIAVEWES				MYKDSQPRGM
9	QPREPQVYTLPPSREEMTKNQ		NGQPENNYKTTPPVLDSDGSFFLYSKLT				AVTISVKVEK
1	VSLSCAVKGfYPSDIAVEWES		VDKSRWQQGNVFSCSVMEALHNHYTQK				ISTLSVENKI
	NGQPENNYKTTPPVLDSDGSF		SLSLSPGKAAPVEDNfINFVAMKFIDN				ISFKEMNPPD
	FLVSKLTfVDKSRWQQGNVFSC		TLyFIAEDDENLESDFGKLESKLSVIR				NIKDTKSDII
	SVMHEALHNRTQKSLSLSPG		NLNDQVLfIDQGNRPLfEDMTDSdVRdN				FFQRSVPGHd
	K (SEQ ID NO:1)		APRTIfIISMYKDSQPRGMATfISVKVE				NKMQFESSY
			KISTLSVENKIISFKEMNPPDNIKDTKS				EGYFLAVEKE
			DIIFQRSVFGHDNMKQFESSYEGYFL				RDLfKLILKK

		AVEKERDLFKLILKKEDELGDRSIMFTV QNEID (SEQ ID NO:71)				EDELGDRSIM FTVQNEID (SEQ ID NO:100)
F	EPKSSDKHTHTCPQCPAPPELLG	0	EPKSSDKHTHTCPQCPAPPELLGSPSVFLF	AAEPVEDNhI		1
U	GPSVFLFPKPKDITMISRTF		PPKPKDITMISRTPEVTCVVVDVSHEDP	NFVAMKFIDN		0
S	EVTGVVDVSHEDPEVKENWY		EVKENWYVDGVEVHNAKTKPREEQYNST	TLIFYIAEDDE		
E	VDGVEVHNAKTKPREEQYNST		YRVVSVLTVLHQDWLNGKEYKCKVSNKA	NLESD (SEQ		
-	YRVVSVLTVLHQDWLNGKEYK		LPAPIETKTSKAKQCPREPQVYTLPPSR	ID NO:86)		
8	CKVSNKALPAPIETKTSKAG		EEMTKNQVSLWCLVKGYFSPSDIAVEWES			
9	QPREPQVYTLPPSREEMTRNQ		NGQPENNYKTTTPVLDSDGSFFLYSKLT			
2	VSLSCAVKGFPSPDIAVEWES		VDSRWQQGNVFSCSVMEALHNHYTQK			
	NGQPENNYKTTTPVLDSDGSF		SLSLSPGKAAEPVEDNhIFVAMKEIDN			
	FLVSKLTVDKSRWQQGNVFSC		TLIFYIAEDDENLESDFYEGKLESKLSVIR			
	SVMEALHNRFQKLSLSLSPG		NLNDQVLFIDQGNRFLFEDMTDSVDRDN			
	K (SEQ ID NO:1)		APRTIFLIISMYKDSQPRGMVATISVKVE			
			KISTLSVENKIISFKEMNPPDNIIKDIKS			
			DIIFQORSVPGHDKMQFESSSYEGYFL			
			AVEKERDLFKLILKKEDELGDRSIMFTV			
			QNEID (SEQ ID NO:72)			

Table 2. Nucleotide sequences of respective polypeptides of Table 1.

	<u>Polynucleotide 1</u>	<u>Polynucleotide2</u>	<u>Polynucleotide3</u>
F	GAGCCCAAAATCTTCTGACAAAACCTCACACATGC	GAGCCCAAAATCTTCTGACAAAACCTCACACATGCCACCG	
U	CCACCGTGCCCGAGCACCTGAACCTCTGGGGGA	TGCCCGAGCACCTGAACCTCTGGGGGACCGCTCAGTCTTC	
S	CCGTGAGTCTTCCCTTCTCCGCCAAAACCCCAAG	CTCTTCTCCGCCAAAACCCCAAGCACACCTCATGATCTCC	
E	GACACCTCATGATCTCCCGGACCCCGGAGGTC	CGGACCCCGGAGGTACATGCGTGGTGGTGGACGTGAGC	
-	ACATGGGTGGTGGTGGACGTGAGCCACGAGAC	CACGAAGACCCCTGAGGTCAAGTTCACTGGTACGTGGAC	
4	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC	GGCGTGGAGGTGCATATATGCCAAGACAAAGCCGGGAG	
2	GTGAGGTGCATATATGCCAAGACAAAGCCGGG	GAGCAGTACACACACACGTCACCGTGTGGTACGCTCCTC	
2	GAGGACGAGTACACACGACGTACCGTGTGGTC	ACGCTCTGACACGAGGACTGGGTGAATGGCAAGGATAC	
	AGCGTCTCACCGTCTGCACCGAGACTGGCTG	AAGTGAAGGTCTCCACAAAGCCCTCCAGCCCCCATC	
	AATGCAAGGAGTACAAGTGCAGGTCTCCAC	GAGAAAACCATCTCCAAAGCCAAAGGCGAGCCCCGAGAA	

	AAAGCCCTCCAGGCCCCATCGAGAAAAACCATC TCCAAAGCCAAAGGGCAGCCCCGAGAACACAG GIGTACACCCCTGCCCCATCCCGGAGGAGATG ACCAAGAACCAAGTCAGCCTGAGCTGCGCCGTC AAAGGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGCGAGCCGGAGAACAACTAC AAGACCAAGCCCTCCCGTGTGGACTCCGACGGC TCCCTCTCTCTGTGAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGCAGGGGAAGCTTCTCA TGTCCGTAATGCAATGAGGCTCTGCACAACCG TTCACGAGAAAGCCCTCTCCCTGTCTCCCGGT AAA (SEQ ID NO:114)	CCACAGGTGTACACCCCTGCCCCATCCCGGAGGAGATG ACCAAGAACCAAGGTGAGCTGTGGTGCTGCTCAAGGC TTCTATCCAGGACATCGCCGTGGAGTGGGAGAGCAAT GGCAGCCGAGAACCAACTACAGACCAAGCCTCCCGTG CTGGACTCCGACGGCTCTCTCTCTCTACAGCAAGCTC ACCGTGGACAGAGCAAGTGGCAGCAGGGGAAGCTCTTC TCATGTCTCCGTGATGATGAGGCTCTGCACAACTAC ACCCAGAGAGGCTCTCCCTGTCTCCGGTAAAGCTGCT GAACCGTGGAGATAATCTATTAATTTTGTGGCCATG AAGTCAATGATAATACTCTGTATTTCAATCGCCGAAGAT GATGAGAACGACGACGAGCAATAAATATTTCCGAAAACTG GAGTCCAAGCTGAGCGTGTACAGGAACCTGATGATCAG GTGCTGTTCATGACACGGGCAACAGGCCCTGTGTGAG GATATGACCGACAGCGACAGCAGGGGATAACGCTCCCGG ACAATCTTCATCATCTCCAAGTACGGCGATTCCAGGCC AGGGACTGGCCGTGACCATCAGCGTGAATCTGAGAAG ATCTCCACCTGAGCTCCGAAAAACAGATCATCAGCTTC AAGGAGATGAACCCCGACACACATTAAGCACACAAA TCCGACATCATCTTCTCCAGAGATCCGTGCCCGGCCAC GACAAAAAGTGCAGTTCGAGTCTCTCTACGAGGGC TACTTTCTGGCTCCGAAAAAGAAAGGACCTGTTCAG CTCATCTGAGAGGAGGACGAACCTGGGGACAGGAGC ATCATGTTCAACGTGCAGAACGAGGACATCATGTTCACC GTGCAGAACGAGGAC (SEQ ID NO:133)
F U S E - 4 2 3	GAGCCCAATCTTCTGACAAAACTCACACATGC CCACGTGCCCCAGCCTGAACCTCTGGGGGA CCGTGAGTCTTCTCTTCCCCCAAAACCCAG GACACCCCTCATGATCTCCCGGACCCCGAGGTC ACATGGTGGTGGTGACGTGAGCCACGAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGAGGTGCATATATGCCAAGACAAAGCCGGG GAGGACAGTACACAGCACGTAACGTGTGGTC AGCGTCTCACCGTCCGTGCACCAAGACTGGCTG AATGGCAAGGAGTACAAGTGAAGTCTCCAAC AAAGCCCTCCAGCCCCATCGAGAAAAACCATC TCCAAAGCCAAAGGGCAGCCCCGAGAACACAG GIGTACACCCCTGCCCCATCCCGGAGGAGATG	GAGCCCAATCTTCTGACAAAACTCACACATGCCACCG TGCCACGACCTGAACCTCTGGGGGACCGTCACTCTTC CTCTTCCCCCAAAACCCAGACACCCCTCATGATCTCC CGGACCCCGAGGTACATGCGTGTGGTGGACGTGAGC CAGAAAGACCCGTGAGGTCAAGTCAACTGGTACGTGGAC GGCGTGGAGTGCATATATGCCAAGACAAAGCCGGGAG GAGCAGTACACAGCACGTAACGTGTGGTACGCTCTCTC ACCGTCTGCACAGGACTGGGTGAATGGCAGGAGTAC AAGTGAAGTCTCCAAACAAAGCCCTCCAGCCCCCATC GAGAAAAACCATCTCCAAGCCAAAGGGCAGCCCGAGAA CCACAGGTGTACACCTGCCCCATCCCGGAGGAGATG ACCAAGAACCAAGGTGAGCTGTGGTGCTGCTCAAGGC TTCTATCCAGGACATCGCCGTGGAGTGGGAGAGCAAT

	ACCAGAACCAAGGTACGCTGAGCTGAGCTGCGCGCTC AAAGGCTTCTATCCAGCGACATCGCGTGGAG TGGGAGAGCAATGGGACAGCCGGGAGAACAACTAC AAGACCACGCTCCCGTGTGACTCCGACGGC TCTTCTTCTCGTGAGCAAGCTCACCGTGGAC AAGACAGGTGGACAGGAGGAACTCTTCTCA TGCTCCGTGATGATGAGGCTCTGCACAAACCGG TTTACGCAGAGAGGCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	GGGACGCCGGAGAACAACTACAGACCACGCTCCCGTG CTGGACTCCGAGCGCTCTTCTTCTCTACAGCAAGCTC ACCGTGGACAAAGACAGGTGGGACAGGGGACGTCTTC TCATGCTCCGTGATGCATGAGCTCTGCACACCACTAC ACGCAGAAAGAGCTCTCCCTGTCTCCGGTAAAGCTGCT GAAACCGTGGAGATTAATGCCATTAATTTTGTGGCCATG AATTCATCGATAACACCTCTACTTTATTTGGCGAGGAT GATGAAAATGATGATGATGACAAATACTTCGGCAAACTG GATCCAAAGCTCTCCGTGATCAGGAACCTGATGATCAG GTCTGTTCATGTACACAGGCAACCGCCCTGTTCGAG GACATGACCGATCCGATGCCAGGGACACGACCCCGG ACCATCTTTCATCATCTCTAAGTACGGAGACTCCAGCCA AGGGCCCTGGCGTGACCATCTCCGTGAAGCCCGAGAAA ATTTCACCCCTGTCCGCGGAAACAAATCATCTCCTTC AAAGAGATGAACCCCGGACAAACATCAAGGACACCAAA TCGACATCATCTTCTTCCAGCGCTCCGTGCCGGCCAC GACAAACAAAGTGCAGTTCGAGTCCAGTCTCTACGAGGC TACTTCTTGGCGCGCGAAAGGAAAGGGACCTGTCAAG CTGATCCTGAAGAAGGAGGACGAGCTGGTGACAGGAGC ATCATGTTACCCGTGCAGAACAGGAC (SEQ ID NO:134)	
F U S E - 4 2 4	GAGCCCAATCTTCTGACAAAACATCACACATGC CCACCGTGGCAGCACTGAATCTTGGGGGA CGGTGAGTCTTCTCTTCCCGGCAAAACCAAG GACACCTCATGATCTCCCGGACCCCGGAGGTC ACATGGTGTGTGGACGTGAGCACGAGAGAC 4 CCTGAGGTCAAGTCAACTGGTACGTGGACGGC 2 GTGGAGGTGCATTAATGCCAAGACAAAGCCGGG 4 GAGGAGCAGTACACAGCACGTAACGTGTGGTC AGCGTCCTCACCGTCTGCACCGAGACTGGCTG AATGGCAAGGAGTACAAAGTGCAAGGTCTCCAAC AAAGCCCTCCAGCCCTCATCGAGAAAACCATC TCCAAAGCCAAAGGCGAGCCCGGAGAACCCACAG GTGTACACCTTGCCCTCATCCCGGAGGAGATG ACCAGAACCAGGTACGCTGAGCTGCGCGCTC AAAGGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGACAGCCGGGAGAACACTAC	GAGCCCAATCTTCTGACAAAACATCACACATGCCACCG TGCCACGCACTGAATCTCCTGGGGGACCGTCAGTCTTC CTCTTCCCGGCAAAACCAAGGACACCTTCATGATCTCC CGGACCCCGAGGTCAATGCGTGGTGGTGGACGTGAGC CAGGAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGTGCATTAATGCCAAGACAAAGCCCGGGAG GACAGTACAAACAGCACGTAACGTGTGGTCAAGCTCCTC ACCGTCTGCACAGGACTGGCTGAATGGCAAGGAGTAC AAGTCAAGGTCTCCAAACAAAGCCCTCCAGCCCTCATC GGAAAACCATCTCCAAAGCCAAAGGCGAGCCCGGAGAA CCACAGGTGTACACCTTGCCCTCATCCCGGAGGAGATG ACCAAGAACCCAGTTCAGCTGTGGTGGTGGTCAAGGC TTCTATCCAGGACATCGCCGTGGAGTGGGAGAGCAAT GGGACAGCCGGGAGAACAACTACAGACCACGCTCCCGTG CTGGACTCCGAGCGCTCTTCTTCTCTACAGCAAGCTC ACCGTGGACAAAGACAGGTTGGGACAGGGGACGTCTTC	

69

	TGCTCCGTGATGCATGAGGCTCTGCACAAACGG TTTCACGCAGAGAGAGCCCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	AAGCTGAGTGTGATCAGGAACCTGAACGACACAGGTGCTG TTTATCGACAGGGCAATAGGCCACTGTTTGGAGATATG ACAGATTCCGAGCTGAGGACACAACGCTCCCGGACCATC TTCAATTATCAGTAAGTATGGCGACTCCAGCCAAGGGGC CTGGCTGTGACCATCAGCGTGAAGTGGAGAGATTAGC ACACTGTCCGTGGAGAACAAAGATCATCTCTTCAAGGAG ATGAACCCCCCGACACAATCAAAAGACACCAAGTCCGAC ATCATTTTCTTCCAGAGGTCCGTGCCCTGGACACGACAAC AAAGTGCAGTTGAGTCTCTCTCTACGAGGGCTACTTTC CTGGCCGTGGAATAAAGAGCGGACCTGTTCAGCTGATC CTGAAGAGGAGGACGAGCTGGGGACACAGGAGCATCATG TTCAACCTGCAGAACGAGGAC (SEQ ID NO:136)
F D S E - 4 4 2	GAGCCCAATCTTCTGACAAAACCTACACATGC CCACCGTGCCAGCACTGAACCTCTGGGGGA CCGTACGTCTTCTCTTCCCCCAAAACCCAAG GACACCTCATGATCTCCCGGACCCCGAGGTC ACATGGGTGGTGGTGGACGTGAGCCACGAAGAC 4 CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC 4 GTGGAGGTGCATAATGCCAAGACAAAGCCGGG 2 GAGGACAGTACACAGCACGTACCGTGTGGTC AGCGTCTCAACCTCTGCAACGAGACTGGCTG AATGGCAAGGAGTACAGTGCAGGTCTCCAAC AAAGCCCTCCAGCCCCCATCGAGAAAACCATC TCCAAAGCCAAAGGCGAGCCCGGAGAACACAG GTGTACACCTTGCCCCCATCCGGGAGGAGATG ACCAAGAACCCAGTCAAGCTGTGGTGCCTGTCAAAGGC TTCTATCCCGAGCACATCGCCGTGGAGTGGAGAGCAAT GGGACCCGGAGAACAACTACAGACCACGCTCCCGTG CTGGACTCCGACGGTCTCTCTCTCTACAGCAAGCTC ACCGTGGACACAGCAGGTGGCGAGCGGGAAACGTCTTC TCATGCTCCGTGATGATGATGAGGCTCTGCACACCATAC ACCCAGAGAGCTCTCCCTGTCTCCGGTAAA GCTGTGAACCCGTGGAAGATATGTGATCAATTTGTG GCCATGAATTTATTGACACAACCCCTGTATTTTCATCGCC GAAGATGATGAACAGATGATGATGATAGTACTTTGGA AAACTGGAATCAAAGCTGAGCGTATCCGGAACCTGAAT GATCAGGTGCTGTTCATCGACCGGCAACAGGCCCTTG TTTGAGGACATGACCGACTCCGACGTGAGGACAAAGCT CCCCGACCATTTTCATCATCTCTATGTACAGGACAGC	

		CAGCCCAGGGGTATGGCCGTGACCATTTAGCGTGAAGGTG GAGAAGATTAGCACACTGTCCGTGGAGAACAAAATCATC TCCTTCAAGGAATGAACCCCCCGACACATCAAGAC ACCAAGAGCGACATCATCTTCTTCCAGAGGAGCGTGGCC GGGCACGACACAAAATGCAGTTCGAATCCAGCTCCTAC GAGGGCTACTTCTTGGCCGTGGAGAAAGAGAGGGACCTG TTCAAGCTGATCCTGAAGAAGGAGGACGAGCTGGGGAC AGGAGCATCATGTTTCAACCGTGCAGAACGAGGAC (SEQ ID NO:137)	
F U S E - 4 6 2	GAGCCCAATCTTCTGACAAAACCTCACACATGC CCACCGTGCCAGCACTGAACCTCTGGGGGACCGTCACTTC CCGTGAGTCTTCTTCCCCCAAAACCCCAAG GACACCTCATGATCTCCCGGACCCCGAGGTC ACATGCGTGGTGGTGAACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGGAGGTGCATAATGCCAAGACAAAGCCGGG GAGGACGAGTACACAGCACGTACCGTGTGGTC AGCGTCTCACCGTCTGCACAGGACTGGGTG AATGGCAAGGAGTACAAGTGAAGGTCTCCAC AAAGCCCTCCAGCCCCCATCCAGAAAAACCATC TCCAAAGCCAAAGGCGAGCCCGGAGAACCCAG GTGTACACCTGTCCCCCATCCCGGAGGAGATG ACCAAGAACCCAGGTCAAGCTGAGCTGGCCGTC AAAGGTTCTTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTAC AAGACCAAGCCCTCCCGTGTGCTGACTCCGAGCGC TCCCTTCTTCTGAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGGGAACGTCTTCTCA TGTCTCGGTGATGATGAGGTCTGCACAAACGG TTCAAGCAGAAAGCCCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	GAGCCCAATCTTCTGACAAAACCTCACACATGCCACCG TGCCAGCACTGAACCTCTCTGGGGGACCGTCACTTCTTC CTCTTCCCCCAAAACCCCAAGCACCCCTCATGATCTCC CGGACCCCGAGGTCACTGCGTGGTGGACCGTGGAC CAGGAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGGGAG GAGCAGTACACAGCACGTACCGTGTGGTCAAGCTCTTC ACCGTCTGCACCGAGGACTGGCTGAATGGCAAGGAGTAC AAGTGCAGGTCTCCACAAAGCCCTCCAGCCCCCATC GAGAAAACCACTCTCCAAAGCCAAAGGCGAGCCCGAGAA CCACAGGTGTACACCTGCCCCCATCCCGGGAGGAGATG ACCAAGACCACTGAGCTGCTGGTGTCTGTTCAAAGGC TTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGGCAGCCGGAGAACAACTACAGACCACCGCTCCCGTG CTGGACTCCGACGGTCCCTTCTTCTCTACAGCAAGCTC ACCGTGGACAAAGACAGGTGGCGAGCAGGGGAACGTCTTC TCATGCTCCGTGATGCATGAGGCTCTGCACAAACCACTAC ACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA GCTGCTGAACCTGTGGAAGATAATGTGATCAATTTCTGTG GCCATGAATTCATTGACAAACACCCCTGTACTTCTATCGCT GAAGATGATGAACAACTCGAGCAGGACTATTTCCGAAAA CTGGAAGCAAACTGAGCGTGCATCAGGAACCTGAACGAC CAGGTGCTGTTTATCGACCGAGGCAACAGGCCCTCTGTC GAAGATATGACCGACAGCGACGTGAGGACAAACGCTCCT AGAACATCTTTCATCATCTCCAAAGTACGGCGACTCCCGAC	

	CCAAGGGGACTGGCTGTGACCAATTTCCGTGAAAGTGGAG AAGATCTCCACACTGAGCGTGGAAACAAATCATCTCC TTCAAGGAGATGAACCCCCCGACACATTAAGACACC AAAAGGATATCATCTTCTCCAGAGAGTGTGCCCGGC CAGGATAACAAGTGCAGTTCAGAGAGTCTCTCTACGAG GGATACTTTCTGGCCGTCGAAAAGGAGAGGGACCTGTTT AAGCTGATCTGAAGAAGGAGGACGAGCTGGGGACAGA TCAATTATGTTCAACCGTGCAGANTGAGGAC (SEQ ID NO:138)	
F U S E - 4 8 0	GAGCCCAATCTTCTGACAAAACCTACACATGCCACCG TGCCAGCACTGAACCTCTGGGGGACCGTCACTCTTC CTCTTTCCCCCAAAACCAAGGACACCCCTCATGATCTCC CGGACCCCGAGGTCACTGCGTGGTGGACCGTGGAC CAGCAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGGGAG GAGCAGTACACAGCACGTACCGTGTGGTCAAGCTCTTC ACCGTCTCTCACCGAGACTGGCTGAATGGCAAGGAGTAC AAGTGCAGGTCTCCAAACAAAGCCCTCCAGCCCCCATC GAGAAAACCATCTCCAAAGCCAAAGGCGAGCCCCGAGAA CCACAGGTGTACACCTGCCCCCATCCCGGGAGGAGATG ACCAAGACCAAGCTCAGCTGTGGTGGTCTGTTCAAGGC TTCTATCCAGCGACATCGCGTGGAGTGGGAGAGCAAT GGGACGCGGAGAACAACTACAGACCAACCGCTCCCGTG CTGGACTCCGACGGTCTCTTCTCTCTACAGCAAGCTC ACCGTGGACAAAGCAGGTGGCAGCAGGGGAAACGTCTTC TCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC ACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA GCTGCTGAACCTGTGGAAGATAATCTTAACTTCGTG GCCATGAATTCATCGATAAATCTGTACTTCATCGCC GAAGATGATGAATGACGACGATGACAGTACTTCGGT AAACTGGAGTCAAGCTGTCCGTGATCAGGAACCTGAAT GATCAGGTGCTGTTCTATTGACCGGCGACAGGCCCTG TTTGAGGATATGACCGACTCCGACTCTAGAGATAAGCC CCCCAACATCTTCTCATCATGATGTACAGGACTCC	

		CAGCCCAGGGGAATGGCTGTGACCATTAGCGTGAAGTCC GAGAAGATTAGCAACCCCTGTCTCCTCCGAGAACAAAGATCATC TCCITTCAAAGAGATGAACCCCCCGACAAACATCAAGAGAC ACCAAGAGCGACATCATCTTCTTCCAGAGGAGCGTGGCC GGCCATGATAACAAAATGCAGTTCGAAAGCTCCTCCTAC GAGGGCTACTTCTTGGCAATCCGAAAAGGAAAGGGACCTG TTCAAACCTGATCCTGAAGAAGGAGGATGAGCTGGGGAC AGGTCCATCATGTTTCAACCGTCCAGAACGAGGAC (SEQ ID NO:139)	
F U S E - 4 8 1	GAGCCCAATCTTCTGACAAAACCTACACATGC CCACCGTGCCAGCACTGAACCTCTGGGGGACCGTCAGTCTTC CCGTACGTCTTCTTCCCCCAAAACCCAAAG GACACCTCATGATCTCCCGGACCCCGAGGTC ACATGCGTGGTGGTGAACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGGAGGTGCATAATGCCAAGACAAAGCCGGG GAGGAGCAGTACACAGCACGTACCGTGTGGTC AGCGTCTCACCGTCTGCAACGAGACTGGCTG AATGGCAAGGAGTACAAGTGAAGGTCTCCAC AAAGCCCTCCAGACCCCCCATCCAGAAAAACCATC TCCAAAGCCAAAGGCGAGCCCGGAGAACCCAG GTGTACACCTGTCCCCATCCCGGAGGAGATG ACCAAGAACCGGTCAAGCTGAGCTGGCCGTC AAAGGTTCTTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTAC AAGACCAAGCCCTCCCGTGTGCTGACTCCGAGCGC TCCCTTCTTCTCCTGAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGGAGGAACGTCTTCTCA TGTCTCCGTGATGCATGAGGCTCTGCACAAACGG TTCCAGGCAGAAAGCCCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	GAGCCCAATCTTCTGACAAAACCTACACATGCCACCG TGCCAGCACTGAACCTCTGGGGGACCGTCAGTCTTC CTCTTCCCCCAAAACCCAAAGCACCCCTCATGATCTCC CGGACCCCGAGGTCACTACATGCGTGGTGGACCTGAGC CAGGAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGGGAG GAGCAGTACAAAGCACGATACCGTGTGGTCAAGCTCTC ACCGTCTGCACCCAGGACTGGCTGAATGGCAAGGAGTAC AAGTGAAGGTCTCCAAACAAAGCCCTCCAGCCCCATC GAGAAAACCATCTCCAAAGCCAAAGGCGAGCCCCGAGAA CCACAGGTGTACACCTGTGCCCCCATCCCGGGAGGAGATG ACCAAGACCAAGCTCAGCTGTGGTGTCTGTTCAAAGGC TTCTATCCAGCGACATCGCGTGGAGTGGGAGAGCAAT GGGACGCGGAGAACAACTACAGACCACCGCTCCCGTG CTGACTCCGACGGTCCCTTCTTCTCTACAGCAAGCTC ACCGTGGACAAAGACAGGTGGCAGCAGGGGAACGTCTTC TCATGTCTCCGTGATGCATGAGGCTCTGCACAAACCACTAC ACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA GCTGCTGAACCTGTGGAAGATAATGCCATTAATTCGTG GCCATGAAGTTTCAATTGACAAACACCCCTGTACTCTCATCGCC GAGGATGATGAGAACGACGACGACGATAAATATTCGGA AAGCTGGAGTCCAAAGCTGAGCGTATCAGGAACCTGAAT GATCAGGTGCTGTTTATTGACCGAGGGCAACAGGCCCTG TTTGAGGATATGACCGACAGCGACGCCAGGGATACGCT CCTAGAACATCTTTCATCATCTCTATGTACAAAGACTCC	

		CAGCCCAGGGGAATGGCTGTGACCATTTCCGTGAAGGCC GAGAAGATTTCCACCCTGTCAGCCGAAACAAAGATCATC TCCTTCAAAGAGATGAACCCCCCGACACACATCAAGAC ACCAAATCCGACATCATCTTCTTCCAGCGCAGCGTGCC GGACATGATAACAAAATGCAGTTCGAAAGCTCCTCCTAC GAGGGTACTTCTCGCAGCAGAAAAGAAAGGAGCCTG TTCAAGCTGATCCTGAAGAAGGAGGACGAGCTGGGGAC AGAAGCATCATGTTTCAACCTGCAGAACGAAGAC (SEQ ID NO:140)	
F U S E - 4 8 4	GAGCCCAATCTTCTGACAAAACACACATGC CCACCGTGCCAGCACTGAACCTCTGGGGGA CCGTACAGTCTTCTTCCCCCAAAACCCAAAG GACACCTCATGATCTCCCGGACCCCGAGGTC ACATCGGTGGTGGTGAACGTGAGCCACGAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGGAGGTGCATAATGCCAAGACAAAGCCGGG GAGGACAGTACACAGCACGTACCGTGTGGTC AGCGTCTCACCGTCTGCACAGGACTGGCTG AATGGCAAGGATACAAAGTCAAGGTCTCCAC AAAGCCCTCCAGCCCCCATCCAGAAAACCATC TCCAAAGCCAAAGGCGAGCCCGGAGAACACAG GTGTACACCTGTCCCCATCCCGGAGGAGATG ACCAAGAACCCAGGTCAAGCTGTGCTGCGCGTC AAAGGCTTCTATCCAGCGACATCGCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACACTAC AAGACCAAGCCCTCCCGTGTGCTGACTCCGAGCGC TCCCTTCTTCTGTCGAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGGGAACGTCTTCTCA TGTCCGCTGATGCATGAGGCTCTGCACAAAGG TTCAAGCAGAAAGACCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	GAGCCCAATCTTCTGACAAAACACACATGCCG TGCCAGCACCTGAACCTCTGGGGGACCGTCAGTCTTC CTCTTCCCCCAAAACCCAAAGCACCCCTCATGATCTCC CGGACCCCGAGGTCACTACATGCGTGGTGGACCTGAGC CAGGAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGGGAG GAGCAGTACACAGCACGTACCGTGTGGTCAAGCTCTC ACCGTCTGCACCGAGGACTGGCTGAATGGCAAGGAGTAC AAGTGCAGGTCTCCAAACAAAGCCCTCCAGCCCCCATC GAGAAAACCATCTCCAAAGCCAAAGGCGAGCCCGAGAA CCACAGGTGTACACCTGCCCCCATCCCGGAGGAGCATG ACCAAGACCAAGCTCAGCTGTGGTGTCTGCTCAAAGGC TTCTATCCAGCGACATCGCGTGGAGTGGGAGAGCAAT GGGCAGCGGGAGAACAACTACAGACCACGCTCCCGTG CTGACTCCGACGGTCTCTTCTTCTCTACAGCAAGCTC ACCGTGGACAAAGCAGGTGGCAGCAGGGGAAACGTCTTC TCATGCTCCGTGATGCATGAGGCTCTGCACAAACCACTAC ACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA GCTGCTGAACCTGTGGAAGATAATGTGATCAATTCGTG GCCATGAATTCATTGACAAACACCCCTGTACTTCATCGCT GAAGATGATGAACACGACGATGATAGTACTTCGGA AAGCTGGACTCCAAGCTGAGCGGTGATTAGGAACCTGAAT GACCAGGTGCTGTTCTATTGACAGGGCAACAGGCCCTC TTTGAGGATATGACCGACTCCGATGTGAGGGACAAAGCC CCTAGAACATCTTTCATCATCTCCAGTACGGCGACTCC	

	GGAGCAAGGGGACTGGCTGTGACCATTTCCGTGAAAGTG GAGAAGATTTCCACCCTGTCCGTGGAGAACAAAGATCATTT TCCTTCAAAGAGATGAACCCCCCAGACAAACATTAGGAC ACAAAGAGCGATATCATCTTCTTCGAGCGCGATGTGCC GGGCATTTCTGGAAAAGTGCAGTTCGAGTCTCTCTCTAC GAGGGTTACTTTCTGGCCGCTCGAAAAGGAAGGGACCTG TTCAAGCTGATCTTGAAGAAGGAGGACGAGCTGGGGAC AGATCCATCATGTTTACCGTGCAGAAATGAGGAC (SEQ ID NO:141)	
F U S E - 4 8 5	GAGCCCAAAATCTTCTGACAAAACCTCACATGCCCCACCG TGCCCGAGACCTGAACCTCTCTGGGGGACCGTCAGTCTTC CTCTTCCCCCAAACCCAAAGACACCCCTCATGATCTCC CGGACCCCGAGGTACATGTC	

		CCAAGGGGCATGGCCGTGACCATCTCCGTCAAGGTGGAG AAGATCTCCACCCCTGTCCGTGGGAAACAAAGATCATCTCC TTCAAAGAGATGAACCCCCCGACACAATCAAGACACA AAATCCGACATCATCTTCTCCAGCGCTCCCTGCTGGG CAGGACAACAAATGAGTTCGAATCTCTCTCTACGAG GGCTACTTCTCGCCCTCGAATAAAGAAAGAGACTTGTTC AAGCTCATCTCAAGAAGGAGGACGAGCTCGGGACAGG TCAATCATGTTCACCCGTGCAGAACGAGGAC (SEQ ID NO:1142)	
F	GAGCCCAATCTTCTGACAAAACCTCACACATGC	GAGCCCAATCTTCTGACAAAACCTCACACATGCCACCG	
U	CCACCGTGCCAGCACTGAACCTCTGGGGGA	TGCCAGCACTGAACCTCTGGGGGACCGTCAGTCTTC	
S	CCGTGAGTCTTCTCTCCCCCAAAACCCAAAG	CTCTTCCCCCAAAACCCAAAGCACCCCTCATGATCTCC	
E	GACACCTCATGATCTCCCGGACCCCGAGGTC	CCGAACCCCGAGTCACTACATGCGTGGTGGACGTGAGC	
-	ACATGGGTGATGTTGGACGTGAGCCACGAAGAC	CAGCAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC	
4	CCTGAGGTCAAGTCAACTGTTAGCTGGACGGC	GGCTGGAGGTGCATAATGCCCAAGACAAAGCCGGGAG	
8	GTGGAGGTGATATATCCCAAGACAAAGCCGGG	GACAGTACACAGCACGTACCGTGTGGTCAAGCTCTTC	
6	GAGGACAGTACACAGCACGTACCGTGTGGTC	ACCGTCTGCAACAGGACTGGCTGAATGGCAAGGAGTAC	
	AGCGTCTCAACGCTCTGCAACAGGACTGGCTG	AAGTCAAGGTCTCCAAACAAAGCCCTCCAGCCCCATC	
	AATGCAAGGAGTACAGTGCAGGTCTCCAAAC	GAGAAACCAATCTCCAAAGCCAAAGGGCAGCCCCGAGAA	
	AAAGCCCTCCAGCCCCCATCCAGAAAAACCATC	CCACAGGTGTACACCTGCCCCCATCCCGGAGGAGATG	
	TCCAAAGCCAAAGGGCAGCCCGGAGAACCCACAG	ACCAAGAACCCAGTCAAGCTGTGGTGCCTGTGTCAAAGGC	
	GTGTACACCCCTGCCCCCATCCCGGAGGAGATG	TTCTATCCCGGACACATCGCCGTGGAGTGGGAGAGCAAT	
	ACCAGAACCAAGGTCAAGCTGAGTGGCCCGTC	GGGCAGCCGGAGAACAACTACAGACCACCGCTCCCGTG	
	AAAGCTTCTATCCAGCGACATCGCCGTGGAG	CTGGACTCCGACGGCTCCTTCTCTCTCTACAGCAAGTCTC	
	TGGGAGAGCAATGGGCAGCCCGGAGAACAACTAC	ACCGTGGACACAGCAGGTGGCGAGCAGGGGACGTCTTC	
	ARGACACGCCCTCCCGTCTGGACTCCGACGGC	TCAATGCTCCGTGATGATGAGGCTCTGCACACCACTAC	
	TCCCTTCTCTCGTACGCAAGTCAACCGTGGAC	ACCCAGAGAGCTCTCCCTGCTCTCCGGGTAAA	
	AAGACAGGTGGCAGGAGGGAACGTCTTCTCA	GCTGTGAACCCGTGGAAGATAATGTGATCAATTTCTGTG	
	TGCTCGTGATGATGAGGCTCTGCACAAACCGG	GGCATGAATTCATTGACACACCCCTGTACTTCACTCGCC	
	TTACGCGAGAAGAGCCCTCTCCCTGTCTCCGGGT	GAGATGATGAATAACGGACCCCTGGGAGTGAAGGGAGGA	
	AAA (SEQ ID NO:114)	TACTTCGGAAGCTGGAGAGCAAGCTGAGCGTATCAGG	
		AATCTGAACACAGGCTGCTGTTCATCGACACGGGCAAC	
		AGGCCCTGTTCGAGGACATCACAGACATCAAGTGAAG	
		GCACACGCCCCCGGACCATCTTCATCATCATATGTAT	

		AAGGACTCCAGCCAAAGGGGATGGCCGTGACCATCTCC GTGAAAAGTGGAGAAAATCAGCACACTGAGCGTGGAGAAC AAGATCATCTCTTCAAGGAGATGAACCCCGGACAAAC ATCAAAGACACAAAATCCGACATCATCTCTTCCAGAGG AGCGTCCCGGCCACGACACAAAATGCAGTTCGAATCC AGCTCTACGAGGGCTACTTCTCTCGCCGTCGAAAAGGAA AGGGACCTGTTCAGACTCATCTGTGAAGAAGGAGACGAG CTGGGGACAGGAGCATCATGTTCAACCGTCCAGAACGAG GAC (SEQ ID NO:143)	
F U S E - 4 8 7	GAGCCCAATCTTCTGACAAAACCTCACACATGCG CCACCGTGCCAGCACTGAACCTCTGGGGGACCGTCACTTTC CCGTGAGTCTTCTCTTCCCGCAAAACCCAAAGCACCCCTCATGATCTCC GACACCCCGAGTCACTCACTGCGTGGTGGACCGTGGAC ACATGGGTGATGTTGACGCTGAGTCAAGTTCACTGGTGGAC 4 CCTGAGGTCAAGTCAACTGCTGAGTGGACGGC 8 GTGAGGTGCATATATCCCAAGACAAAGCCCGG 7 GAGGACAGTCAACAGCACGTAACGTGTGGTC AGCGTCTCACCGTCTGCAACGAGACTGGCTG AATGCAAGGAGTACAAAGTCAAGTCTTCCAAAC AAAGCCCTCCAGCCCGCATCGAGAAAACCATC TCCAAAGCCAAAGGGCAGCCCGGAGAACCATAC GTGTACACCCCTGCCCGCATCCCGGAGGAGATG ACCAAGAACCCAGTCAAGCTGCTGGTGGTGGTCAAGGC TTCTATCCCGAGCACATCGCGTGGAGTGGAGAGCAAT GGGCAGCCGGAGAACAACTACAGACCACCGCTCCCGTG CTGGACTCCGACGGCTCTTCTTCTCTCTACAGCAAGCTC ACCGTGGACACAGACAGGTGGCAGCAGGGGACGTCTTC TCATGCTCCGTGATGATGAGGCTCTGCAACACCATAC ACCCAGAGAGCTCTCCCTGCTCCCGGTAAA GGTGTGAACCCGTGGAAGTAAATGTGATCAATTCGTG GCCATGAAGTTCAATTGACACACCCCTGTACTTCATCGCC GAGATGATGAAAACGTGCATATGCTCTGGGCTTCTG GGACCCGGAGGCTATTTTGGAAAGCTGGAGAGCAAGCTG TCCGTGATCCGCAACCTGAACACCAAGTGTGTTCATC GACCAGGGAACAGGCCCTGTTCCGAGGACATGACCGAC TCTGACGTGAGGACACAGCCCGGAGGACATCTTCATC		

		ATCTCCATGTACAAGGACTCCAGCCCAAGGGCATGGCC GTGACCATCTCCGTGAAGTGGAGAGAAGATCTCCACCCCTG AGCGTGGAGACAAGATCACTCAGCTTCAAGGAGATGAAC CCCCCGACAAACATCAAGACACAAAATCCGACATCATC TTCTTCCAGAGAGCGTCCCTGGCCACGACACAAAATG CAGTTTGAGTCCCTCCTCCTACAGGGGCTACTTCTCTGGCC GTGAAAAGGAAAGGACCTGTTCAAGCTGATCCTGAAG AAGGAGGACGAGTGGCGACAGGTCAATTATGTCTCACC GTGCAGAACGAGGAC (SEQ ID NO:144)
F U S E - 4 9 9	GAGCCCAATCTTCTGACAAAACACTACACATGC CCACCGTGCCAGCACTGAATCTCTGGGGGA CCGTACAGTCTTCTCTCCCTCCCAAAACCCAAAG GACACCTCATGATCTCCCGGACCCCGAGGTC ACATCGGTGGTGGACGTGAGCCACGAAAGAC 4 CCTGAGGTCAAGTCAACTGCTAGCTGGACGGC 9 GTGGAGGTGATATGCAAGACAAAGCCCGGG 9 GAGGACAGTACACAGCACGTACCGTGTGGTC AGCGTCTCACCGTCTCTGCAACGAGACTGGTG AATGCAAGGAGTACAGTGCAGGTCTCCAAAC AAAGCCCTCCAGCCCTCATCGAGAAAACCATC TCCAAAGCCAAAGGGCAGCCCGGAGAACCCACAG GTGTACACCTGCCCCCATCCCGGAGGAGATG ACCAAGAACCAAGGTACGCTGAGTGGCCCGTC AAAGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCCGGAGAACAACTAC AAGACACGCTCCCGTCTGGACTCCGACGGC TCTTCTCTCTCGTACGCAAGTCAACCGTGGAC AAGACAGGTGGCAGGAGGGAACGTCTTCTCA TGCTCGGTGATGATGAGGCTCTGCACAAACCGG TTTACGCGAGAAGAGCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	GGTGTGAACCTGTGGAGATAATGTGATCAATTCGTG GCCATGAAGTTCAATGACAACACCCCTGTACTTCATCGCT GAAGATGATGAAACACCTGGAGTCCGACTACTTCGGAAAA CTGGAATCCAACCTGAGCGTGAATCCGGAACCTGAACGAT CAGGTGCTGTTCATCGACCGGCAATCGGCTCTGTCTT GAGGACATGCGGACAGCGACGTGAGGGATACGCTCCT AGGACCATCTTCATCATCTCCATGTATAAGGACTCCCAG CCAAGGGCATGGCCGTGACCATCTCCGTGAAAGTGGAG AAGATCTCCACTGTCCGTGGAATAACAAGATCATCTCC TTCAAGAGATGAACCCCGGACACATCAAGACACA AAAGCGATATATCTTCTTCCAGCGAGCGTCCCGGG CAGGACAAACAGATGCACTTCGAAAGCTCCTCTACGAG GGATACTTCTGGCCGTGAAAGGAAAGGACCTGTTC AAACTGATTTGAAGAAGGAGACGAGCTGGGGGACAGA AGCATCATGTTCAACCTGCGAAGACGAGGAC GAGCCCAATCTTCTGACAAACTCACACATGCCCCACCG TGCCAGCACTGAATCTCTGGGGGACCGTCACTCTTC CTCTCCCGCAAAACCCAGACACCCCTCATGATCTCC CGAACCCCGAGTCACTGCGTGGTGGTGGACGTGAGC CAGCAAGACCTGAGTCAAGTTCACTGGTACGTGGAC GGCGTGGAGGTGCATATGCCAAGACAAAGCCCGGGAG GAGCAGTACACAGACGTAACCGTGTGGTCAAGCTCTC ACCGTCTGCAACAGGACTGGGTGAATGGCAAGGAGTAC AAGTGCAAGGTCTCCAAAGCCCTCCAGCCCCCATC GAGAAACCATCTCCAAAGCCCAAGGGCAGCCCCGAGAA

	CCACAGGTGTACACCCCTGCCCCCATCCCGGGAGGAGATG ACCAAGAACCCAGGTACGCTGTGGTGCTGGTCAAAGGC TTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGCAGCCGGAGAACAACTACAAGACCAAGCCCTCCCGTG CTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTC ACCGTGGACAAGACGAGTGGCAGCAGGGGAACGTCCTC TCATGCTCCGTGATGATGAGGCTCTGCACAACCACTAC ACGCAGAAGAGCCCTCCTCCTGTCTCCGGGTAAA (SEQ ID NO:145)	
F D S E - 5 0 0	GAGCCCAATCTTCTGACAAAACACTCACACATGC CCACCGTGCCAGCACCTGAACCTCTGGGGGA CCGTACAGTCTTCTCTCCCCCAAAACCCAG GACACCTCATGATCTCCCGACCCCGAGGTC ACATCGGTGTTGGTGGACGTGAGCCACGAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGGAGGTGCATAATGCCAAGACAAAGCCGGG GAGGACAGTCAACAGCACGTACCGTGTGGTC AGCGTCTCACCGTCTGCACACGAGCTGGCTG AATGGCAAGGATACAGTGCAGAGTCTCCAAAC AAAGCCCTCCAGCCCCCATCCAGAAAAACCATC TCCAAAGCCAAAGGCGAGCCCGGAGAACCCAG GTGTACACCTGTCCCCCATCCCGGGAGGAGATG ACCAAGAACCCAGGTACGCTGAGCTGGCCGTC AAAGGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCGAGCCGGGAGAACACTAC AAGACCAAGCCCTCCCGTGTGCTGACTCCGACGGC TCCCTTCTTCTGTCGACCAAGTCAACCGTGGAC AAGACAGGTGGCAGGAGGGAACGCTCTTCTCA TGCTCCGTGATGCATGAGGCTCTGCACAACCGG TTACCGCAGAAAGCCCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	TACTTCGGCAAGCTGGAGTCCAAAGCTGTCCGTGATCCGG AACCTGAACGACCCAGGTGCTGTTCATCGACAGGGCAAC AGGCTCTCTTCGAGGATATACCGACTCCGACGTGAGG GATAAGCTCCAAAGCAATCTTCATCATCTCCATGTAC AAGGACTCCAGCCCGAGGGGAATGGCTGTGACCATTTCC GTGAAAGTGGAGAAGATTAGCACCCCTGAGCGTGGAGAAC AAGATCATCTCTTCAAGGAATGAACCCCGGACAAAC ATCAAAGACACCAAAATCCGACATCATCTTCTTCCAGAGG TCOGTGCCTGGCCACGATAACAAAATGCAAGTTCGAGTCC TCCTCTACGAGGGCTACTTCTGTGGCAGTCCGAAAAGGAG AGGGACCTGTTCAGCTCATCTGCAAGAGGAGGACGAG CTGGGGACAGATCCATCATGTTCACCGTGCAGAACGAG GACGAGCCCAATCTTCTGACAAAACCTCACACATGCCCA CCGTGCCACAGCACCTGAACCTCCTGGGGGACCCGTCACTC TTCTCTTCCCCCAAAACCAAGACACCCCTCATGATC TCCGGACCCCGAGGTCACTGCTGGTGGTGGACGTG AGCCACGAGAACCCCTGAGTCAAGTTCAACTGTTACTGTG GACGGCTGGAGTGCATATGCCAAGACAAAGCCCGGG GAGGAGCAGTACAACAGCACGCTACCGTGTGGTCAGCGTTC CTCACCGTCTGCACACGAGTGGCTGAATGGCAAGGAG TACAAGTGCAGGTCTCCAAACAAAGCCCTCCAGCCCCC ATCGAGAAAACCATCTCCAAAGCCAAAGGCGAGCCCGGA GAACCAAGGTGTACACCTGCCCCCATCCCGGGAGGAG ATGACCAAGAACAGGTGAGCCCTGTGCTGGCTGGTCAAA GGCTTCTATCCACCGACATCCCGCTGGAGTGGGAGAGC

		AATGGGCAGCGGAGAGAACAACTACAGAGACCAGCCCTCCC GTGCTGGACTCGACGGCTCCTTCTTCTCTACAGCAAG CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTG TTCTCATGTCTCCGTGATGCATGAGGCTCTGCACAACCCAC TACACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:146)	
F U S E - 5 0 1	GACGCTCACAAATCCGAGTGGCACACAGGTTT AAGGACCTGGGAGAGAGAACTTCAAAAGCCCTG GTGCTGATTGCAITTTGCCCAGTATCTGCAGCAG TGTCCCTTTGAGGACCAACGTGAAGCTGGTGAAC GAGGTACCCGAATTTGCCAAGACTTGCCTGGCC GACGAGTCCGAGAGAACTGCCGCAAGTCCCTG CATACCCCTGTTTGGGACAAAGCTGTGTACAGTG GCCACCTGGGGAGACATACGGTGAGATGGCC GACTGCTGCGCCAAAGCAGGAACCCGAGAGAAAC GAATGCTTCTGAGCACAAAGGACGACAAACCCC AACCTGCCCCGGCTGCTCAGGCCCGAAGTGGAC GTGATGTGTACCGCTTTCACGACAACGAAGAG ACATTTCTGAGAGAGTACCTGTACGAGATCGCC AGAGGCACCCTTACTTTTACGCCCCCGAGCTG CTGTTCTTTGCCAAGAGGTATAGGCCCGCCTTT ACTGAGTGTGCCAGGCAGCCGACAAGCCGCC TGCCTGCTGCCCAAGCTGGACGAGCTGCCGAC GAGGCAAGGCCTCTCTCCGCTAAGCAGAGGCTG AAGTGGCATCCCTGCAGAAATTTGGCGAGAGA GCCTTCAAGGCATGGGCCGTGGTAGGCTGTCC CAGAGGTTTCCAAAGGCCGAATTTGCCGAGGTG TCCAAGCTGGTGACAGACCTGACCAAGGTGCAC ACCGAGTGTGTACGGGAGACTTGTGTGAGTGC GCCGAGACAGGGCCACCTGGCTAAGTACATC TGTGACACACAGGACTCTATCTCCTCCAAAGCTG		

AAGGAGTGTGTCGGAGAAGCCCCCTGCTGGAGAAA AGCCACTGTATTGCTGAGGTGGAGAACGACGAG ATGCCCGCCGACCTGCCCTCTCTGSCCGCTGAT TTCGTGGAGTCCAGGACGTGTGTAAGAATAC GCCGAGGCCAAGAGCGTGTCCCTGGGATGTTT CTGTATGAGTACGCTAGGAGGCACCCCGATTAC TCCGTGGTGTGCTGCTGAGGCTGGCAAAAACA TACGAAACCAACCTGGAGAAGTGTGCGCGT GCTGACCCCCACGAGTGTATGCCAAGGTGTTT GACGAGTTCAAACCCCTGGTGGAGAACCCAC AACCTGATCAAGCAGAACTGGAGCTGTTCGAA CAGCTGGCGGAGTACAAATCCAGAACGCATG CTGTGAGGTACACCAGAAAGTCCCCAGGTG AGCACCCCCACCTGGTGGAGGTGTCAGGAAC CTGGCAAAAGTGGCAGCAATGCTGCAAGCAC CCCCAGGCCAAAAGATGCCCTGTGCAGAGGAC TACCTGAGTGTGGTCTGAACCACTGTGCGTG CTGCACGAGAAGCACCCCGTGAGCGACAGGTG ACCAAGTGTGTACCGAGTCCCTGGTGAACAGA AGGCCCTGTTTATGTCCTTGGAGTGGATGAG ACTTAGCTGCCTAAGGAGTTCAACGCAGAGACA TTCACCTTCCATGCCGATATTTCACCCCTGTCC GAAAGGAAAGACAGATCAAGAAACAGACCGCC CTGTTGGAGCTGTTGAAACACACAGCCCAAGGCC ACCAAGGAACAGCTGAAAGCCGTGATGGACGAC TTCGCCGCCCTTCTGGAGAAATGCTGCAAGGCC GACGACAAGAACTGTCTTCGCAGAGGAGGA AAGAACTGTTGCCAGCCAGCCAGCCGCCCTG GGACTGGCTGCTGAACCTGTGGAGATATATG ATCAATTTCTGGCCATGAAGTTCATTGACAAC AOCCTGTACTTCACTCGCTGAAGATGATGAAAC GACGATGATGATAAGTACTTCGGAAAGCTGGAG TCCAGCTGAGCGTGATTAGGAACCTGAATGAC CAGTCTCTGTTTCAATGACCAAGGCCAACAGGCC CTCTTTGAGGATATACCCACTCCCATGTGAGG GACACGCCCTAGAACAACTTTCATCATCTCC ATGTACAAGGACTCCACGCCAAGGGAATGGCC	
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		GTGACCAATTTCGTGAAAGTCGAGAAAATTTCC ACCTGTCCGTGGAGAACAAAGATCATCTCCTTC AAAGAAATGAACCCCGACAAACATCAAGGAC ACCAAAATCCGACATCATCTTCTCCAGCGCTCC GTGCCAGGCCATGATAACAAAATGCAGTTCGAG AGCAGCTCCTACGAGGGCTACTTCTGGCAGTC GAAAAGGAAAGGACCTGTTCAAGCTGATCCTG AAGAAGGAGGAGCAGCTGGGGACAGAAGCATC ATGTTCAACCGTGCAGAACGAAGAC (SEQ ID NO:115)	
F U S E - 5 0 2	GACGCTCACAAATCCGAAGTGGCACACAGTTT AAGGACCTGGGAGAGAGAACTTCAAAGCCCTG GTGCTGATTGCATTTGCCAGTATCTGCAGCAG TGTCCCTTTGAGGACCACTGAGTGGTGAAC GAGTGACCGAATTTGCCAAGACTTGGTGGCC GACGAGTCCGACAGAACTGGCACAACTCCCTG CATACCTGTTTGGCGACAAAGCTGTGTACATG GCCACCTCGGGAGAGACATACGGTGAGATGGCC GACTGCTGGCCCAAGCAGGAACCCGAGAGAAAC GAATGCTTCTGTAGCACAAAGACGACAAACCC AACTGCCCGGCTGGTGAGGCCCGAAGTGGAC GTGATGTGTACCCCTTTCAAGACAAACGAAGAG ACATTTCTGAGAAGTACCTGTACGAGATCGCC AGAAGGCACCCCTACTTTTACGCCCGCCGAGCTG CTGTTCTTTGCCAAGAGGTATAAGCCCGCCTTT ACTGAGTGTGCGCAGGCGAGCGACAAAGCCGC TGCTGTGCGCAAGCTGGACGAGCTGCGGAC GAGGCAAGGCTCCTCCGCTAAGCAGAGGCTG AAGTGGCATCCCTGCAGAAATTTGGCGAGAGA		

GCCTTCAAGGCATGGCCGTGGCTAGGCTGTCC CAGAGTTTCCAAAGGCCGAATTTGCCGAGGTG TCCAGCTGGTGACAGACCTGACCAAGGTGCAC ACCGAGTTTGTACGGAGACTTCTGGAGTGC GCCGAGACAGGCCGACCTGGCTAAGTACATC TGTGAGAACCAAGGACTCTATCTCTCCCAAGCTG AAGGAGTCTGGGAGAAGCCCCCTGCTGGAGAAA AGCCACTGTATTGCTGAGGTGGAGAACGACGAG ATGCCGCCGACCTGCCCTCTCTGGCCGCTGAT TTCTGGAGTCCAGGACGTTGTTAAGAACTAC GCCGAGGCCAAAGACGTGTTCCCTGGGGATGTTT CTGTATGAGTACGCTAGGAGGACCCCCGATTAC TCCGTGGTGTGCTGCTGAGGCTGGCAAAACA TACGAAACCACTGGAGAAGTGTGTGCCGCT GCTGACCCCCACGAGTGTCTATGCCAAGGTGTT GACGAGTTCAAACCCCTGGTGGAGAACCCCCAG AACCCTGATCARGCAGAACTGGAGCTGTTGAA CAGCTGGCGAGTACAAATCCAGAACGCACGTG CTGTGAGGTACACCAAGAAAGTGCCCCAGGTG AGACCCCCACCCCTGGTGGAGGTGCCAGGAAC CTGGCAAGTGGGCAGCAATGCTGCAAGCAC CCCCAGGCCAAAGATGCCCTGTGCAGAGGAC TACCTGAGTGTGTGCTGAACCACTGTGCGTG CTGCACGAGAGACACCCGTGAGCGACAGGGTG ACCAAGTGTGTACCGAGTCCCCTGCTGAACAGA AGGCCCTGTTTGTAGTCCCCTGGAAGTGGATGAG ACTTACGTGCTTACGAGTTCAACCCAGAGACA TTCACCTTCCATCCCATATTTGCCACCTGTCC GAAAGGAAAGACAGATCAAGAAACAGACCCGC CTGTGGAGCTGTTGAAACACAGCCCCAAGGCC ACCAAGGAACAGCTGAAAGCCGCTGATGGACGAC TTCCGCCCTTCTGTGAGAAATGCTGCAAGGCC GACGACAAAGAAACCTGCTTCCGACAGGAAGGA AAGAACTGGTGGAGCCAGCCAGGCCGCCCTG GGACTGGCTGCTAAACCTGTGCAACATATGTG ATCAATTCGTGGCCATGAAGTTCATTGACAAC ACCCGTACTTCTATCGCTGAAGATGATGAAAC	
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		GACGATGATGATAAGTACTTCGGAAAGCTGGAG TCCAAGCTGAGCGTGATTAGGAACCTGAATGAC CAGGTGCTGTTCATTGACCAGGGCAACAGGCC CTCTTTGAGGATATGACCGACICCGATGTGAGG GACAAGGCCCTAGAACAAATCTTCATCATCTCC AAGTACGGCGACTCCAGCCAAAGAGGACTGGCT GTGACAAATTAGCGTAAAGTCGAGAGATTTCC ACCCGTCCGTGAGAACAAATCATCTCTTC AAGGAGATGAACCCCGACAAACATCAAGGAC ACCAAAAGCGATATCATCTCTCCAGAGGTC GTCCCGGTACGATAACAAAGTCAGTTCGAG TCTCTCTCTACGAGGTTACTTCTGGCCGTC GAAAGGAGCGGACCTGTTTAACTGATCCTG AAGAGGAGGACGAGTGGGTGACAGGTCCATC ATGTTCAACCGTCCAGAAATGAGGAC (SEQ ID NO: 116)
F U S E - 5 0 3		GACGCTACAAATCCGAAGTGGCACACAGTTT AAGGACCTGGGAGAGAGAACTTCAAAGCCCTG GTGCTGATTCATTTGCCAGTATCTGCAGAG TGTCCCTTTGAGGACCACTGAAGTGGTGAAC GAGTGACCGAATTTGCCAAGACTGCGTGGCC GACGAGTCCGACAGAACTGCGACAAGTCCCTG CATACCCCTGTTTGGCGACAAAGTGTGTACAGTG GCCACCTGGGAGACATACGGTGAGATGGCC GACTGCTGCCCAAGCAGGAACCCGAGAGAAAC GAATGCTTCTGCAGCACAGGACGACAAACCC AACCTGCCCGGCTGTTGAGCCCGAAGTGGAC GTGATGTGTACCCCTTTACGACAAACGAGAG ACATTTCTGARGAAGTACCTGTACAGATCGCC AGAGGCACCCTTACTTTTACGCCCGCCGAGCTG CTGTTCTTTGCCAAGAGGTATAGGCCCGCTTT ACTGAGTGTGCCAGGACGCCGACAAAGCCGCC TGCCTGCTGCCCAAGCTGGACGAGTGGCGGAC GAGGCAAGGCTCTCTCCGCTAAGCACAGGCTG AAGTGGCATCCCTGCGAGAAATTTGGCGAGAGA

GCCTTCAAGGCATGGCCGTGGCTAGGCTGTCC CAGAGGTTTCCAAAGGCCGAATTTGCCGAGGTG TCCAGCTGGTGACAGACCTGACCAAGGTGCAC ACCGAGTTTGTACGGAGACTTCTGGAGTGC GCCGAGCACAGGCCACCTGGCTAAGTACATC TGTGAGAACCAAGGACTCTATCTCTCCCAAGCTG AAGGAGTCTGGGAGAAGCCCCCTGCTGGAGAAA AGCCACTGTATTGCTGAGGTGGAGAACGACGAG ATGCCGCCGACCTGCCCTCTCTGGCCGCTGAT TTCTGGAGTCCAGGACGTTGTTAAGAACTAC GCCGAGGCCAAAGACGTGTTCCCTGGGGATGTTT CTGTATGAGTACGCTAGGAGGACCCCCGATTAC TCCGTGGTGTCTGCTGCTGAGGCTGGCAAAACA TACGAAACCACTGGAGAAGTGTGTGCCGCT GCTGACCCCCACGAGTGTCTATGCCAAGGTGTTT GACGAGTTCAAACCCCTGGTGGAGAACCCCCAG AACCCTGATCAAGCAGAACTGGGAGCTGTTGAA CAGCTGGGCGAGTACAAATCCAGAACGCCACTG CTGTGAGGTACACCAAGAAAGTGCCCCCAGGTG AGACCCCCACCCCTGGTGGAGGTGCCAGGAAC CTGGCAAAAGTGGCGAGCAAAATGCTGCAAGCAC CCCCAGGCCAAAGAAATGCCCTGTGCAGAGGAC TACCTGAGTGTGTGTGCTGAACCACTGTGCGTG CTGCACGAGAGACACCCCGTGAGCGACAGGGTG ACCAAGTGTGTACCGAGTCCCCTGCTGAACAGA AGGCCCTGTTTGTAGTCCCCTGGAAGTGGATGAG ACTTACGTGCTTACGAGTTCAACCCAGAGACA TTCACCTTCCATGCCATATTTGCCACCTGTCC GAAAGGAAAGACAGATCAAGAAACAGACCCGC CTGTGGAGCTGTTGAAACACAGCCCCAAGGCC ACCAAGGAACAGCTGAAAGCCGCTGATGGACGAC TTCCGCCCTTCTGTGAGAAATGCTGCAAGGCC GACGACAAAGAAACCTGCTTCCGACAGGAAGGA AAGAACTGTGGAGCCAGCCAGCCGCCGCCCTG GGACTGGGAGATGACGACCAACAATCTTTGGA AAGCTGGAGAGCAAGCTGAGTGTGATCAGGAAC CTGACGACCAAGGTGCTGTTTATCGACCCAGGCC	
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		AATAGGCCACTGTTTGAGGATATGACAGATTCC GACGTGAGGGACAAAGCTCCAGAAACAATTTTC ATCATCTCTATGACAGGACTCCAGCCCAAGG GGCATGGCTGTGACCAATTTCCGTGAAGGTGGAG AAGATTTCCACCCCTGTCTGTGGAGAACAAAGATC ATCTCCTTCAAGAGATGAACCCCCCGACAAAC ATCAAAAGACACAAAGCGATATCATCTTCTTC CAGAGGTCCGTGCCCGGTCAAGATAACAAATG CAGTTTCAAAGCTCTCTTACGAGGGATACTTTT CTGGCCGTGAAAAGGAACGCGACCTGTTCAAAG CTGATCTCTGAAGAAGGAGGACGAGCTGGGGGAC AGAAGCATCATGTTCACCGTGCAGAAACGAAGAC (SEQ ID NO:117)	
F U S E - 5 0 4	GACGCTACAAATCCGAAGTGGCACACAGGTTT AAGGACCTGGAGAAAGAACTTCAAAGCCCTG GTCTCATTTGCAATTTCCCACTATCTCCAGCAG TGTCCCTTTGAGGACCAAGTGAAGCTGGTGAAC GAGGTGACCGAATTTGCCAAGACTTGGTGGCC GACGAGTCCGACAGAACTGCGACAAGTCCCTG CATACCTGTTTGGCGACAAGCTGTGTACAGTG GCCACCTGCGGAGACATACGGTGAGATGGCC GACTGCTGCGCAAGCAGGAACCCGAGAGAAAC GAATGCTTCCTGCACACAAGCACACACACCCC AACTGCCCGGCTGGTGAGGCCCGAAGTGGAC GTGATGTGTACCGCTTTTCCACACAACGAAGAG ACATTTCTGAAGAAGTACCTGTACGAGATCGCC AGAAGGCACCTTACTTTTACGCCCCCGAGCTG CTGTCTTTGCCAAGAGGTATAAGGCCGCGCTTT ACTGAGTGTCTGCAGGACGCGACAAGCCGCGC TGCTGTGTGCCAAGCTGGACGAGCTGCGCGAC GAGGCAAGGCTCTCTCCGCTAAGCAGAGGCTG AAGTGGCATCCCTGCAGAAATTTGGCGAGAGA GCCTTCAAGGATGGGCCGTGGCTAGGCTGTCC CAGAGGTTTCCAAAGCCCGAATTTGCCGAGGTG		

TCCAAAGCTGGTGACAGACCTGACCAAGGTGCAC ACCGAGTGTGTACGGGAGACTTGTCTGGAGTGC GCCGACGACAGGCGGACCTGGCTAAGTACATC TGTGAGAACCAAGACTCTATCTCTCCAAAGCTG AAGGAGTGTGCGAAGAGCCCTGCTGGAGAAA AGCACTGTATTGCTGAGGTGGAGAACGACGAG ATGCCGCGGACCTGCCCTCTCTGGCCGCTGAT TTCTGTGGAGTCCAGGACGTGTGTAAGAACTAC GCGGAGGCCAAAGACGTGTCTCTGGGATGTTT CTGTATGAGTACGTAGGAGGACACCCCGATTAC TCCGTGGTGTCTGTGTGTGAGGCTGGCAAAAACA TACGAAACCAACCTGGAGAAGTGTGTGCCGCT GCTGACCCCCACGAGTGTCTATCCAAAGGTGTTT GACGAGTTCAAACCCCTGGTGGAGAACCCAG AACCTGATCAAGCAGAACTGCGAGCTGTTGAA CAGCTGGCGGAGTACAAATTCCAGAACGCACTG CTGTTGAGGTACCAAGAAAGTGTCCAGGAAC AGCAACCCCAACCTGGTGGAGTGTCCAGGAAC CTGGCAAAAGTGGCGAGCAATGCTGCAAGCAC CCGAGGCCAAAGAAATGCCCTGTGCAAGAGGAC TACCTGAGTGTGGTGTGTGAACCACTGTGTGGTG CTGCACGAGAGACACCCGTGAGCGACAGGGTG ACCAACTGTTGTACCGAGTCCCTGCTGTGAACAGA AGGCCCTGTTTGTAGTCCCTGGAGTGGATGAG ACTTACGTGCCCTAAGGAGTTCAACGCAAGAGACA TTCACTTCCATGCGGATATTGTCAACCTGTCC GAAAGGAAGACAGATCAAGAACAGACCGCC CTGCTGAGCTGTGAACACACAGCCCAAGGCC ACCAAGGAACRGCTGAAAGCCGTGATGGACGAC TTCGCCGCCCTCTGTGGAGAAATGCTGCAAGGCC GACGACAAGAACTGCTTCCGACAGGAGGA AAGAACTGGTGGAGCCAGCCAGGCCGCCCTG GGACTGGGAGATGACGACGACAAGTACTTTGGA AAGCTGGAGAGCAAGCTGAGTGTGATCAGGAAC CTGAACGACCAAGTGTCTTTATCCACCAAGGCC AATAGGCCACTGTTTGTAGGATATGACAGATTCC GACGTGAGGGACACGCTCCCGAACAATTTTC	
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ATCATCTCTAAGTAGGAGACTCCAGCCAAAGG GGCCTGGCTGTGACCATCTCCGTGAAGTGGAG AAATCTCCACACTGTCCGTGGAGAACAAAGATC ATCTCTTCAAGGAATGAACCCCGGACAAAC ATCAGGACACCAATCCGACATCATCTTCTTTC CAGGCTCCGTGCCGGACATGATAACAAGGTC CAGTTCGAGTCCAGCAGCTACGAGGGATACTTT CTGGCCGTGAAAAGGAAAGGACCTCTTCAAA CTGTATCTTGAAGAAGGAGGACGAGCTGGGGAC AGAAGCATTAATGTTTACCGGTGCAGAACGAGGAC (SEQ ID NO:118)		GAGCCCAAATCTTCTGACAAAACTCACACATGCCGACCG TGCCACGACCTGAACCTCTGGGGGACCGTCAATGATCTTC CTCTTCCCGCCAAACCCAAAGCACCCCTCATGATCTCC CGACCCCGAGGTCACTGCTGGTGGTGGACGTGAGC CAGCAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCTGGAGTGCATATGCCAAGACAAAGCCCGGGAG GAGCAGTACAAAGCACGTACCGTGTGGTCAGCGTCTC ACCGTCTGTCAACAGGACTGGCTGAATGGCAAGGAGTAC AAGTGCAAGTCTCCAAAGCCCTCCAGCCCCCATC GAGAAACCATCTCCAAAGCCAAAGGCGAGCCCCGAGAA CCACAGGTGTACACCTGCCCGCATCCCGGAGGAGATG ACCAAGAACCAGGTCAAGCTGTGGTGGCTGGTCAAGGC TTCTATCCCGGACACATCGCCGTGGAGTGGGAGAGCAAT GGCAGCCGGAGAACAACTACAAGACCACCGCTCCCGTG CTGGACTCCGACGGCTCTTCTTCTCTACAGCAAGTTC ACCGTGGACAAAGCAGGTGGCGAGCAGGGGAACTCTTC TCATGTCTCGTATGATGATGAGGCTGTGCACAACCACTAC ACCCAGAGAGCCCTTCCCTGTCTCCGGGTAAGACGAT GACGACAACTATTTCGGAAGCTGGAAAGCAAGCTGAGC
F U S E - 5 0 5	GAGCCCAAATCTTCTGACAAAACTCACACATGC CCACCGTGCCAGCACCTGAACCTCTGGGGGA CCGTGAGTCTTCTCTTCCCGCCAAACCCAAAG GACACCTCATGATCTCCCGGACCCCGGAGGTC ACATGGTGTGGTGGACGTGAGCCACGPAAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGGAGGTGCATATGCCAAGACAAAGCCGGG GAGGACAGTACACAGCACGTACCGTGTGGTC AGGTCTCTACCGTCTGTCCACCGACCTGGGTG AATGGCAAGGAGTACAAGTGCAAGTCTCCAAC AAAGCCCTCCAGCCCGCATCGAGAAAACCATC TCCAAAGCCAAAGGCAGCCCGGAGAACACAG GTGTACACCTTGCCCGCATCCCGGAGGAGATG ACCAGAACCAGGTCAAGCTGAGTGGCGCGTC AAGGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTAC AAGACCAAGCCTCCCGTGTGGACTCCGAGCGC TCTTCTTCTCGTGAGCAAGTCAACCGTGGAC AAGACAGGTGGCAGGGGAACGTCTTCTCA	

TGCTCCGTGATGATGAGGCTCTGCACAAACCCGG TTACGCAGAGAGGCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	GTGATCAGGAACCTGAACGACGACGAGGTGCTGTTCATCGAC CAGGGAACAGGCCCTGTTTGAGGACATGACCGACAGC GACGTGAGGGATAACGCCCTAGAACAACTTCATTAATC TCCATGTATAAGACTCCAGCCAAAGGGGAATGGCCGTG ACCATTTCCGTGAAGGTCGAGAAAATCTCCACACTGAGC GTGGAGAACAGATCATCTCCCTCAAGAGATGAACCCC CCCGACAAATCAAAGACACAAAGAGCGGACATCATCTTC TTCCAGAGGAGCGTCCCGGCCCATGATAACAGATGCAG TTCCGAAAGCTCCTCTACGAAAGCTACTTCCCTGGCCGTC GAAAAGGAAAGGACCTGTTCAAAATGATCCTCAAGAAG GAGACGAGCTGGGGACAGAGCATCATGTTCACCCGTG CAGAACGAGGAC (SEQ ID NO:147)
F U S E - 5 0 7 TCCAAAGCCAAAGGACAGCCGAGGAACACAG GTCACACCCCTGCCCCCTCCAGGAGGAAATG ACCAGAACCAGTCACTTAATTCCTGGTT AAAGCTTCTACCCCTCCGACATCGCTGTGGAG TGGAGTCCAACGCGCAGCCCGAGAACAACTAC AAACACACACACCCCGTCTCGACTCCGACGGC TCCCTCTCTCTACTCCAAACTGACAGTGGAC AAGTCCAGGTGGAGCAGGGCAAGTCTTTTCC TGCTCCGTGATGACAGAGGCCCTGCACAAACCAC TATACCCAGAACTCCCTGTCCCTGTCCCGGGC AAAGCCCGAGCGCTGTGGAGGACAACGTGATC AACTTTGTGCCCATGAAGTTCAICGACAAACACA CTGTACTTTCATCGCAGAGGACGACGAGAACGAC GACGACGACAAGTACTTCGGAATACTGGAGTCC	

	AAGCTGTCCGTGATCAGGAACCTGAATGATCAG GTGCTCTTCATCGACCAGGGCAACAGGCCCTG TTTGAGGATATGACGACAGCGAGCTGAGGGAC AAGCACCCAGGACAATTTTCATCATTTCTATG TACAGGACTCCAGGCCAGGGGATGGCCGTG ACCATCAGCGTGAGGTGGAGAGATCAGCACA CTGAGCGTGGAGAACAAAGATCACTCCTTCAAG GAGATCAACCCCCCGACAAACATCAAGACACC AAAGCGATATCATCTTCTTTCAGAGGAGCGTG CCGGCCACGACAAACAAATGCAGTTCGAGTCC TCTCCTACGAGGGCTACTTCTCGCCGTCGAA AAGGAAAGGGACCTGTTCAAGCTGATCCTGAAG AAGGAGACGAGCTGGGGACAGAGCATCATG TTCACCGTGCAGAACGAGGAC (SEQ ID NO: 119)	
F U S E - 5 0 8	GAGCTAAATCCGAGACAAACACACATGC CCCCCTGCCCGCCCTGAACGTGGGAGGA CCCAGGTGTTTCTGTTCCCCCAACCCAAAG GACACCTGATGATCTCCAGGACCCCGAGGTG ACCTCGGTGTCGTGGACGTCGCCACGAGGAC CCGAGGTGAAGTTAATTGGTACGTGGACGGC GTTGAGGTGCACACGCCCAAGACCAACCCAGG GAGGACAGTACACAGTACATACAGGGTGGTG TCCGTGCTGACCGTGTGCACCGAGCTGGCTG AAGGCAAGGAGTACAAAGTGCAAGGTGCCAAC AAGCACTCCCGCACCAATTGAATAAACCATC TCCAAAGCCAAAGGACAGCCCGAGGAAACCACAG GTCTACACCTGCCCCCTCCAGGAGGAAATG ACCAAGAACCCAGGTACAGTTAACTGCCTGGTT AAAGCTTCTACCCCTCCGACATCGCTGTGGAG TGGAGTCCAAACGGCCAGCCCGAGAACAACTAC AAACACACACCCCGTGTCTCGACTCCGACGGC TCCCTCTTCTCTACTCCAAACTGACAGTGGAC AAGTCCAGGTGGCAGCAGGGCAAGCTTTTCC TGCTCCGTGATGCACGAGGCCCTGCACAAACCAC TATACCCAGAGTCCCTGTCCCTGTCCCCCGGGC AAA	

		GACGACGACGATAAGTACTTTCGGCAAACTCGAG AGCAAGTTGTCCGTGATTCGCAACCTGAACGAC CAGGTCCCTCTTCATCGAACAGGGCAACCGCCCC CTGTCGAGGACATGACCGACTCCGACGTGAGG GACAAGCTCCCGCACCATCTTCATATATCAGT ATGTATAAGGATTCGACGCCCGCGGCATGGCC GTGACCATCTCCGTGAAGGTGGAGAAGATTTCC ACATGTCCGTGGAGAACAAAGATCATCTCTTC AAAGAGATGAACCCCCCGACAAACATCAAGGAC ACAAATCCGACATCATCTTCCTCCAGAGGAGT GTGCGCGGCCACGACAAACAAATGCAGTTCGAA TCCAGCTCCTACGAGGGCTACTTCTCGCGGTC GAAAGGAAAGGACCTGTTCAAGCTGATCCTG AAGAAGGAGGATGAGCTGGGGACAGATCCATC ATGTTCAACCGTGCAGAACGAGGAC (SEQ ID NO:120)	
F D S E - 5 0 9	F D S E - 5 0 9	GAGTCTAAGTACGGGCCCCCAUGCCCTCTGCG CCCCCTCCTGAATTTTGGGCGGCCCTCCGTT TTTTTGTTCCTCCCAAGCCCCAAGGACACCTG ATGATTTCCGCAACCCGAGGTACCTGCGTC GTCGTCGACGTCTCCAGGAAGATCCCGAGGTC CAGTTTAATTGGTACGTGGACGGCGTGAAGTC CACACGCCAAGACCAAGCCCCCGGAGGAACAG TTCAATTCACCTACAGGGTGGTCCGTCTC ACCGTGTGCTCATCAGGATTTGGCTGAACGGCAAG GAATACAAGTGCAAGGTGTCCAACAAGGCTC CCCTCCTCTATCGAGAAACCACTCTCCAAAGCC AAAGGCCAGCCAGGGAACCCCGAGGTGTACACC CTGCCCCCTCCAGGAAGAAATGAACCAAGAAC CAGGTGAGCTGACATGCCCTCGTGAAGGGCTTC TACCCCTCCGACATCGCCGTGGAATGGGAGTCC AACGCCAGCCGCAAAACAACTACAAACCCACA CCCCCGTGTCTGACTCCGACGGCTCCTTCCTC CTCTACTCTAGTTGACCGTGGACAAGTCCAGG TGGCAGGAGGGCAACGCTCTTTCTCTGCTCCGTG ATGCACGAGGCGCTCCACAACCACTATACCCAG AAGTCCCTGTCCCTGTCCCTCGGCAAGGCAGCC	

	GAACGTGTGGAGGACAACGTGATCAACTTCGTG GCCATGAAGTTCATCGATAACACCCGTGACTTC ATCGCAGAAGATGATGAACACGACGACGACGAC AAATACTTCGGCAACTGGAGTCCAAAGCTGAGC GTGATTAGGAACCTGAATGATCAGTGCTCTTC ATTGACCAAGGCCAACAGGCCCTCTTTTGAGGAC ATGACCGACTCCGACGTGAGGGACAACGCCCCC CGCACCATCTTCATCATCTCCATGTACAGGAC TCCAGCCAGGGCATGGCCGTGACCATTTCC GTGAGGTGGAGAAATCTCCACACTGCTGIG GAGACAAATCATCTCTCTTCAAGAGATGAAC CCCCCGACACATCAAAAGACACAAAAAGGAT ATCATTTCTTCCAGAGTCCGTGCCGCCAC GACACAAAATGCAGTTCGAATCCTCCAGCTAC GAGGCTACTTCTGGCCGTGGAAGGAAAGG GACCTGTTCAAGTCAATCTGAAGAGGAGGAC GAGTCGGTGACAGGTCCATCATGTTCACCGTC CAGACGAGGAC (SEQ ID NO:121)		
F U S E - 5 1 0	GAGTCTAAGTACGGGCCCTCATGCCCCCTCTGC CCGCTCCTGAATTTTGGGGGGCCCTCCGTT TTTTTGTTCCTCCCAAGCCCCAAGACACCCCTG ATGATTTCCCGCACACCCGAGTCACTGCGTC GTCTCGACGTCTCCAGGAAGATCCCGAGGTC CAGTTTAATTTGTAAGTGGACGGGTGGAAGTC CACACGCCCAAGACCAAGCCCCCGAGGAAACAG TTCAAATCAACTACAGGGTGGTGTCCGTCTCTC ACCGTCTGCATCAGGATTTGGCTGAACGGCAAG GAATACAAAGTCAAGGTGTCCAAACAAAGGCTC CCCTCCTCTATCGAGAAAACCATCTCCAAGCC AAAGCCAGCCCCAGGGAACCCAGGTGTACACC CTGCCCCCTCCAGGAAGAAATGACCAAGAAC CAGGTGAGCCTGACATGCCCTCGTGAAGGGCTTC TACCCCTCCGACATCGCCGTGGAATGGAGTCC AAGGCCAGCCCCGAAACAACTACAAAAACACA CCCCCGGTGCTCGACTCCGACGGCTCCTTCTTC CTTACTCTAGGTTGACCCGTGGACAAGTCCAGG TGGCAGGAGGGCAACGCTCTTTTCTCTGCTCCGTG		

	ATGACGAGGCGCTCCACAACCACTATATACCCAG AAGTCCCTGTCCCTGTCCCTCGGCAAGGACGAC GACGATAAGTACTTCGGCAAACTGGAGAGCAAG CTGTCCGTGATCCGCAATCTGAACGATCAGETC CTCTCATCGACAGGCAACCGCCCTGTTC GAGACATGACCGACAGCGACGTGAGGGACAAC GCCCCAGGACAATCTTCATCAITTCATGTAC AAGGATAGCCAGCCAGGGGCATGCGAGTGACC ATCTCCGTGAAAGTGAGAAATCAGCACTTG AGCGTGAGAACAAAGATCATCAGCTTCAAGGAG ATGAACCCCGACAAATCAAGGACACCAAA TCCGACATCATCTTCTCCAGGGTCCGTGCCY GGCCAGCACAAATAATGCAGTTCGAGTCCAGC AGCTACGAAGGCTACTTCTGCGCGTCGAAAAG GAAGGGACCTGTTCAAGCTGATCTGAAGAAG GAGAGGAGCTGGGGACAGGACATCATGTTC ACCGTCCAGAACGAAGAC (SEQ ID NO: 122)		
F	GAGCCCAAAATCTTCTGACAAAACCTCACACATGC	GAGGTGCAGCTGCTGGAGTCCGGAGGAGGACTGCTCAG	
U	CCACCGTCCCGACGACCTGAACCTCGGGGGGA	GCTGGAGGAAGCTGAGGCTGCTCGCTGCTCCGGA	
S	CCGTGAGTCTTCCCTTCCCGCCAAACCAACCAAG	AGGACCTTTAGTCTCTATGCTATGGGTGGTTAGGCAG	
E	GACACCTCATGATCTCCCGGACCCCGAGGTC	GCCCTGGAAAGAGAGGGAGTTTGTGGTGGCCATTAACT	
-	ACATGGTGGTGGTGGACGTGAGCCACGAAGAC	TGGAGTAGCGGAAGCACTACTACGCCGACAGTGTGAAG	
5	CTTGAGGTCAAGTTCAACTGGTACGTGGACGGC	GGACGGTTCACAAATCTCCAGGGACAATGCTAAGAACAACA	
1	GTGGAGGTGCATATATGCCAAGACAAGCCCGCGG	ATGTATCTGCAGATGAACAGCCTGAAGCCTGAGGACACC	
6	GAGGACAGTACACAGCACGTACCGTGTGGTC	GCGGTGATATTACTGCGCAGCTGGATACCAAGATCAATAGC	
	AGCGTCTTCAACCGTCTGACCCAGGACTGGCTG	GGAAACTACAACTTCAAGGACTACGAATACGACTACTGG	
	AATGCAAGGAGTACAAGTGCAGGTCTCCAAC	GGCCAGGGCACACAGGTGACCGTGTCTCTCC	
	AAAGCCCTCCAGCCCATCGAGAAAACCATC	GAGCCCAAAATCTCTGACAAAACCTCACACATGCCCAACCG	
	TCCAAAGCCAAAGGCGAGCCCGGAGAACCCACAG	TGCCCCAGCACCTGAACCTCTGGGGGGACCGTCACTCTTC	
	GTGTACACCTGCCCCCATCCCGGGAGGAGATG	CTCTTCCCCCAAAACCAAGGACACCCCTCATGTATCTCC	
	ACCAGAACCCAGTTCAGCCTGAGTGTGCGCGTC	CGGACCCCGAGGTTCATGCTGTGGTGGACGTGAGC	
	AAAGCTTCTATCCCGAGCGACATCCCGGTGGAG	CACGAAGACCCCTGAGGTCAAGTCAACTGTGTACGTGGAC	
	TGGGAGAGCAATGGCGAGCCCGGAGAACAACTAC	GGCGTGGAGGTGCATATGCCAAGACAAAGCCGCGGAG	
	AAGACCAACGCTTCCCGTGTGGACTCCCGACGGC	GAGCAGTACACAGCACGTACCGTGTGGTCAAGGTCTCTC	
	TCTTCTTCTCTGTGAGCAAGCTACCGTGGAC	ACCGTCTTGCACAGGACTGGGTGAATGGCAAGGAGTAC	
	AAGACAGGTGGCAGAGGGGAGCTTCTCTCA	AACTGCAAGGTCTCCACAACACCCCTCCACAGCCCCCATC	

TGCTCCGTGATGATGAGGCTCTGCACAACCCGG TTCACGCAGAGAGCCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	GAGAAAACCATCTCCAAAGCCAAAGGCGAGCCCCGAGAA CCACAGGTGTACACCTGCCCCCATCCCGGAGGAGATG ACCAAGAACCAAGTCAGCCTGTGGTGCCTGGTCAAGGC TTCTATCCAGCGACATCGCCGTGGAGTGGAGAGCAAT GGCAGCCGGAGAACAACTACAGACCACCGCTCCCGTG CTGGACTCCGACGGCTCTTCTTCCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGACGTCTTC TCAATGCTCCGTGATGCATGAGGCTCTGCACACCACTAC ACGCAGAAGAGCTCTCCCTGTCTCCGGGTAAA GCTGCTGAACCTGTGGAGATAATGTATCAATTCGIG GCCATGAAGTTCATTGACAACACCCCTGTACTTCATCGCT GAAGATGATGAACAACATCGAGCAGGACTATTCGGAAA CTGGAAAGCAACTGAGCGTGATCAGGAACCTGAACGAC CAGGTGCTGTTTATCGACCCAGGCAACAGGCCCTGTTC GAAGATATGACCGACAGCGCTCAGGGACAACGCTCCT AGAACAATCTTCATCATCTCCAAAGTAACGCACTCCAG CCAAGGGGACTGGCTGTGACCATTTCCGTGAAAGTGGAG AAGATCTCCACACTGAGCTGGGAAACAAATCATCTCC TTCAAGGAGATGAACCCCCCGACACATTAAAGACAC AAAAGCGATATCATCTTCTTCAGAGAGTGTGCCCGGC CAGCATACAAGTGCAGTTCGAGAGCAGCTCCTACGAG GGATACTTTCTGGCCGTGCGAAAGGAGAGGACCTGTTC AAGCTGATCCTGAAGAAGGAGGACGAGCTGGGGACAGA TCAATCATGTTCCACCGTGCAGAACGAAGAC (SEQ ID NO:148)
--	--

F	GAGCCCAAAATCTTCTGTGACAAAACACACATGC	CAGGTGCAGCTGAAGCAGTCTGGACCAGGACTCGTGCAG	GACATTCTGTGTACCCAGAGCCC
U	CCACCGTGCCCAAGCACTGAACCTCTGGGGGGA	CCAAAGTCAGTCTCTCCATCACATGCACTCTCCGGC	CGTGATCTGAGCGTGAGCCCGG
S	CCGTCAGTCTTCTCTTCCCCCAAAACCAAG	TTCTCCCTCACAACTACGGCTCCACTGGGTGGACAG	GAGAGAGTGAAGCTTTAGCTGC
E	GACACCTCATGATCTCCCGGACCCCGAGETC	TCACCTGGAAAGGCTCGAATGGCTGGCGTGTCTGG	AGAGCCAGCCAGAGCATCGGCAC
-	ACATGGTGTGTGGACGTGAGCCACGAAGAC	TCGGAGGAATACCGACTACAAACACCCCTTTACCTCC	CAACATCCACTGGTATCAGCAGC
5	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC	AGGCTGCATCAACAAAGGATAATCCAAGTCCAGGTG	CGACCAACGGCAGCCCCAGACTG
1	GTGGAGGTGCATATATGCCAAGACAAGCCGGG	TTCTTCAAGTCAATAGCTCTGAGTCCACATACCGGC	CTGATCAAGTACGCCAGCTGAGAG
7	GAGGACAGTACAACAGCACGTACCGTGTGGTC	ATCTACTACTGCCAGGGCTCTGACATCTACAGCTAC	CATCAGCGGATCCCTTCTAGGT
	AGCGTCTCACCGTCTGTGCAACAGACTGGCTG	GAGTTCGCTACTGGGGCCAGGAACACTGTGACCGTG	TCAGCGGATCAGCGAGCGGCACC
	AATGGCAAGGAGTACAAGTGCAGGTCTCCAAC	TCGGCTGCTAGACCAAGGGCCCATCGGTCTTCCCCG	GACTTCACCTGAGTATCAACAG
	AAAGCCTCCAGCCCCATCGAGAAAACCATC	GCACCTCTCTCAAGAGCACCTCTGGGGGCACAGCGGC	CGTGGAAAGCAAGACATCGCGG
	TCCAAGCCAAAGGGCAGCCCGGAGAACCAAG	CTGGGCTGCCGTGCTCAAGGACTACTTCCCCGAACCGGTG	ACTATTACTGTCCAGCAGAACAT
	GTGTACACCTGCCCCATCCCGGAGGAGATG	ACGGTGTCTGTGAACCTCAGCGCCCTGACAGCGGGGTG	AACTGGCCCCACACTTCGGCGC
	ACCAGAACCAGTCAAGCTGAGCTGGCGGTC	CACACCTTCCCGCTGTCTACAGTCTCTCAGACTCTAC	CGGCACCAAGCTGGAATGAAC
	AAAGGCTCTATCCAGCGACATCGCCGTGGAG	TCCTCAGCAGGTGTGACCGTCCCTCCAGCAGCTTG	GTACGGTGGTGCACCATCTGTC
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	AAGACACGCTCCCGTGTCTGACTCCGACGGC	AGCAACACCAAGTGGACAAAGAAATGAGTCCAAATCT	GCAGTTGAATCTGGAACYGCT
	TCTTCTTCTCTGTGAGCAAGTCAACGTTGGAC	TGTGACAAATCACACATGCCAACCGTGGCCAGCACCT	CTGTTGTGTGCTGCTGATTAAC
	AAGAGCAGGTGGCAGCGGGAAGCTTCTCTCA	GAACTCCTGGGGGACCGTCACTCTTCTTCCCCCA	TTCTATCCAGAGAGGCCAAAGT
	TGTCGGTGATGATGAGGCTCTGCAACAACCGG	AAACCAAGGACACCTCATGATCTCCCGGACCCCGGAG	ACAGTGGAAAGTGGATAACGCC
	TTACGGCAGAAAGCCTCTCCCTGTCTTCCGGGT	GTACATGGTGTGTGGTGGACGTGAGCCACAAAGACCT	TCCAATCGGTAACTCCAGGAG
	AAA (SEQ ID NO:114)	GAGGTCAAGTTCAACTGTTGTTGACGTGACGGCTGGAGTG	AGTGTACAGAGCAGGACAGCAA
		CATAATGCCAAGACAAAGCCGGGAGGAGCAGTACAAC	GGACAGCACCTACAGCCTCAGCA
		AGCACGTACCGTGTGGTCAAGCTCTCAACGCTCTGCAC	GCACCCCTGAGCGTGAGCAAGCA
		CAGGACTGGTGAATGGCAAGGAGTACAAGTGAAGGTC	GACTACGAGAAACACAAAGTCTA
		TCCAACAAGCCCTCCAGCCCCCATCGAGAAACCATC	CGCTGGGAAGTCAACCATCAGG
		TCCAAGCCAAAGGGCAGCCCCGAGAACACAGGTGTAC	GCCTGAGTTCGCCCCGTCAACAAG
		ACCTGCCCCATCCCGGAGGAGATGACCAAGAACCCAG	AGCTTCAACAGGGGAGTGT
		GTACGCTGTGTGCTGTCAAGGCTTCTATCCGAGC	(SEQ ID NO:186)
		GACATCGCGTGGAGTGGAGACAAATGGCAGCCGGAG	
		AACAACACAGAACCCCTCCCGTGTGGACTCCGAC	
		GGCTCTTCTCTCTACAGCAAGCTCACCGTGGACAAG	
		AGCAGGTGGCAGCAGGGGAACCTTCTCATGCTCCGTG	
		ATGCATGAGGTCTGCACAACCACTACACGAGAGAGC	
		CTCTCCCTCTCTCCGGTAAAGCTGCTCAACCTCTGGAA	
		GATAATGTGATCAATTTCTGTGGCCATGAAGTTCATTGAC	
		AACACCTGTACTTCTATCGCTGAAGATGATGAACATC	

		GAGCAGGACTATTTCGGAAACTGGAAAGCAAACTGAGC GTGATCAGGAACCTGAACGACAGGTGCTGTTTATCGAC CAGGGCAACAGGCCCTGTTCGAAGATATGACCGACAGC GACGTCAGGGACAACGCTCCTAGAACAACTTCATCATC TCCAAGTACGGGACTCCAGCCAAGGGGACTGGCTGTG ACCATTTCCGTGAAAGTGGAGAGATCTCCACTGAGC GTGGAAAACAATATCATCTCCTTCAAGGAGATGAACCC CCGACAACATTAAGACACCCAAAAGCGATATCATCTTC TTCCAGAGAGTGTGCCCGCCACGATAACAAAGTGCAG TTCGAGAGCAGCTCCTACGAGGATACCTTCTGCGCGTC GAAAAGGAGAGGACCTGTTCAAGCTGATCCTGAAGAAG GAGGACGAGCTGGGGACAGATCAATCATGTTCAACGTG CAGAACGARGAC (SEQ ID NO:149)	
F	GAGCCCAAATCTTCGACAAAACCTCACACATGC	TACTTCGGCAAGCTGGAGTCCAGGTGTCCTGTGATCCGG	
U	CCACCGTGCCACGACACCTGAACCTCTGGGGGA	AACCTGAACGACAGGTGCTGTTCATCGACAGGGCAAC	
S	CCGTCAGTCTTCTCTTCCCCCAAAACCCAAAG	AGGCTCTCTTCGAGGATATGACCCGACTCCAGCTGAGG	
E	GACACCTCATGATCTCCCGGACCCCGGAGGTC	GATAACGCTCCAAAGGACAATCTTCATCATCTCCAAGTAT	
-	ACATCGGTGGTGGACGTGAGCCACGAAGAC	GGAGACTCCCAAGCAAGGGGACTCGCTGTGACCATTTCC	
5	CCTGAGGTCAAGTTCAACTGTTAGCTGGACGGC	GTGAAGTGGAGAAGATCAGCACACTCTCCGTGAAAAC	
4	GTGGAGGTGCATAATGCCAAGACAAGCCCGGG	AAGATCATCAGTTCAAGAGATGAACCCCGCCGACAAC	
5	GAGGACAGTACAACAGCACGTACCGTGTGGTC	ATCAAGGACACCAAAATCCGACATCATCTTCTTCCAGCGC	
	AGCGTCTCACCGTCTGCACCAAGACTGGCTG	TCCGTGCTGGCCATGATAACAAAGTGCAGTTCGAGTCC	
	AATGGCAAGGAGTACAAAGTGCMAAGTCTCCAAC	AGCTCTACGAGGGATACTTTCTCGCGCTCGAAAAGGAA	
	AAAGCCTTCCAGCCCCCATCGAGAAAACCATC	AGGGACCTGTTCAAGCTCATCTGAAGAAGGAGGACGAA	
	TCCAAAGCCAAAGGGCAGCCCGAGAACCACAG	CTGGGCGACAGGTCCATTATGTTACCGTCCAGAAATGAG	
	GTGTACACCTTGCCCCATCCCGGAGGAGATG	GACGAGCCCAATCTTCTGACAAAACCTCACACATGCCCA	
	ACCAAGAACCCAGTCAGCTGAGCTGGCGCGTC	CCGTGCCCCAGACCTGAACCTCTGGGGGACCGTCACTC	
	AAAGCTTCTATCCAGCGACATCGCGGTGGAG	TTCTCTTCCCCCAAAACCCAAAGGACACCCCTCATGATC	
	TGGGAGAGCAATGGGACGCCCGGAGAACAACATAC	TCCCGGACCCCGAGGTCAATGCTGCTGGTGGTGGACGTG	
	AAGACCAAGCTCCCGTGTGGACTCCGACGCGC	AGCCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTG	
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	AAGACAGGTGGAGAGGGGAACGCTCTCTCA	GAGGAGCAGTACAACAGCACCGTACCGTGTGGTCAAGCTC	
	TGCTCCGTGATGCATGAGGCTCTGCACAACCGG	CTCACCGTCTGACCAAGGACTGGGTGATGCAAGGAGGAG	
	TTCAGCAGAGAGGCTCTCCCTGTCTCCGGGT	TACAAGTGCAGGTCTCCAAACAAGCCCTCCAGCCCCC	
	AAA (SEQ ID NO:114)	ATCGAGAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	
		GAAACACAGGTGTACACCTGCCCCCATCCCGGAGGAGAG	
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		GGCTTCTATCCACGCGACATCGCCGTGGAGTGGGAGAGC AATGGGACGCGGAGAACAACTACAAAGACACGCCTCCC GTGCTGGACTCCGACGGCTCCTTCTTCCITACAGCAAG CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGAACGTC TTCTCATGCTCCGTGATGATGAGGCTCTGCACAACCAC TACACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:150)
F	GAGCCCAATCTTCTGACAAAACACACATGC	TACTTCGGCAAGCTGAAGTCAAGCTGTCCGTGATCCGG
U	CCACCGTCCCCAGCACTGAACCTCTGGGGGA	AACCTGAACGACAGGCTGCTGTTTCATCGACAGGCAAC
S	CGTCAGTCTTCTCTTCCCCCAAAACCCAAAG	AGGCACTCTTCAGGATATGACCGACTCCGACGTGAGG
E	GACACCTCATGATCTCCGACCCCGGAGGTC	GACAACTCTCTAGAACCATCTTCATCATCTCCATGTAC
-	ACATGGGTGGTGGTGGACGTGAGCCACGAGAC	GGAGACTCCAGGCCAAGGGGAATGGCTGTGACAATTTCC
5	CCTGAGGTCAAGTTCAACTGTTACGTGGACGGC	GTGAAGTGGAGAAAATTTCCACACTGTCCGTGGAAAAC
4	GTGAGGTGCATAATGCCAAGACAAAGCCGGG	AAGATCATTTCTTCRAGGAGATGAACCCCGACAAAC
6	GAGGACAGTACACACAGCACGTAACGTTGTGTC	ATTAAAGACACCAAGAGCGACATCATCTTCTCCAGCGC
	AGCTCCTCAACCTCTGCAACGAGACTGGCTG	TCTGTCCCGGCATCATACAAAGATGCAGTTCCAGTCC
	AATGGCAAGGAGTACAGTGCAGGTCTCCAAC	AGCTCCTACGAGGGCTACTTCTGGCCGTCGAAAAGGAA
	AAAGCCCTCCAGCCCCCATCGAGAAAACCATC	AGGACCTCTTCAAACTGATCCTGAAGAAGGAGGACGAA
	TCCAAAGCCAAAGGCGAGCCCGAGAACCCACAG	CTGGGGACAGGAGCATCATGTTACCGTGCAGATGAG
	GTGTACACCTGCCCCCATCCGGGAGGAGATG	GAC
	ACCBAAGACAGTCAAGCTGAGTGGCCCGTC	GAGCCCAATCTTCTGACAAAACACTCACATGCCCCACCG
	AAAGCTTCTATCCAGCGACATCCCGTGGAG	TGCCAGCACCTGAACCTCCTGGGGGACCGTCAGTCTTC
	TGGGAGAGCAATGGGACGCGGAGAACAACTAC	CTCTTCCCCCAAAACCAAGACACCCCTCATGATCTCC
	AAGACCAAGCCTCCCGTCTGGACTCCGACGGC	CGGACCCCGAGGTCACATGCGTGGTGGTGGACGTGAGC
	TCCTTCTTCTCGTGAAGCAAGCTCACCGTGGAC	CACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGAC
	AAGCAGGTGGACAGGAGGAGAGCTTCTCA	GGGTGGAGGTGCATATGCCAAGACAAAGCCCGGGAG
	TGCTCCGTGATGCATGAGGCTCTGCACAACCGG	GAGCAGTACACAGCACGTAACCGTGTGGTCAAGCTCCTC
	TTCAAGCAGAGAGCCTCTCCCTGTCTCCGGGT	ACCGTCTGCAACAGGACTGGCTGAATGGCAAGGAGTAC
	AAA (SEQ ID NO:114)	AAGTGCAAGGTCTCCAACAAGCCCTCCAGCCCCCATC
		GAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAA
		CCACAGGTGTACACCTTCCCCCATCCCCGAGGAGATG
		ACCAAGAACCGGTGAGCTGTGGTGCCTCAAGGC
		TTCTATCCAGGACATCGCCGTGGAGTGGGAGAGCAAT
		GGCAGCCGGAGAACAACTACAAGACCAAGCCCTCCCGTG
		CTGGACTCCGACGGCTCTTCTTCTCTACAGCAAGCTC
		ACCGTGGACAGAGCAGTGGCAGCAGGGGAGACGTCTTC
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		ACGCAGAGAGAGCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:151)	
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U	CCACCGTGCCCAAGCACCTGAACCTCTGGGGGA	AACCTGAACGACAGAGGTGCTGTTCATCGACAGGGCAAC	
S	COGTGAGTCTTCTCTTCCCTCCCAAAACCCCAAG	AGGCCTCTCTTCAGAGATATGACCGACTCCGACGTGAGG	
E	GACACCCCTCATGATCTCCCGGACCCCGAGGTC	GACAACGCTCCTAGAACCATCTTTCATCATCTCCATGTAC	
-	ACATCGGTGGTGGTGACGTGAGCCACGAGAC	GGAGACTCCAGCCAAAGGGGATGGCTGTGACAATTTCC	
5	CCTGAGGTCAAGTTCAACTGTAAGTGGACGGC	GTCAAGGTGGAGAAAATTTCCACACTGTCCGTGAAAAC	
4	GTGGAGGTGCATATATGCCAAGACAAAGCCGGG	AAGATCATTTCTCTCAAGGATGAACCCCGGACAAAC	
7	GAGGACAGTACACAGCACGTACCGTGTGGTC	ATTAAAGACACCAAGAGCGACATCATCTTCTTCCAGCGC	
	AGCGTCTCTACCGTCTGTGACCCAGACTGGCTG	TCTGTCCCGGCATGATACAGATGCACTTCGAGTCC	
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	AAAGCCCTCCAGCCCCCATCGAGAAAACCATC	AGGACCTGTTCAAACCTGATCCTGAAGAAGAGGACGAA	
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	ACCAGAACCCAGTCAAGCTGAGCTGCGCGGTC	CCGTGCCCAGCACTGAACCTCTGGGGGACCGTCACTC	
	AAAGGCTTCTATCCAGCGACATGCCCGTGGAG	TTCTCTTCCCGCCAAAACCCAAAGGACACCCCTCATGATC	
	TGGGAGAGCAATGGGCAGCCGGAGAACAACTAC	TCCCGACCCCGAGGTCAATGCGGTGGTGGACGTG	
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F	TCCCTTCTCTCTGAGCAAGCTACCGTGGAC	GACGGCTGGAGTGCATATGCCAAGACAAAGCCCGG	
	AAGACAGGTGGCAGCAGGGGAACCTCTTCTCA	GAGGACAGTACAACAGCACGTACCGTGTGTCAGCGTC	
	TGCTCCGTGATGATGAGGCTCTGCACAACCGG	CTCACCGTCTGCACCAGGACTGGCTGAATGGCAAGGAG	
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	AAA (SEQ ID NO:114)	ATCGAGAAACCATCTCCAAGCCAAAGGGCAGCCCCGA	
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		ATGACCAAGAACCAAGTCAAGCTGTGGTGGTGTCAA	
		GGCTTCTATCCAGCGACATCGCGTGGAGTGGAGAGC	
		AATGGCAGCCGGAGAACAACTACAAAGACCAAGCCCTCCC	
		GTGCTGGACTCCGACGGCTCTCTTCTTCTCTACAGCAAG	
		CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC	
		TTCTCATGCTCCGTGATGATGAGGCTCTGCACAACCCAC	
		TACACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:152)	

F	CAGTGCAGCTGAAGCAGTCTGGACAGGACTC	CAGGTGCAGCTGAAGCAGTCTGGACAGGACTC	GACATTCGTGTGACCCAGAGCCC
U	GTGAGGCCAAGTCACTCTCTCTCCATCACATGC	CCAAGTCACTCTCTCTCCATCACATGCACACTCTCGGC	CGTGATCCTGAGCGTGAGCCCCG
S	ACAGTCTCCGGCTCTCCCTCACAACTACGGC	TTCTCCCTCACAACTACGGCTCCACTGGTGGACAG	GAGAGAGTGAAGCTTTAGCTGC
E	GTCCACTGGGTGGGACAGTCACTGGAAAGGC	TCACCTGGAAAGGCCTCGAATGGCTGGCTGATCTGG	AGAGCCAGCCAGAGCATCGGCAC
-	CTCGAATGGCTCGGCGTGAICTGGTCCGGAGGA	TCGGAGGAATACCGACTACAAACACCCCTTTACCTCC	CAACATCCACTGGTATCAGCAGC
5	AATACCGACTACAAACCCCTTTACCTCCAGG	ATCTTCAAGTCAACAAAGGATAATTTCAAGTCCAGGTG	CGACCAACGGCAGCCCCAGACTG
5	GTGTCCATCAAGAGGATAATTTCAAGTCCAG	TTCTTCAAGTCAACAAAGGATAATTTCAAGTCCAGGTG	GTGATCAAGTACGCCAGCTGAGAG
5	GTGTCTTCAAGTGAATAGCTGCAGTCCAAC	ATCTACTACTGCCAGGGCTCTGACATCTACAGACTAC	CATCAGCGGATCCCTTCTAGGT
	GATACCGCCATCTACTACTGCGCCAGGGCTCTG	GAGTTGCGCTACTTGGGGCCAGGAACACTGTFACCGTG	TCAGCGGATCAGGCAGCGGCACC
	ACATACTAGACTACGAGTTCGCTACTTGGGC	TCGCTGCTAGACCAAGGGCCCATCGTCTTCCCCG	GACTTCACCTGAGTATCAACAG
	CAGGAACACTGGTGACCGTGTCCGCTGTAGC	GCACCTCTCTCAAGAGCACCTCTGGGGCCACAGCGGC	CGTGGAAAGCGAAGACATCGCGG
	ACCAAGGGCCCATCGGTCTTCCCTTGGCAACC	CTGGGCTGCCCTGCTCAAGGACTACTTCCCCGAACCGGTG	ACTATTACTTGGCCAGCAGAACAT
	TCCTCCAGAGCACTCTGGGGCCACAGCGGC	ACGGTGTCTGTAACCTCAGCGCCCTGACAGCGCGGTG	AACTGGCCCCACACTTCGGGCGC
	CTGGGCTGCCGTCAAGGACTTCTCCCGAA	CACACCTTCCCGCTGTCTACAGTCTCTCAGACTCTAC	CGGCACCAAGCTGGAATGAAC
	CCGTTGACGGTGTCTGGAACTCAGCGCCCTG	TCCTCAGCAGGTGTGACCGTCCCTCCAGCAGCTTG	GTACGGTGGTGCACCATCTGTC
	ACGAGCGCGTGTACACCTTCCCGCTGTCTTA	GGCACCCAGACTACATCTGCAACGTGAATCACAAAGCCC	TTCACTCTTCCCGCATCTGATGA
	CAGTCTCAGGACTTACTCTCTCAGCAGCGTG	AGCAACACCAAGTGGACAAAGAAATGAGCCAAATCT	GCAGTTGAATCTGGAACCTGCT
	GTGACCGTGCCCTCCAGCAGCTTGGCAACCCAG	TGTGACAAATCTACACATGCCACCGTGGCCAGCACT	CTGTTGTGTGCTGCTGATTAAC
	ACCTACATCTGCAAGCTGAATCAAGCCCGAGC	GAACTCTGGGGGACCGTCACTCTTCTTCCCCCA	TTCTATCCAGAGAGGCCCCAAGT
	AAACCAAGGTGGAAGAAAGTTGAGCCCAAA	AAACCCAGGACACCTCATGATCTCCCGACCCCCGAG	ACAGTGGAAAGTGGATAACGCC
	TTCTGTGACAAACTCACACATGCCACCGTGC	GTCAATCGGTGTGGTGGACGTGAGCCACAAAGACCT	TCCAATCGGTAACTCCAGGAG
	CCAGCACTGAATCTCTGGGGACCGTCACTC	GAGTCAAGTTCACTGTGTAAGTGGACCGCTGGAGGTG	AGTGTACAGAGCAGGACAGCAA
	TTCTCTTCCCCCAAAACCAAGCACACCTC	CATAATGCCAAGACAAAGCCGGGAGGAGCAGTACAAC	GGACAGCACTACAGCCTCAGCA
	ATGATCTCCCGACCCCGAGGTCACTGGTG	AGCACGTACCGTGTGGTCAAGCTCTCAACGCTCTGCAC	GCACCCCTGAGCGTGAGCAAGCA
	GTGTGGACGTGAGCCACGAAGACCTGAGGTG	CAGGACTGGTGAATGGCAAGGAGTCAAGTGAAGGTG	GACTACGAGAAACACAAAGTCTA
	AAGTTCACTGTAGTGGACGGCTGGAGGTG	TCCAACAAAGCCCTCCAGCCCTCATGAGAAACCATC	CGCTGGGAAGTCAACCATCAGG
	CATATGCCAAGCAAGCCCGCGGAGGAGCAG	TCCAAGCCAAAGGGCAGCCCCGAGAACACAGGTGTAC	GCCTGAGTTCCCGCTCACAAG
	TACACAGCAAGTACCGTGTGTCAGCGTCTC	ACCTTCCCCCATCCCGGAGGAGATGACCAAGACCCAG	AGCTTCAACAGGGGAGGTGT
	ACCGTCTGACCGAGCTGGTGAATGGCAAG	GTACGCTGTGTCCTGGTCAAGGCTTCTATCCCCAGC	(SEQ ID NO:186)
	GAGTACAAGTGAAGTCTCCACAAGACCCCTC	GACATCGCGTGGAGTGGAGCAATGGCAGCCCGGAG	
	CCAGCCCCATCGAGAAACCATCTCCAAGCC	AACAACACAGACACACCGCTCCCGTGTGGACTCCGAC	
	AAAGGCAGCCCCGAGAACACAGGTGTACAC	GGCTCTTCTTCTCTACAGCAAGTCAACCTGGACAAG	
	CTGCCCCCATCCCGGAGGAGATGACCAAGAAC	AGCAGGTGGCAGAGGGGAACCTTCTCTCATGCTCCGTG	
	CAGTCACTGAGTCCGCGCTCAAGAGGCTTC	ATGCATGAGGTCTGCACAACACTACACGCAAGAGGC	
	TATCCACAGCATCGCCCTGAGTGGGAGAGC	CTCTCCCTGTCTCCGGTAAAGTGGCGGAGGTCTGCT	
	AATGGGCAGCCGGAGAACAACTACAGAACCAAG	GGTGGAGGATCCGGGGAGGAGTTCAGGAGCGGGGGA	
	CCTCCCGTCTGGACTCCGACCGCTCTCTCTC	AGTCTGCTGACCTGTGGAGAGATAATGTGATCAATTC	

	CTCTGTGAGCAAGCTCACCGTGGACAAAGAGCAGG TGGCAGCAGGGGAAGCTCTTCTCATGTCTCCGTG ATGCATGAGGCTCTGCACAAACCGCTTCAAGCAG AAGAGCCTCTCCCTGTCTCTCCGGGTAAA (SEQ ID NO:123)	GTGGCCATGAAGTTTCATTGACAACACCCCTGACTTCATC GCTGAAGATGATGAATAAACAATCGAGCAGGACTATTTCCGA AACTGGAAAGCAAACTGAGCCTGATCAGGAACTGAAC GACCAGTGTCTGTTTATCGACAGGGCAACAGCCCCTG TTTGAAGATATGACCGACAGACGTCAGGGACAACGCT COTAGAACAATCTTCATCATCTCCAAATACGGGACTCC CAGCCAAGGGACTGGCTGTGACCAATTTCCGTGAAAGTG GAGAAGATCTCCACACTGAGCGTGGAAACAAATCATC TCCTTCAAGGAGATGAACCCCCCGACAACATTAAGAC ACCAAAAGGATATCATCTTCTCCAGAGAGTGTGCC GGCCACGATAACAAGTGCAGTTCGAGAGCAGCTCCTAC GAGGGATACCTTCTGGCCGTCGAAAGAGAGGGACCTG TTCAAGCTGATCCTGAAGAAGGAGGACGAGCTGGGGAC AGATCAATCATGTTCACCGTGCAGAAACGAGAC (SEQ ID NO:153)
F	GAGCCAAATCTTCTGACAAAACCTACACATGC U CCACCGTCCCCAGCAGCTGAACCTCTGGGGGA S CCGTCAGTCTTCTCTTCCCCCCHAAACCCAAAG E GACACCCCTCATGATCTCCCGGACCCCGGAGGTC - ACATCGGTGGTGGACGTGAGCCACGAAGAC 5 CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC 5 GTGAGGTGCATATGCCAAGACAAGCCCGGG 6 GAGGACAGTACACAGCACGTACCGTGTGGTC AGCGTCTCACCGTCTGCAACAGGACTGGCTG AATGGCAAGGAGTACAAGTGCAAGTCTCCAAC AAAGCCCTCCAGCCCCATCGAGAAAACCATC TCCBAAGCCAAAGGCAGCCCCCGAGAACCCACAG GTGTACACCCCTGCCCCATCCCGGAGGAGATG ACCRAGAACCAGGTACAGCTGAGCTGGCGCGTC AAAGGCTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCCGGAGAACAACTAC AAGACCAGCCCTCCCGTGTCTGGACTCCGACGGC TCCCTCTCTCTCGTGAGCAAGTCAACCGTGGAC AAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA TGTCCCGTGTGATGATGAGGCTCTGCACAAACCGG TTTACGCAGAGAGCCTCTCCCTGTCTCTCCGGGT AAA (SEQ ID NO:114)	GGAGGTTCACAATCTCCAGGACAATGTAAGAACA ATGTATCTGCAGATGAACAGCCTCAAGCCTGAGGACACC GCCGTTTACTATTGCCGCGCTGGATACCAATCAACAGC GGCAACTACAACCTCAAGGACTATGAGTATGACTACTGG GGCCAGGGCACACAGGTGACAGTTTCATCCGAGCCCCAA TCTTCTGACAAAACCTCACATGCCCCACCGTGCCCCAGCA CTTGAACCTCTGGGGGACCGTCAGCTTCTCTCTTCCCC CCAAAACCCCAAGCACACCCCTCATGATCTCCCGACCCCC GAGGTCACATGGCTGGTGGTGGACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGCTGGAG GTGCATAATGCCAAGACAAGCCCGGGAGGAGCAGTAC AACAGCACGTACCGTGTGGTCAAGCTCTCTACCGTCTCTG CACCAGGACTGCTGAATGSCAAGGAGTACAAGTGAAG GTCTCCAAACAGCCCTCCAGCCCCCATCGAGAAAAC ATCTCCAAAGCAAAAGGCGAGCCCCGAGAACCAAGGTG TACACCCCTGCCCCATCCCGGAGGAGATGACCAAGAAC CAGGTCAGCCTGTGGTGCCTGGTCAAGGCTTCTATCCC

		AGCGACATCGCGGTGGAGTGGAGAGCAATGGCGAGCGG GAGAACAACTACAGAACACCGCTCCGTTGCTGGACTCC GACGGCTCTTTCTTCTCTCTACAGCAAGCTACCGTGGAC AAGAGCAGGTGCGCAGCAGGGGAACGTTCTTCATGCTCC GTGATGCATGAGGCTCTGCACAACCACTACAGCGAGAAG AGCCTCTCCCTGTCTTCCGGGTAAA (SEQ ID No:154)	
F	GAGCCCAAAATCTTGTGACAAAACATCACACATGC	TACTTCGGCAAGCTGGCTTCCAAGCTGTCCGTGATCAGG	
U	CCACGTGCCCCAGACCTGAACCTCTGTGGGGGA	AACCTGAACGATCAGGTGCTGTTCATCGATCAGGGCAAC	
S	CCGTGAGTCTTCTCTTCCCCCCCCAAACCCAAAG	AGGCCCCCTGTTTCGAGGATATGACCGACTCCGATGTGGC	
E	GACACCCCTCATGATCTCCCGGACCCCGAGGTC	GACAACGCACCTAGAACCAATCTTCATCATCTCTATGTAC	
-	ACATGGTGGTGGTGGACGTGAGCCACGAAGAC	GGCGATTCCCAAGCAAGGGGATGGCTGTGACAATTTCC	
5	CCTGAGGTCAAGTTCAACTGGTGAACGTGGACGGC	GTCAAGGTGGAGAAGATCTCCACCCCTGTCCGTGGA AAC	
8	GTGGAGGTGCATTAATGCCAAGACAAAGCCCGGG	AAATCATTTCTTCAAGGAGATGAACCCCCCGACAAAC	
3	GAGGACAGTACACAGCACGTACCGTGTGCTG	ATCAAGGACACTAAAGGACATCATCTTCTTCCAGAGG	
	AGGTCCTCACCGTCCGTGCAACCCAGCACTGGCTG	AGCGTGCCCGGCATGATAACAAATGCACTTCGATCC	
	AATGGCAAGGAGTAAAGTGCAAGTCTCCAAC	AGCTCCTACGAAGGCTACTTCTCGCCCGTCGAAAGGAA	
	AAAGCCCTCCAGCCCCCATCGAGAAAACCATC	AGGACCTGTTCAAAACATGATCCTCAAGAGGAGGACGAG	
	TCCAAGCCAAAGGGCAGCCCCGGAGAACCAACAG	TTGGGGGACAGATCCATTATGTTCACCGTTCAGAACGAG	
	GTGTACACCCCTGCCCCCATCCCGGGAGGAGATG	GAC	
	ACCAGAACCCAGTCAAGCTGAGCTGGCGGCTC	GAGCCCCAATCTTCTGACAAAACATCACACATGCCAACCG	
	AAAGGCTTCTATCCAGCGACATGCCCGTGGAG	TGCCCAGCACCTGAACCTCCTGGGGGACCCGTCAGTCTTC	
	TGGGAGAGCAATGGCAGCCCGGAGAACAACTAC	CTCTTCCCCCAAAACCCAAAGCACCCCTCATGATCTCC	
	AAGACCAAGCCCTCCCGTCTGGACTCCGACGGC	CGGACCCCGGAGGTACATGCGTGGTGGTGGACGTGAGC	
	TCCTTCTTCTCTGTGAGCAAGTCAACCGTGGAC	CACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGAC	
	AAGAGCAGGTGGCAGCAGGGGAACGTTCTCTCA	GGCGTGGAGGTGCATATATGCCAAGACAAAGCCGGGAG	
	TGCTCCGTGATGATGAGGCTCTGCACAACCCG	GAGCAGTACACAGCACACGTACCGTGTGGTCAAGCTCTC	
	TTACGCAGAAAGCCCTCTCCCTGTCTTCCGGGT	ACCGTCTGTACAGGACTGGGTGAATGGCAAGGAGTAC	
	AAA (SEQ ID No:114)	AACTGCAAGGTCTCCACAACAAGCCCTCCAGCCCCCATC	
		GAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAA	
		CCACAGGTGTACACCTGTGCCCCCATCCCGGAGGAGATG	

		ACCAAGAACCCAGGTACGCTGTGGTGCCTGGTCAAGGC TTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGGCAGCCGGAGAACAACTACAAGACCACGCCCTCCCGTGG CTGGACTCCGACCGCTCTCTTCTTCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAAACGTCCTTC TTCATGCTCCGTGATGCTAGGTGAGGCTCTGCACAACCACTAC ACGCAGAAAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:155)	
F U S E - 5 8 4	GAGCCCAATCTTCTGACAAAACCTCACACATGC CCACCGTGCCAGCACCTGAACCTCTGGGGGA CCCTCAGTCTTCTCTTCCCTCCCAAAACCCAAAG GACACCCCTCATGATCTCCCGGACCCCGGAGGTC ACATCGGTGGTGGACGCTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGGAGGTGCATAATGCCAAGACAAAGCCCGGG GAGGACAGTACACAGCACGTAACCGTGTGGTC AGCGTCTCAACGCTCTGACCCAGGACTGGCTG AATGGCAAGGATACAACTGCAAGGTCTCCAAC AAAGCCCTCCAGCCCCCATCGAGAAAACCATC TCCAAGCCAAAGGGCAGCCCGGAGAACCCACAG GTGTACACCCCTGCCCTCATCCGGGAGGAGATG ACCAAGAACCCAGGTACGCTGAGCTGGCGGCTC AAAGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGCAGCCCGGAGAACAACTAC AAGACCAACGCTCCCGTGTGTAACCTCCGACGGC TCCCTTCTCTGCTGAGCAAGCTACCCGTGGAC AAGACAGGTGGCAGCAGGGGAGACGTTCTCTCA TGCTCCGTGATGATGAGGCTCTGCACAACCGG TTTCACGCAGAAAGAGCCCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	TACTTGGCAAGCTGCACCTCCAAAGCTCCGTCCGTATCCGG AACCTGAAGCCAGGCTGCTCTTCATCGACACGAGGCAAC AGGCCCTCTTTCGAGGATATGACCGACTCCGACGTGGC GATAAGGCTCTTAGAACCATCTTCATCATCTCCATGTAC GGGACTCCAGCCAGCCAGAGGAATGGCTGTGACAAATTTCC GTGAAGGTGGAGAAAATCTCCACCTGTCCGTGGAGAAC AAGATCATCTCTTCAAGAGATGAACCCCGCCGCAAC ATCAAGACACCAAGAGCGACATCATCTTTTCCAGCC TCTGTCCCGGCCACGATAATAAAATGCAGTTCGAATCC AGTCTCTACGAAGGCTACTTCTCCCGCTCGAAAAGGAA AGGACCTCTTCAAGTTGATCCTGAAGAGGAGGAGGAA CTGGGGACAGGAGCATCATGTTCAACCGTGCAGAACGAG GAC GAGCCCAATCTTCTGACAAAACCTCACACATGCCCAACCG TGCCACGACCTGAACCTCTGGGGGACCGTCACTCTTC CTCTTCCCCCAAAACCCAGGACACCCCTCATGATCTCC CGGACCCCGAGGTACATGCGTGGTGGTGGACGTGAGC CAGGAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGTGCATATATGCCAAGACAAAGCCCGGGAG GACAGTACAACAGCACGTACCGTGTGGTCAAGCTCTC ACCGTCTCTCACAGGACTGGCTGAATGGCAAGGAGTAC AAGTGAAGGTCTCCAAACAAAGCCCTCCAGCCCCCATC GAGAAACCAATCTCCAAGCCAAAGGCGAGCCCCGAGAA CCACAGGTGTACACCTGGCCCCCATCCCGGAGGAGATG ACCAAGAACCCAGGTACGCTGTGGTGCCTGGTCAAGGC TTTCTATCCAGGACATCGCCGTGGAGTGGGAGAGCAAT GGGCAGCCGGAGAACAACTACAAGACCACGCCCTCCCGTGG CTGGACTCCGACGGCTCTTCTTCTCTACAGCAAGCTC ACCGTGGACAGAGCAGGTGGCAGCAGGGGAAACGTCCTTC	

		TCATGCTCCGTGATGATGATGAGGCTCTGCACAACCACTAC ACGCAGAAAGAGCCTCTCCCTGTCTCCGGGTA AAA (SEQ ID NO:156)	
F	GAGCCCAAAATCTTCTGACAAAACATCACACATGC	TACTTCGGCAAGCTGCGTTCCAAAGCTGTCCGTGATCCGG	
U	CCACGTGCCCCAGACCTGAACCTCCTGGGGGA	AACCTGAACGACACAGGTGCTGTTCATCGACAGGGCAAC	
S	CCGTGAGTCTTCTCTTCCCCCAAAACCCAAAG	AGGCTCTCTTTCGAGGATATGACCGACTCCGACGTGAGG	
E	GACACCCCTCATGATCTCCCGGACCCCGGAGTTC	GACAACGCTCCAGAACCAATCTTCATCATCTCCATGTAC	
-	ACATGGTGGTGGTGACGTGAGCCACGAAGAC	GAAGATTCTCAACCCAGGGGATGCCGTGACAATTTCC	
5	CCTGAGGTCAAGTTCAACTGGTGTGGACGGC	GTTAAGGTGGAGAAAATCTCCACACTGTCCGTGGAAAAC	
8	GTGGAGGTGCATATATGCCAAGACAAAGCCCGGG	AAATCATCTCTCTCAAGAGATGAACCCCGGACAAAC	
5	GAGGACAGTACACAGCACGTACCGTGTGGTC	ATTAAAGACACAAAAGCGATATCATCTTCTTCCAGAGG	
	AGCTTCCTCACCGTCCGTGCACCCAGCACTGGCTG	AGCGTGCCCGGGCATGATAACAAGATGCACTTCGAAAGC	
	AATGGCAAGGAGTACAAAGTGCAAGTCTCCAAC	TCTCTCTACGAAGGCTACTTCTGCGCGTCCGAAAAGGAA	
	AAAGCCCTCCAGCCCCCATCGAGAAAACCATC	AGGACCTGTTCAAAACATGATCTGTGAAGAGGAGGATGAA	
	TCCAAAGCCAAAGGGCAGCCCCGGAGAACCAACAG	TTGGGCGACAGGTCCATTATGTTCACAGTGCAGAACGAG	
	GTGTACACCTGCCCCCATCCCGGGAGGAGATG	GACGAGCCCCAATCTTCTGACAAAACATCACACATGCCCA	
	ACCAGAACCCAGTCAAGCCTGAGCTGCGGCGCTC	CCGTGCCCAGCACTGAACTCTGTGGGGGACCGTCACTC	
	AAAGGCTTCTATCCAGCGACATGCGCGTGGAG	TTCTCTTTCGCCCAAAACCAAGGACACCCCTCATGATC	
	TGGGAGAGCAATGGCAGCCCGGAGAACAACTAC	TCCCGGACCCCGAGGTCAATGCGTGGTGGTGGACGTG	
	AAGACCAAGCCTCCCGTCTGGACTCCGACGGC	AGCCACGAAGACCTGAGGTCAAGTTCACCTGGTACGTG	
	TCCTTCTTCTCTGTGAGCAAGTCAACCGTGGAC	GACGGCGTGGAGTGCATAATGCCAAGACAAAGCCGGG	
	AAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA	GAGGAGCAGTACAACAGCACGTACCGTGTGTGTCAGCTC	
	TGCTCCGTGATGATGAGGCTCTGCACAACCCG	CTCACCGTCTGCACCAAGCACTGGCTGAATGGCAAGGAG	
	TTACCGCAGAGAGCCTCTCCCTGTCTCCCGGGT	TTCAAGTGCAGGTCTCCAAACAAGCCCTCCAGCCCCC	
	AAA (SEQ ID NO:114)	ATCGAGAAAACCATCTCCAAAGCCAAAGGGAGCCCCGA	
		GHACCAAGTGTACACCCCTGCCCCATCCCGGAGGAG	
		ATGACCAAGAACCAAGTCAAGCTGTGGTGGTCAAA	

		GGCTTCTATCCACAGCGACATCGCCGTGGAGTGGGAGAGC AATGGGCAGCCGGAGAACAACTACAAAGACACGCCTCCC GTGCTGGACTCCGACGGCTCCTTCTTCCITACAGCAAG CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC TTCTCATGTCCGTGATGCATGAGGCTCTGCACAACCAC TACACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:157)
F	GAGCCCAAAATCTTCTGACAAAACATCACACATGC CCACCGTCCCCAGACCTGAACCTCTGGGGGA CCGTCAGTCTTCTCTTCCCCCAAAACCCAAAG GACACCCCTCATGATCTCCCGGACCCCGAGGTC ACATGGTGGTGGTGGACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGTTAGCTGGACGGC GTGGAGGTGCATATATGCCAAGACAAAGCCGGG GAGGACAGTACACAGCACGTAACGCTGTGTC AGCTCTCTACCCGTCCTGCACCCAGCACTGGCTG AATGCCAAGGAGTAAAGTGCAGGTCTCCAAC AAAGCCCTCCAGCCCCATCGAGAAAACCATC TCCAAAGCCAAAGGGCAGCCCGGAGAACCAAG GTGTACACCTGCCCCCATCCCGGGAGGAGATG ACCAGAACCCAGTCAAGCTGAGCTGGCGGCTC AAAGGCTTCTATCCACGCGACATGCCCGTGGAG TGGGAGAGCAATGGCAGCCCGGAGAACAACTAC AAGACACGCCCTCCCGTCTGGACTCCGACGGC TCCTTCTTCTCTGTGAGCAAGTCAACGTTGGAC AAGACAGGTGGCAGCAGGGGAACGCTCTCTCA TGCTCCGTTGATGCATGAGGCTCTGCACAACCGG TTACGCGAGAGAGCCCTCTCCCTGTCTCCCGGT AAA (SEQ ID NO:114)	TACTTCGGCAAGCTGCAGTCCAGCTGTCCGTGATCCGG AACCTGAACGACGAGGTGTGTTCATCGACAGGGCAAC AGGCTCTCTTTCGAGGATATGACCGACTCCGACGTGAGG GATAACGCTCCAAAGGACCATCTTCATCATCTCCATGTAC GCCGACTCCACGCAAGGGGAATGGCTGTGACAATCTCC GTCAAAGTGGAGAAGATTAGCACCCCTGTCCGTGGA AAC AAGTCATCTCTCTTCAAAGAGATGAACCCCGGACAAAC ATCAAAGACACCAAAATCCGACATCATCTTCTTCCAGCGC TCTGTGCTGGCAGCATAAACAAAATGCAGTTCGAAAGC TCTCTCTAGGAGGATACCTTCTCGCCCGTCGAAAAGGAA AGGACCTGTTCAGCTGATCTCTGAAGAAGAGGACGAG CTGGGGGACAGAGCATCATGTTCACCGTTCAGAACGAG GACGAGCCCAATCTTCTGACAAAACCTCACACATGCCCA CCGTGCCCAGCACTGAACCTCTGGGGGACCGTCACTC TTCTCTTCCCGCCAAACCAAGGACACCCCTCATGATC TCCCGGACCCCGAGGTCAATGCTGCTGGTGGACGTG AGCCACGAAGACCTGAGGTCAAGTTCAACTGGTACGTG GACGGCTGGAGTGCATAATGCCAAGACAAAGCCGGG GAGGAGCAGTACAACAGCACGTCACGCTGTGTGTCAGGTC CTCACCGTCTGCACGAGGACTGGCTGAATGGCAAGGAG TTCAGTGCAGGTCTCCAAAGCCCTCCAGCCCTCCAGCCCTC ATCGAGAAACCATCTCCAAAGCCAAAGGGAGCCCTCGA GACACAGGTGTACACCTGCCCTGCCCATCCCGGAGGAG ATGACCAAGACGAGGTCAAGCTGTGGTGGTCAAA

		GGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGC AATGGGCGACCGGAGAACAACTACAAAGACCGCTCCC GTGCTGGACTCCGACGGCTCCTTCTTCCITACAGCAAG CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC TTCTCATGTCCGTGATGCATGAGGCTCTGCACAACCAC TACACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:158)	
F	GAGCCAAATCTTGTGACAAAACCTCACACATGC	GAGCCAAATCTTGTGACAAAACCTCACACATGCCACCG TGCCAGACACTGAACCTCTGGGGGACCGTCAGTCTTC CTCTTCCCCCAAAACCCAAAGACACCCCTCATGATCTCC CGGACCCCGGAGTCAATGCTGGTGGTGGACGTGAGC CACGAAGACCTGAGGTCAAGTCAACTGTTACGTGGAC GGCTGGAGTGCATATGCCAAGACAAAGCCGGGAG GAGCAGTACACAGACAGTACCGTGTGGTCAAGGTCTTC ACCGTCTGCACAGGACTGGCTGATGGCAGGAGTAC AAGTCAAGTCTCCAAACAAAGCCCTCCAGCCCCATC GAGAAAACCATCTCCAAAGCCAAAGGCGAGCCCGAGAA CCACAGGTGTACACCTTGCCCCCATCCCGGAGGAGATG ACCAAGAACAGGTACGCTGTGGTGCCTGCTCAAGGC TTCTATCCAGGACATCGCCGTGGAGTGGGAGAGCAAT GGCAGCCGGAGAACAACTACAAAGACCAAGCCCTCCGTC CTGGACTCCGAGGCTCCTTCTTCTCTACAGCAAGCTC ACCGTGGACAGAGCAGGTGGCAGCAGGGGAACGTCTTC TCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC ACCCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA GGCTGTGAACCCGTGGAGATAATGTGATCAATTTGCTG GGCATGAAGTTCAATGACAAACCCCTGTACTTCATCGCC GAGATGATGAACAGGAGGAGGAGGAAGCCACTGGGA TTCCAGGCCAGGTGTGGGAGGAGGAGGACACA ATCGAACAGGACTACTTCGGAAAACTGGATCCAAACTG AGCGTGATCAGGAACCTGAACACACAGGTGCTGTCTATC	
U	CCACGTGCCCCAGACCTGAACCTCTGGGGGA		
S	CCGTGAGTCTTCTCTTCCCCCAAAACCCAAAG		
E	GACACCTCAIGATCTCCCGGACCCCGAGGTC		
-	ACATGGTGGTGGTGACGTGAGCACGGAAGAC		
5	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC		
8	GTGGAGGTGCATATATGCCAAGACAAAGCCGGG		
7	GAGGACAGTACACAGCACGTACCGTGTGTC		
	AGCTCTCTACCGTCTGTGACCCAGACTGGCTG		
	AATGGCAAGGAGTAAAGTGCAGGTCTCCAAC		
	AAAGCCCTCCAGCCCCCATCGAGAAAACCATC		
	TCCAAGCCAAAGGGAGCCCGGAGAACCAAG		
	GTGTACACCTGCCCCCATCCCGGGAGGAGATG		
	ACCAGAACCCAGTCAAGCTGAGCTGGCGGCTC		
	AAAGGCTTCTATCCAGCGACATGCCCGTGGAG		
	TGGGAGAGCAATGGCAGCCCGGAGAACAACTAC		
	AAGACCAAGCTCCCGTCTGGACTCCGACGGC		
	TCCTTCTTCTCTGTGAGCAAGTCAACGTGGAC		
	AAGAGCAGGTGGCAGCGGGAACCTCTTCTCA		
	TGCTCCGTGATGATGAGGCTCTGCACAACCGG		
	TTACGCAGAGAGCCCTCTCCCTGTCTCCGGGT		
	AAA (SEQ ID NO:114)		

		GACCAGGGCAATCGCCCTCTTTGAGGACATGACCGAC TCCGACGTCCGGGACAAAGCTCCAGGACCATCTTCATC ATCTCCATGTACAAAGACTCCAGCCCAAGGGCATGGCC GTGACCATCTCCGTCAAGGTGAGAGATCTCCACCCIG TCCGTGGAACAAGATCATCTCTTCAAGAGATGAAC CCCCCGACACATCAAGACACAAAATCCGACATCATC TTCTTCCAGGCTCCGTGCTGGGCAAGACACAAAATG CAGTTGAAATCTCTCTCTACGAGGGCTACTTCTCTGOC GTCGAAAAGAAAGAGACTTGTCAAGCTCATCTCAAG AAGCAGGACGAGCTCGGGACAGGTCAATCATGTCAAC GTGCAGAACGAGGAC (SEQ ID NO:159)
F U S E - 5 9 9	GAGCCCAAAATCTTGTGACAAAACATCACACATGC CCACGTGCCAGACCTGAACCTCTGGGGGA CCGTGAGTCTTCTCTTCCCCCAAAACCCAAAG GACACCTCAIGATCTCCCGGACCCCGAGGTC ACATGGTGGTGGGACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGGTGTGGACGGC GTGGAGGTGCATATGCCAAAGACAAAGCCGGG GAGGACAGTACACAGCACGACGACGTGTGTC AGCTCTCTACCGTCTGTGACCCAGACTGGCTG AATGCCAAGGAGTAAAGTGCAGGTCTCCAAC AAAGCCCTCCAGCCCCATCGAGAAAACATC TCCAAAGCCAAAGGGAGCCCGAGAACCCACAG GTGTACACCTGCCCCCATCCCGGAGGAGATG ACCAGAACCCAGTCAAGCTGAGCTGGCGGCTC AAAGGCTTCTATCCAGCGACATGCCCGTGGAG TGGGAGAGCAATGGCAGCCGGAGAACAACTAC AAGACACGCCCTCCGTCTGGACTCCGACGGC TCCTTCTCTCTGTGAGCAAGTCAACGTGGAC AAGACAGGTGGCAGCAGGGGAAGCTCTCTCA TGCTCCGTGATGCATGAGGCTCTGCACAAACCG TTACGCGAGAGAGCTCTCCCTGTCTCCCGGT AAA (SEQ ID NO:114)	TACTTCGGCAAGCTGAAGTCCAGCTGTCCGTGATCCGG AACTGAACGACAGGCTGTGTTCATCGACAGGGCAAC AGGCCACTCTTCGAGGATATGACCGACTCCGACGTGAGG GACAAAGCTCTTGAAGAACATCTTCATCATCTCCACTAC GGCGACTCCAGCAAGAGGAATGGCTGTACAATTTCC GTCAAAGTGGAGAAAATCTCCACCTGTCCGTGAGAAC AAGATCATCTCTTCAAGGAGATGAACCCCGGACAAAC ATCAAGACACCAAGAGCGACATCATCTTCTTCCAGCGC TCTGTGCCCGCATGATAACAAAATGCAGTTCGAAAGC TCTCTCTACGAGGCTACTTCTCCGAGTCGAAAAGAA AGGACCTGTTCAGTTCATCTGAAAGAGAGGACGAA CTGGGGACAGGACATCATGTTCACCGTGCAGAACGAG GACGAGCCCAATCTTCTGACAAAACATCACACATGCCA CCGTGCCAGCACTGAACCTCTGGGGGACCGTCAGTC TTCTCTTCCCGCCAAACCAAGGACACCCCTCATGATC TCCCGGACCCCGAGGTCAATGCGTGGTGGTGGACGTG AGCCACGAAGACCTGAGGTCAAGTTCACCTGGTACGTG GACGGCTGGAGTGCATAATGCCAAGACAAAGCCGGG GAGGAGCAGTACAACAGCACGTACCGTGTGTGAGGTC CTCACCGTCTGCACGAGGACTGGCTGAATGGCAAGGAG TTCAGTGCAGGTCTCCAAAGCCCTCCAGCCCTCCAGCCCTC ATCGAGAAACCATCTCCAAAGCCAAAGGGACCCCGA GACACAGGTGTACACCTGCCCTGCCCATCCCGGAGGAG ATGACCAAGAACAGGTCAGCTGTGGTGGTCAAA

		GGCTTCTATCCACAGCGACATCGCCGTGGAGTGGGAGAGC AATGGGCAGCCGGAGAACAACTACAAAGACACGCCTCCC GTGCTGGACTCCGACGGCTCCTTCTTCCITACAGCAAG CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC TTCTCATGTCCGTGATGATGAGGCTCTGCACAACCAC TACACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:160)
F U S E - 6 O O	GAGCCCAAAATCTTCTGACAAAACATCACACATGC CCACGTGCCCCAGACCTGAACCTCTGGGGGA CCGTGAGTCTTCTCTTCCCCCAAAACCCAAAG GACACCTCAIGATCTCCCGGACCCCGAGGTC ACATGGTGGTGGGACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGTTAGCTGGACGGC GTGGAGTGCAATAATGCCAAGACAAAGCCGGG GAGGACAGTACACAGCACGACGACGTGTGTC AGCTCTCTACCGTCTGTGACCCAGACTGGCTG AATGCCAAGGAGTAAAGTGCAGGTCTCCAAC AAAGCCCTCCAGCCCCATCGAGAAAACCATC TCCAAAGCCAAAGGGCAGCCCCGAGAACCCACAG GTGTACACCTGCCCCCATCCCGGGAGGAGATG ACCAAGAACCAAGTCAGCCTGAGCTGGCGGCTC AAAGGCTTCTATCCACGCGACATGCCCGTGGAG TGGGAGAGCAATGGCAGCCCGGAGAACAACTAC AAGACACGCCCTCCCGTCTGGACTCCGACGGC TCCTTCTTCTCTGTGAGCAAGTCAACGTGGAC AAGACAGGTGGCAGCAGGGGAACGTCTCTCA TGCTCCGTGATGATGAGGCTCTGCACAACCGG TTACGCAGAGAGCCCTCTCCCTGTCTCCCGGT AAA (SEQ ID NO:114)	TACTTCGGCAAGCTGAAGTCCAAAGCTGTCCGTGATCCGG AACCTGAACGACGAGGTGCTGTTCATCGACAGGGCAAC AGGCCACTCTTCGAGGATATGACCGACTCCGACGTGAGG GACAACGCTCCAGAACCAATCTTCATCATCTCCAAGTAC GGAGACTCCACGCAAGGGGAATGGCTGTACAATTTCC GTCAAGGTGGAGAAAATCTCCACCCCTGTCCGTGGAGAAC AAGATCATCAGTTCAAGAGATGAACCCGCCGACAAAC ATCAAGACACCAAGAGCGACATCATCTTCTTCCAGCGC TCTGTGCCGTCACGATAACAAAATGCAAGTTCGATCC AGCTCCTACGAGGCTACTTCTCGCAGTCGAAAAGGAA AGGACCTCTTCAAGTTGATCCTGAAGAAGAGGACGAG CTGGGGGACAGATCCATCATGTTCACCGTTCAGAACGAG GACGAGCCCCAATCTTCTGACAAAACCTCACACATGCCCA CCGTGCCCAGCACTGAACCTCTGGGGGACCGTCAGTC TTCTCTTCCCGCCAAACCAAGGACACCCCTCATGATC TCCCGGACCCCGAGGTCAATGCGTGGTGGTGGACGTG AGCCACGAAGACCTGAGGTCAAGTTCAACTGGTACGTG GACGGCTGGAGTGCATAATGCCAAGACAAAGCCGGG GAGGAGCAGTACAACAGCACGTCACGCTGTGTGTCAGGTC CTCACCGTCTCGACCAAGGACTGGCTGAATGGCAAGGAG TTCAGTGCAGGTCTCCAAAGCCCTCCAGCCCTCCAGCCCTC ATCGAGAAAACCATCTCCAAAGCCAAAGGGACGCCCGA GACACAGGTGTACACCTGCCCTGCCCATCCCGGAGGAG ATGACCAAGACCAAGTCAAGCTGTGGTGGTCAAA

		GGCTTCTATCCACAGCGACATCGCCGTGGAGTGGGAGAGC AATGGGCAGCCGGAGAACAACTACAAAGACACGCCTCCC GTGCTGGACTCCGACGGCTCCTTCTTCCITACAGCAAG CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC TTCTCATGTCCGTGATGCATGAGGCTCTGCACAACCAC TACACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:161)
F U S E - 6 0 1	GAGCCCAAAATCTTCTGACAAAACATCACACATGC CCACGTGCCAGACCTGAACCTCTGGGGGA CCGTGAGTCTTCTCTTCCCCCAAAACCCAAAG GACACCTCAIGATCTCCCGGACCCCGAGGTC ACATGGTGGTGGGACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGTTAGCTGGACGGC GTGGAGTGCAATAATGCCAAGACAAAGCCGGG GAGGACAGTACACAGCACGACGCTGTGTGTC AGCTCTCTACCGTCCGTGACCCAGACTGGCTG AATGCCAAGGAGTAAAGTGCAGGTCTCCAAC AAAGCCCTCCAGCCCCATCGAGAAAACCATC TCCAAAGCCAAAGGGAGCCCGAGAACCCACAG GTGTACACCTGCCCCCATCCCGGGAGGAGATG ACCAGAACCCAGTCAAGCTGAGCTGGCGGCTC AAAGGCTTCTATCCACGACATCGCCGTGGAG TGGGAGAGCAATGGCAGCCGGAGAACAACTAC AAGACACGCCCTCCCGTCTGGACTCCGACGGC TCCTTCTTCTCTGTGAGCAAGTCAACGTGGAC AAGACAGGTGGCAGCAGGGGAACGTCTCTCA TGCTCCGTGATGATGAGGCTCTGCACAACCGG TTACGCGAGAGAGCCCTCTCCCTGTCTCCCGGT AAA (SEQ ID NO:114)	TACTTCGGCAAGTGGAGTCCAGCTGTCCGTGATCCGG AACCTGAACGACGAGGTGTGTTCATCGACAGGGCAAC AGGCTCTCTTTCGAGGATATGACCGACTCCGACGTGAGG GATAACGCTCCAAAGGACAACTTTCATCATCTCCACTAC GCCGACTCCACGCAAGAGGAATCGCTGTACCATCTCC GTCAAGGTGGAGAAAATTAGCACACTGAGCGTGGAGAAC AAGATCATCTCTTCAAGGAGATGAACCCCGGACAAAC ATCAAGGACACCAAAAGCGACATCATCTTCTTCCAGCGC AGCGTGCCCGGACATGATAACAAAATCCAGTTCGATCC TCCAGCTACGAGGCTACTTCTGCGCGCTCGAAAAGGAA AGAGACTTGTCAAGTTGATCCTGAAGAAGAGGACGAG CTGGGGACAGAGCATCATGTTCACCGTTCAGAACGAA GACGAGCCCAATCTTCTGACAAAACCTCACACATGCCCA CCGTGCCAGCACTGAACTCTGGGGGACCGTCACTC TTCTCTTCCCGCCAAACCAAGGACACCGCTCATGATC TCCCGGACCCCGAGGTCAATGCGTGGTGGTGGACGTG AGCCACGAAGACCTGAGGTCAAGTTCAACTGGTACGTG GACGGCTGGAGTGCATAATGCCAAGACAAAGCCGGG GAGGAGCAGTACAACAGCACGCTACCGTGTGTGTCAGGTC CTCACCGTCTGCACGAGGACTGGCTGAATGGCAAGGAG TTCAGTGCAGGTCTCCAAAGCCCTCCAGCCCTCCAGCCCTC ATCGAGAAACCATCTCCAAAGCCAAAGGGAGCCCGGA GACACAGGTGTACACCTGCCCTGCCCATCCCGGAGGAG ATGACCAAGACGAGGTCAAGCTGTGGTGGTGGTCAAA

		GGCTTCTATCCACAGCGACATCGCCGTGGAGTGGGAGAGC AATGGGCAGCCGGAGAACAACTACAAAGACACGCCTCCC GTGCTGGACTCCGACGGCTCCTTCTTCCITACAGCAAG CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC TTCTCATGTCCGTGATGATGAGGCTCTGCACAACCAC TACACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:162)
F	GAGCCCAAAATCTTCTGACAAAACATCACACATGC	TACTTCGGCAAGCTGGAGTCCAAAGCTGTCCGTGATCCGG
U	CCACGTGCCCCAGACCTGAACCTCTGGGGGA	AACCTGAACGACGAGGTGTGTTCATCGACAGGGCAAC
S	CCGTGAGTCTTCTCTTCCCCCAAAACCCAAAG	AGGCTCTCTTTCGAGGATATGACCGACTCCGACGTGAGG
E	GACACCTCAIGATCTCCCGGACCCCGAGGTC	GATAACGCTCCAAAGGACAATCTTCATCATCTCCAAGTAT
-	ACATGGTGGTGGTGACGTGAGCCACGAAGAC	GGCGACTCCACGCAAGGGGAATCGCTGTGACAATTTCC
6	CCTGAGGTCAAGTTCAACTGTGACGTGGACGGC	GTCAAAGTGGAGAAGATCTCCACCCCTGTCCGTGGA AAC
0	GTGGAGGTGCATATATGCCAAGACAAAGCCGGG	AAGATCATCTCTCTCAAAGAGATGAACCCGCCGACAAAC
2	GAGGACAGTACACAGCACGTAACGTGTGTC	ATCAAGGACACCAAATCCGACATCATCTTCTTCCAGCGC
	AGCGTCTCACCGTCCGTGCAACCAAGACTGGCTG	TCTGTGCTGGGCACGATAACAAATCCAGTTCGATCC
	AATGCCAAGGAGTAAAGTGCAGGTCTCCAAC	AGCTCCTACGAGGCTACTTTCTCGCCGCTCGAAAAGGAA
	AAAGCCCTCCAGCCCCATCGAGAAAACCATC	AGGGACCTGTTCAAAACATCATCTGAAGAAGAGGACGAA
	TCCAAAGCCAAAGGGCAGCCCCGAGAACCAACAG	CTGGGAGACAGATCCATCATGTTCACAGTGCAGAACGAG
	GTGTACACCTGCCCCCATCCCGGGAGGAGATG	GACGAGCCCCAATCTTCTGACAAAACATCACACATGCCCA
	ACCAGAACCCAGTCAAGCTGAGCTGGCGGCTC	CCGTGCCCAGCACTGAACCTCTGGGGGACCGTCACTC
	AAAGGCTTCTATCCACGACATGCGCGTGGAG	TTCCCTCTTCCCCCAAAACCAAGGACACCCCTCATGATC
	TGGGAGAGCAATGGCAGCCGGAGAACAACTAC	TCCCGGACCCCGAGGTCAATGCGTGGTGGTGGACGTG
	AAGACACGCCCTCCCGTCTGGACTCCGACGGC	AGCCACGAAGACCTGAGGTCAAGTTCAACTGGTACGTG
	TCCTTCTTCTCTGTGAGCAAGTCAACGTGGAC	GACGGCTGGAGTGCATAATGCCAAGACAAAGCCGGG
	AAGACAGGTGGCAGCAGGGGAAGCTCTTCTCA	GAGGAGCAGTACAACAGCACGTCACGCTGTGTGTCAGGTC
	TGCTCCGTGATGATGAGGCTCTGCACAACCGG	CTCACCGTCTGCACCAAGGACTGGCTGAATGGCAAGGAG
	TTACGCGAGAGAGCCCTCTCCCTGTCTCCCGGT	TTCAAGTGCAGGTCTCCAAAGCCCTCCAGCCCTCCAGCCCC
	AAA (SEQ ID NO:114)	ATCGAGAAACCATCTCCAAAGCCAAAGGGAGCCCCGA
		GHACACAGTGTACACCCCTGCCCCATCCCGGAGGAG
		ATGACCAAGAACCAAGTCAAGCTGTGGTGGTGTCAA

		GGCTTCTATCCACGCGACATCGCCGTGGAGTGGGAGAGC AATGGCGAGCCGGAGAACAACTACAAAGACCGCTCCC GTGCTGGACTCCGACGGCTCCTTCTTCCITACAGCAAG CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACTGTC TTCTCATGCTCCGTGATGCTAGGCTCTGCACAACCCAC TACACGCAGAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:163)	
F	CAGGTGCAGCTGAAGCAGTCTGGACCAAGGACTC	CAGGTGCAGCTGAAGCAGTCTGGACCAAGGACTCGTGCAG	GACATTCTGTGATGCCAGAGCCC
U	GTGAGCCCAAGTCACTCTCTCTCCATACATGCATGCTCCGGC	CCAAGTCAGTCTCTCTCCATACATGCATGCTCCGGC	CGTGATCCTGAGCGTGAGCCCG
S	ACAGTCTCCGGCTTCTCCCTCACAACTACGGCTCCACTGGGTGGACAG	TTCTCCCTCACAACTACGGCGTCCACTGGGTGGACAG	GAGAGAGAGTGAAGCTTTAGCTGC
E	GTCCACTGGGTGGACAGTCACTGGGAAAGGC	TCACCTGGAAAGGCCCTCGAATGGCTGGCGTGAATCTGG	AGAGCCAGCCAGAGCATCGGCAC
-	CTCGAATGGCTCGGGGTGATCTGGTCCGGAGGA	TCGGGAGGAATACCGGACTACAACACCCCTTTACCTCC	CAACATCCACTGTTATCAGCAGC
6	AATACCGACTACAACACCCCTTTACCTCCAGG	AGGCTGTCCATCAACAAGGATAAATCCAAGTCCAGGTG	GGACCAACGGCAGCCCCAGACTG
2	CTGTCCATCAACAAGGATAATTCGAAGTCCAG	TTCTTCAAGATCAATAGCTTCAGTCCCACTATACCGCC	CTGATCAAGTACGCCAGTGAAG
4	GTGTCTTCAAGTGAATAGCTTCAGTCCAAAC	ATCTACTACTGGCCAGGGCTCTGACATCTACGACTAC	CATCAGCGGAATCCCTTCTAGGT
	GATACCGCCATCTACTACTGCGCCAGGGCTCTG	GACTTCGCTACTTGGGGCCAGGGAACACTGTTGACCGTG	TCAGCGGATCAGGCAGCGGCACC
	ACATACTACGACTACGAGTTCGCTACTTGGGC	TCGGCTGCTAGCACCAAGGGCCCATCGTCTTCCCTTG	GACTTCACCCTGAGTATCAACAG
	CAGGAACACTGGTGACCGTGTCCGCTGTAGC	GGACCCCTCTCAAGAGCACCTCTGGGGGACAGCGGC	CGTGGAAAGCAAGACATCGCCG
	ACCAAGGGCCCATCGGTCTTCCCTTGGCAACC	CTGGGCTGCCGTGTCAGGACTACTTCCCGCAACCGGTG	ACTATTACTGCGCAGCAGAACAT
	TCCTCCAAGAGCACTCTGGGGGACAGCGGC	ACGGTGTCTGGAAGTCAAGGCTCAGGGCCCTGACCGCGCGTG	AACTGGCCCACTACCTTCGGCGC
	CTGGCTGCCGTGTCAGGACTACTTCCCGGAA	CACACCTTCCCGCTGTCTTACGTCTCAGTCTCAGACTCTAC	CGGCACCAAGCTGGAACCTGAAC
	CCGTTGACGGTGTGTTGGAACCTCAGCGCGCCCTG	TCCTTCAGCAGCGTGTGACCGTCCCTCCAGCAGCTTG	GTACGGTGGGTGCACCATCTGTG
	ACCAGCGCGTGCACACCTTCCCGCTGTCTTA	GGACCCAGACTACATCTGCAACGTGAATCAACAAGCC	TTTCACTTCCCGCCATCTGATGA
	CAGTCTCAGGACTACTTCCCTCAGCAGCGTG	AGCAACACCAAGTGGACAAAGAAAGTTGAGTCCCAATCT	GCAGTTGAATCTGGAACCTGCT
	GTGACCGTGCCCTCCAGCAGCTTGGCACCCAG	TGTGACAAACTCACACATGCCACCGTGGCCAGCACCT	CTGTTGTGTGCTGCTGTAATAC
	ACCTACATCTGCAACGTGAATCAAGCCGAGC	GAACTCCTGGGGACCGTCACTCTTCTTCCCTTCCCTTCC	TTCTATCCAGAGAGGCCAAAGT
	AACACCAAGTGGACAAGAAAGTTGAGCCCAAA	AAACCCAGGACACCTCATGATCTCCGGACCCCGGAG	ACAGTGGAGGTGGATAACGCC
	TCTTGTGACAAAACACACATGCCACCGTG	GTACATGCGTGTGGTGGACGTGAGCCACAAAGACCT	TCCAATCGGTAACTCCAGGAG
	CCAGCACTGAATCTCTGGGGGACCGTCACTC	GAGGTCAAGTTCACTGTTAGTGGACGGCTGGAGGTG	ACTGTCAACAGCAGGACAGCAA
	TTCTCTTCCCCCAAAACCAAGACACCCCTC	CATAATGCCAAGACAAAGCCGGGAGGAGGAGTACAAC	GGACAGCACCTACAGCTCAGCA
	ATGATCTCCCGGACCCCGAGGTCAATGCGTG	AGCAGGTACCGTGTGTCAGCTCTCAACCTCTCCCTGCAAC	GCACCCCTGACGCTGAGCAAGCA

	GTGGTGGACGTGAGCCACGAGACCCCTGAGGTG AAGTTCAACTGTTACGTGGACGGCGTGGAGGTG CATATAATGCCAAGACAAGCCCGGGAGGAGCAG TACAAACAGCACGTAACCGTGTGTGTCAGCGTCTTC ACCGTCTGCACCGAGGACTGGCTGAATGGCAAG GAGTACAAGTGCAGAGTCTCCAAACAAGCCCTC CCAGCCCCCATCGAGAAAACCATCTCCAAAGCC AAGGGCAGCCCGAGAACCCACAGGTGTACACC CTGCCCCCATCCCGGGAGGAGATGACCAAGAAC CAGGTACGCTGAGCTGGCGCGTCAAGGCTTTC TATCCAGCGACATCGCGTGGAGTGGGAGAGC AATGGGCAGCCGAGAACAACTACAAGACCAG CCTCCCGTGTGGACTCCGACCGCTCCTTCTTC CTCGTGAGCAAGTCAACCGTGGACAAGCAGG TGGCAGCAGGGGAACGCTCTTCTCATGCTCCGTG ATGCATGAGGCTGTGCACAACCGCTTCAAGCAG AAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:123)	CAGGACTGGCTGAATGGCAAGGATACAAGTCAAGGTC TCCAAACAAGCCCTCCAGCCCCCATCGAGAAAACCATC TCCAAAGCCAAAGGGCAGCCCGAGAACCCAGGTTGAC ACCGTGGCCCATCCCGGGAGGAGATGAACCAAGACAG GTACAGCTGTGGTGGCTGGTCAAAAGGTTCTATCCAGC GACATCGCCGTGGAGTGGGAGCAATGGGCAGCCGGAG AACAACATAAAGACCACCGCTCCCGTGTGGACTCCGAC GGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAG AGCAGGTGGCAGCAGGGGAACGCTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCCACTACACGACGACAGAC CTCTCCCTGTCTCCGGGTAAAGGTGGCGGAGGCTCTGCT GGTGGAGGATCCGGGGAGGAGGTTCAGGAGCGCGGGGA AGTCTGTCTGAACCTGTGGGAAGATAATGTGATCAATTTT GTGGCCATGAATTTATTTGACAACACCCCTGTATTTCAIC GCCGAAGATGATGAATAACCGCGGAGGAGGAAAACCCCTG GGACTGCAGGCTAGAGTGTGGGAGGAGGAGGAACCATC GAGCAGGACTACTTCGGGAAACTGGAATCTAAGCTGTCA GTTATCAGGAACCTGAACGATCAGGTGCTGTTCATTTGAC CAGGGCAACAGGCCCTTGTCTTGGAGTATGACAGACAGC GAGCTGAGGACAACGCTCCAGAACCATCTTCAATTATC TCCAAGTACGGAGACAGCCAGCCAGGGGATGGCTGTT ACCATCTCCGTGAAGTGGAGAGAATTTCCACCTGTGTC GTGGAGACAATAATCATCTCTTCAAGAGATGAACCCC CCCGACAACATCAAGGACACCAAGTCCGACATCATCTTC TTCCAGCGCTCTGTGCCCTGGGCACGACAACAAGTCCAG TTCGAGAGCTCCAGCTACGAGGGCTACTTTCTGGCCGTC GAGAAGGAACGGACCTGTTCAAACTCATCTTGAAAAAG GAGGACGACTGGGAGACAGGTCATCATGTTCCACCGTG CAGATGAAGAC (SEQ ID NO:164)	GACTACGAGAAACACAAAAGTCTA CCCTCCGAGTCAACCATCAGG GCCTGAGTTCGCCCGTACAAAAG AGCTTCAACAGGGGAGGTGT (SEQ ID NO:186)
F	GAAGTGCAGCTGTGTGAGAGCGGAGGAGGATTG GTGCAGCCTGGAGGAAGCTTGAGGCTGAGTTGT GCCGCTAGTGGGTTTAAATCAAGACACATAC ATCCACTGGGTGAGCAGGCCCGCGGAAAGGA TTGGAGTGGGTGGCACGGATTACCCCAACCAAT GGATACACAAGGTACGCCGACTCCGTGAAGGGC 2 AGGTTACCATCTCCGCTGACACAAGCAAGAAC 5 ACAGCCTACCTGCAGATGAATCCCTGAGGGCA	GAACTCCAGATGAACCCAGTCCCC ATCTCCCTGTCTGTCTGTGG GAGACAGGGTGACCATCACCTGC AGAGCTTCCCAGGACGTGAACAC AGCCTGGAATAAGCCCCCAAGCTG CTGATCTACTCCGCTCCTTCTTCT GTATTCGGGCTGCCTTCCCGGT	

GAAGATACTGCTGTGTACTATTGCTCCAGGTGG GGAGGAGACGGATTCTATGCAATGGACTACTGG GGCCAGGGAACACTGGTGAACCGTGTCTAGCGCT AGCAACCAAGGGCCCATCGGTCTTCCCTTGSCA CCCTCCTCCAAGAGCACTCTGGGGCACAGCG GCCCTGGGCTGCCCTGGTCAAGACTACTTCCCT GAACCGGTGACGGTGTGCTGGAACCTCAGGCGCC CTGACACGGCGGTGCACACCTTCCCGGCTGTC CTACAGTCCCTCAGGACTCTACTCCCTCAGCAGC GTGTGACCCGTGCTCCAGCAGCTGGGCACC CAGACTACATCTGCAACGTGAATCACAAGCCC AGCAACACCAAGTGGACAAAGAGTTGAGCCC AAATCTGTGACAAAACCTCACACATGCCACCG TGCCACAGCACTGAATCCTGGGGGACCGTCA GTCTTCCCTCTCCCCCAAAACCAAGGACACC CTCATGATCTCCCGACCCCGAGTCAATGC GTGTGGTGGACGTGAGCCACAGACACCTGAG GTCAAGTTCACTGTGACGTGGACGGCTGGAG GTGCATAATGCCAAGACAAAGCCGGGGAGGAG CAGTACAACAGCAGTACCCTGTGTGTACGGTCT CTACCGTCTGCAACAGGACTGGCTGAATGGC AAGGATACAAGTCAAGGTCTCCAAACAAGCC CTCCAGCCCCATCGAGAAACCAATCTCCAAA GCCAAGGGCAGCCCGAGAACCAACAGGTGTAC ACCTGCCCCATCCCGGAGGAGATGACCAAG AACAGGTACGCTGAGCTGGCCGTCAAAGGC TTCTATCCAGCGACATCGCGTGGAGTGGAG AGCAATGGCCAGCCGAGAACAACTACAAGACC AOGCTCCCGTGTGGACTCCGACGCTCCCTTC TTCTCTGTGACCAAGCTACCGTGGACAAAGAGC AGGTGGCAGCAGGGGAACGTCTTCTCATGCTCC GTGATCATGAGGCTCTGCACACCGCTTCAG CAGAGAGCCCTCTCCCTGTCTCCGGTAAA (SEQ ID NO:124)	TATGCAATGGAATACTGGGGCAGGGAACACTGGTGACC GTGCTTAGCGCTAGCACCAAGGGCCCATCGGTCTTCCCC CTGGCAACCTTCTCCAAAGACACTCTGGGGCACAGCG GCCCTGGGCTGCTGGTCAAGGACTACTTCCCGAAACCG GTACAGGTGTGTGGAACTCAGCGCCCTGACACGCGGC GTGCACACCTTCCCGGCTGTCTACAGTCTCTCAGGACTC TACTCCCTCAGCAGCTGTGTGACCGTCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGATCACAAG CCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCAAA TCTGTGTACAAAACCTCACACATGCCACCGTCCAGCA CCTGAACTCTGGGGGACCGTCAAGTCTTCTCTTCCCC CCAAAACCAAGGACACCTCATGATCTCCCGACCCCC GAGGTCACTGGTGTGTGGTGGACGTGAGCACGAAGAC CCTGAGGTCAAGTTCACTGTGTGACGTGGACGGGTGGAG GTGCATAATGCCAAGACAAAGCCGGGGAGGAGCAGTAC AAGACGACGTACCGTGTGTGTGACCGTCTCTACCGTCTG CACCAGGACTGGTGAATGGCAAGGAGTACAGTGAAG GTCTCCAAACAAGCCCTCCAGCCCTCCAGAAAACCC ATCTCCAAAGCAAGGGCAGCCCGAGAACCAACACAGGTG TACAACCTGCCCCCATCCCGGAGGAGATGACCAAGAAC CAGGTACGCTGTGTGTGCTGGTCAAGGCTTCTATCCC AGGACATCGCCCTGGAGTGGGAGAGCAATGGGCAGCCG GAGAACAACCTACAAGAACCAAGCTCCCTGTGTGACTCC GACGGCTCCTTCTTCTCTACAGCAAGCTCACCCTGGAC AAGAGCAGTGGCAGCAGGGGAACGTCTTCTCATGCTCC GTGATGCATGAGCTCTGCACAACCACTACAGCAGAAG AGCTCTCCCTGTCTCCGGTAAAGGTGGCGGAGGCTCT GCTGTGGAGATCCGGGGAGGAGTTCAGGAGCGGG GGAAGTGTGTGAACCTGTGGAAGATAATGTGATCAAT TTTGTGGCAATGAATTTATTACAACACCTGTATTTTC ATCGCCGAAGATGATGAAAACGGCGGAGGAGGAAAACCC CTGGGACTGCAGGCTAGAGTGGTGGGAGGAGGAGAACCC ATCGAGCAGGACTACTTCGGGAACTGGAATCTAAGCTG TCAGTTATCAGGAACCTGAACATCAGGTGTGTTCATT GACACGGCAACAGGCCCTTCTTTGAGGATATCACAGAC AGGACGTGAGGACAAAGCTCCCGAACCATCTTCATT ATCTCCAAGTACGGAGACACAGCCAGGCCAGGGGATGGCT	TTTCCGGAAGCAGGTCGTGTGATCA GACTTCACCCCTGACCATCTCTCTC CCTGCAGCCTGAAGATTTTTCTA CCTACTACTGCAGCAGCACTAC ACCACCCCTCTACATTTCGGCA GGGTACAAAAGTGGAAATCAAAC GTACGGTGGCTGCACCATCTGTG TTTCACTTCCCGCCACTCTGATGA GCAGTTGAAATCTGGAACCTGCT CTGTGTGTGCTGTGCTGAATAAC TTCTATCCAGAGGTCGATTAAGT ACAGTGGAAAGTGGATTAACGAT GGCTTCAACAGGGGAGAGTGT (SEQ ID NO:187)
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	GTACCATCTCCGTGAAAGTGGAGAAGATTTCACACCTTG TCAGTGGAGAACAAAATCATCTCCTTCAAAGAGATGAAC CCCCCGACAAACATCAAGGACACCAAGTCCGACATCATC TTCTTCCAGCGCTCTGTGCTTGGCAACGACAAACAAGTC CAGTTGGAGAGTCCAGCTACGAGGGCTACTTTCTGGCC GTGAGAAAGGAACGCGACCTGTTCAAACTCATCTCTGAAA AAGGAGGACGAACCTGGGAGACAGGTCCATCATGTTCACC GTGCAGAAATGAAGAC (SEQ ID NO:165)	GAATGCAGCTGCTGCAGCGGAGGAGATTGCTGCAG GCAGGAGAGCCTGAGGCTGASTTGTGCCGCTAGTGGGA AGGACATTTAGTTCTCTATGCAATGGGTGTTTCAGGCAG GCCCCAGAAAGGAAAGGGAGTTTGTGCTGGCCATCAAC TGGAGTAGCGGATCTACATACTACGCTGATTCTGTGAAG GGCAGGTTCAACATCAGCGGGACAAATGCTAAGAACACC ATGTACCTGCAGATGAACAGCCTGAAGCCTGAGGACACC GCCGTGTACTATTGCCCGCTCGATATCAGATCAATTC GGCAACTACAACTTCAAGGACTACGAGTATGACTACTGG GGCCAGGGCACACAGGTGACAGTGTCTATCCGAACCTAAA TCTCTCGACAAAACCCACACCTGCCCGCTTGCCTGCT CCTGAAGCTGCTGGAGGACCTTCCGTGTTTCTGTTTCCC CCCAAGCCCAAGGACACCCCTCATGATCTCCAGGACCC GAGGTCACTGCGTTGTTGTGGACGTGTCCACGAGAT CCTGAAGTTAAATTTAACTGTACGTGGACGGGTGGAA GTGCACAAAGCCCAAGACAAAACCCCGGAGGACAGTAT AACTCCACCTACAGGCTGTGAGCGTGTGACAGTGTG CACGAGGACTGGCTGAAGGCAAGGAATACAAAGTGCAAG GTGTCCAAAGGCCCTGGCGCTCCTATTGAGAAAAC ATTCTTAAAGCAAGGACAGCCCGGGAGCCACAGTT TACACACTGCTCCCTCCAGGGAAGAGATGAACCAAGAAC CAGGTCAAGCTGTGGTGCCTGGTGAAGGATTTCTACCC TCCGACATGCCCTGGAAATGGGAAAGCAACGGCCAGCCT GAGAACACTACAAAACCCCGGAGTGTGCTGGACTCC GACGGATCTTTCTCTCTGACTCTAAGTTGACCGTGGAC AAGTCCAGGTGGCAGCAGGGAACGTTCTCTCTGCTCT GTGATGACAGGAGCCCTGCACAAACCACTATACCCAGAG AGTTGTCTCCTGTCCCGGCAAGGCTGTGAACCTGTG GAGATAATGTGATCAATTTGTGGCCATGAATTTATT
F U S E - 6 2 7	GAACCTAAATCCTCCGACAAAACCCACACCTGC CCCCCTGCCCTGCTCTCTGAAGCTGCTGGAGGA CCTTCGGTGTCTGTTTCCCCCAAGCCCAAG GACACCTCATGATCTCCAGGACCCCGGAGGTC ACCTCGGTGTGTGGACGTGTCCACGAGAT CCTGAAGTTAAATTTAACTGGTACGTGGACGGC GTGGAAGTGCACAAAGCCCAAGACAAAACCCCGC GAGAACAGTATAACTCCACCTACAGGGTGGTG AGGTGCTGACAGTGTGCACCCAGGACTGGCTG AAGCCCAAGGAATACAAAGTGCAGGTGTCCAAC AAGGCCCTGGGGCTCTATTGAGAAAATATT TCTAAGCCCAAGGGACAGCCCGGAGCCACAG GTTTACACACTGCTCCCTCCAGGGAAGAGATG ACCAAGAACCAAGTACAGCTGTCTCTGGCTGTT AAGGCTTCTACCCCTCCGACATCCCGGTGGAA TGGGAATCCATGGCCAGCCCGAGAACAACTAC AAACCCACCCCGCTGCTGGACTCCGATGGA TCTTTCTTCTGTGTCTCAAGCTGACCGTGGAC AAGTCCAGATGGCAGCAGGGCAATGTCTTTTCC TGCTCCGTGATGCAGAGGCCCTCCATAACAGA TTTACCCAGAAAGTCCCTGTCCCTGTCTCCCGGA AAG (SEQ ID NO:125)	

		GACAAACACCCCTGTATTTCATCGCCGAAGATGATGAAAAC ATTGAACAGGACTATTTTCGGAAAGCTGGAAATCCAAATTG AGCGTGATCCGGAACTGAACGATCAGGTCGTGTTCATC GACCAGGGCAACAGGCCCTCTGTCGAGGACATGACCGAC TCCGACGTGAGGACAAACGCCCTAGAACAAATCTTCATC ATCTCCAAGTACGGAGACTCCAGCCAAAGGGCCCTGGCT GTTACAATCTCCGTGAAGTGGAGAGATCTCCACCCCTG TCCGTGGAGAACAAAGATCATCTCCTTCAAGGAGATGAAC CCCCCGACAAATCAAGGACACCAAAATCCGACATCATC TTCCTCCAGGCTCCGTGCCCTGGGCACGATAACAAAGTC CAGTTCGAGTCCAGCTCCTACGAGGGTACTTCTCTGGCC GTGGAAGAGGAAGGACCTGTTCAGCTGATCCTGAAG AAGGAGGACGCTGGGAGACAGGAGCATCATGTTCACC GTCCAGAAOAGGAC (SEQ ID NO:166)
F	GAGCCCAATCTTCTGACAAAACCTCACACATGC	GAAGTCAGCTGTGTGGAGAGGGAGGAGGATTGGTGCAG
U	CCACGTCGCCAGACACTGAATCTCTGGGGGA	GCAGGAGGAAGCTCAGGCTGAGTTGTGCCCTAGTGGG
S	CCGTCAGTCTTCTCTTCCCCCAAAACCCAAAG	AGGACATTTAGTTCTTATGCAATGGGTGGTTCAGGCAG
E	GACACCTCATGATCTCCCGGACCCCGGAGGTC	GCCCCAGGAAGGAAGGGAGTTGTGGTGGCCATCAAC
-	ACATCGGTGGTGGAGCTGAGCCACGAAGAC	TGGAGTAGCGGATCTACATACTACGCTGATTCGTGAAG
6	CCTGAGGTCAGTTCAACTGGTGGAGCGGC	GGCAGGTTCCACATCAGCCGGACAAATGCTAAGAACAAC
4	GTGAGGTGCATATGCCAAGACAAGCCGCGG	ATGTACCTGCAGATGAACAGCOTGAAGCCTGAGGACACC
5	GAGGACAGTACACAGCACGTAACGTTGGTC	GCGGTGACTATTGCCCGCTGGATATCAGATCAATTC
	AGCGTCTCACCGTCTGCACCGAGACTGGCTG	GGCAACTACAATTCAGGACTACGAGTATGACTACTGG
	AATGGCAAGGAGTACAAGTGCAGGTCTCCAAC	GGCCAGGGCACAGGTGACAGTGTCTATCCGAACCTAAA
	AAAGCCCTCCAGCCCATCGAGAAAACCATC	TCTCCTCCGACAAAACCTCACATGCCCCACCGTCCCCAGCA
	TCCAAGCCAAAGGCAGCCCGGAGAACCAAG	CTGAACTCTTGGGGGACCGTCAGTCTTCTCTTCCCC
	GTGTACACCTGCCCCATCCCGGAGGAGATG	CTAAACCCAGGACACCCCTCATGATCTCCCGGACCCCC
	ACCAGAACCCAGTCAAGCTGAGCTGCGCGGTC	GAGGTCACATGGGTGGTGGTGGACGTGAGCCACGAAGAC
	AAAGGCTTCTATCCAGCGACATCGCCGTGGAG	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAG
	TGGGAGAGCAATGGGCAGCCGGAGAACAACTAC	GTGCATAATGCCAAGACAAGCCCGGGAGGAGCAGTAC
	AAGACCAGCTTCCGTGTGACTCCGACGGC	AAAGCAGCTACCGTGTGTGTCAGCGTCTCTACCGTCTTG
	TCTTCTTCTCTGTGAGCAAGCTCACCGTGGAC	CACACGAGTGGCTGAATGGCAAGGAGTACAGTGCAG
	AAGACAGGTGGACAGGAGGAACTCTTCTCA	GTCTCCAAACAAGCCCTCCCAGCCCCCATCCGAGAAAACC
	TGCTCCGTGATGCAATGAGGCTCTGCACAACCGG	ATCTCCAAAGCAAGGGCAGCCCGGAGAACACACAGGTG
	TTCACGCAGAAAGACCTCTCCCTGTCTCCGGGT	TACACCTTGCCTCCATCCCGGAGGAGATGACCAAGAAC
	AAA (SEQ ID NO:114)	CAGGTCAGCCTGTGTGGTGGCTGGTCAAGGCTTCTATCCC
		ACCGACATCGCCGTGGAGTGGAGAGCAATCGGCAGCCG

	GAGAACAACTACAAGACCACGCTCCCGTGGTGGACTCC GACGGCTCCTTCTTCTCTACAGCAAGCTCAACCGTGGAC AAGAGCAGGTGGCAGCAGGGGAACGTCCTCTCATGCTCC GTGATGCATGAGGCTCTGCACAAACCACTACACGACAAG AGCCTCTCCCTGTCTCCGGGTAAAGCTGCTGAACCTGTG GAAGATAATTCTATTAAATTTCGTGGCCATGAATTTCATC GATAATACTCTGTACTTTCATCGCCGAAGATGATGAAAAT ATTGAACAGGACTATTTCCGAAAGCTGGAAGCAAACTG AGCGTGATCAGGAACCTGAACGATCAGGTGCTGTTCATC GACCAGGGCAACCGCCCTCTGTTCGAGGATATGACCGAC TCCGACAGCAGGGACAAACGCAACCAAGGACCATCTTCATC ATCTCCAGTACGGCGACTCCAGCCCAAGGGGACTGGCT GTTACCATCTCCGTGAAGTCCGAGAGAATTTCCACCCCTG AGCTCCGAGAACAAAGATCATTTCTTCAAGGAGATGAAC CCCCCGACAACTCAAGACACCAAAATCCGACATCATC TTCTTCCAGCGCAGCTGCCCGGACACGATACCAAAAGTG CAGTTTGAGTCCAGCTCCTACGAGGGTACTTCTCTGGCC TCCGAAAAGGAAGGGACCTGTTCAAGCTGATCCTCAAG AAGGAGGACGAGTTGGGGACAGGTCAATTATGTTCACC GTTACAGAACGAGGAC (SEQ ID NO:167)	
F	GAGCCCAATCTTCTGACAAAACCTACACATGC	GAAATGACGCTGGTGGAAAGCGGAGGAGGATTTGTCGAG
U	CCACCGTGCCAGCACTGAACCTCTGGGGGA	GCAGSAGGAAGTCTGAGGCTGAGTTGTGCCCTAGCGGT
S	CCGTGAGTCTTCTCTTCCCCCAAAACCCAAAG	AGAACATTTAGTAGTTATGCTATGGGTGGTTTAGGCAG
E	GACACCCCTCATGATCTCCCGGACCCCGAGGTC	GCTCTCTGGAAGGAGGAGGAGTTCTGTGGTGGCTATCAAC
-	ACATGGTGGTGGTGGACGTGAGCCACGGAAGAC	TGGAGCAGCGGCTCTACATACTACGCTGATTCCTGGAAG
6	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC	GGAAAGTTCAAAATCTCCAGGGACAATGCTAAGAACACA
5	GTGAGGTGCATATGCCAAGACAAAGCCCGGG	ATGTATCTGCAGATGAACAGCCTCAAGCCTGAGGACACC
8	GAGGACAGTACACAGCACGTACCGTGTGCTC	GCCGTTTACTATTGGCCGCTGGATACCAATCAACAGC
	AGCCTCTCACCGTCTGTGACACGAGACTGGCTG	GGCAACTACAACCTTCAAGGACTATGATATGACTACTGG
	AATGGCAAGGAGTACAAGTGGAAGTCTCCAAC	GGCCAGGGCACACAGGTGACAGTTTCATCCGAGCCCAAA
	AAAGCCCTCCAGCCCCCATCGAGAAAACCATC	TCCTTCTGACAAAACCTCACATGCCACCGTGGCCAGCA
	TCCAAAGCCCAAGGGCAGCCCCGAGAACCCACAG	CCTGAACCTCTGGGGGACCGTCAAGTCTTCTCTTCCCC
	GTGTACACCCCTGCCCCCATCCCGGAGGAGATG	CCAAAACCCCAAGGACACCCCTCATGATCTCCCGGACCCCC
	ACCAAGAACCCAGGTACAGCTGAGCTGCGCGCTC	GAGGTACATGGCTGGTGGACGTGAGCCACGAAGAC
	AAAGGCTTCTATCCAGCGACATCGCCCGTGGAG	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGGTGGAG
	TGGGAGAGCAATGGGACGCCGGAGAACAACTAC	GTGCATAATGCCAAGACAAAGCCCGGGGAGGAGCAGTAC
	AAGACCAAGCCCTCCCGTCTGGACTCCGACGGC	AACAGCACGTACCGTGTGGTCAAGCTCTCAACCGTCTG

	TCTTCTTCTCTCGTGAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA TGCTCCGTGATGCATGAGGCTCTGACAAACCGG TTTACGCAGAAAGAGCTCTCCCTGTCTCCGGGT AAAGCCCGGAGCGCGTCCGAGGCAACGTGATT AATTTCGTGGCTATGAAGTTCAATCGATAACACA CTCTATTATTATCGCTGAGGACGATGAGAAATTT GGCAACAGTCTCTATTTCGGCAAGTTGGAAGC AAGCTGTCACTGATCCGCAATCTCAATGATCAG GTGCTGTTTATTGATCAGGGCAATAGGCCACTC TTTGAAGATATGACCGATTTCTGATGTCCGGGAC AATGCACCTAGAACTATCTTTATTATTTCGAAG TATGGGGACAGTCAGCCTCGGGGACTGGCAGTC ACTATTTCCTCAAGGTGGAGAGATTAGCACT CTCAGCGTTGAGAAACAAATTAATCTCTTTCAAG GAGATGAACCCACAGATAACATTAAAGGACACA AAGTCGGATATCATCTTCTTCCAGCGAAGCGTT CCAGGCCATGATATAAAGGTGCAGTTCGAGTCT AGCAGTATGAGGGCTATTTCTGGCGGTTGAG AAGAGCGAGATTGTTTAAAGTCATCTCTGAAG AAGGAGATGAGTTGGGGATAGAGATATCATG TTTACTGTCCAGAACGAGGAT (SEQ ID NO:126)	CACCAGGACTGGTGAATGGGAAGGAGTACAAGTGAAG GTCTCCAAACAAGCCCTCCGAGCCCCCATCGAGAAACC ATCTCCAAAGCAAAAGGCGAGCCCCGAGAACACAGGTG TACACCTTCCCCCATCCCGGAGGAGATGACCAAGAAC CAGGTCAAGCTGTGGTGGTGGTCTGCTCAAGGCTTCTATCCC AGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG GGAACAACACTACAAGAACCAACGCTCCCGTGTGGACTCC GACGGCTCTTCTCTCTCTACAGCAAGCTCACCGTGGAC AAGAGCAGTGGCAGCAGGGGAACGTCTTCTCATGTCTCC GTGATGCAAGGCTCTGCAACCAACCACTACACGCAAG AGCCTCTCCCTGTCTCTCCGGTAAAA (SEQ ID NO:154)	
F U S E - 6 5 9	GAGCCCAAAATCTTCTGACAAAACCTCACACATGC CCACCGTCCCAGCACCTGAACCTCTGGGGGA CCGTGAGTCTTCTCTCTTCCCCCAAAACCCAAAG GACACCTCATGATCTCCCGGACCCCGGAGGTC ACATCGGTGGTGTGGACGTGAGCAACGAAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGAGGTGCATATATGCCAAGACAAGCCCGGG GAGGACAGTACACAGCACGTACCGTGTGGTC AGCGTCTCTACCGTCTGACACGAGACTGGCTG AATGCAAGGAGTACAAGTCAAGTCTCCAAC AAAGCCCTCCAGCCCATCGAGAAAAACCATC TCCAAAGCCAAAGGCGAGCCCGAGAACACAG GTGTACACCTTGCCCCATCCCGGAGGAGATG ACCAAGAACCGGTACGCTGAGCTGGCGGCTC	GAAGTGCAGCTGGTGGAAAGCGGAGGAGGATTGGTGCAG GCAGGAGGAAGTCTGAGGCTGAGTTGTCCGCTAGCGGT AGAACATTTAGTAGTTATGCTATGGGGTGGTTTAGGCAG GCTCTGGAAGAGAGAGGAGTCTGGTGGCTATCAAC TGGAGCAGCGGCTCTACATACTACGCTGATTCCGTGAAG GGAAGGTTTCAAAATCTCCAGGACAAATGCTAAGAACA ATCTATCTGCAGATGAACAGCCTCAAGCCTGAGGACACC GCCGTTTACTATTGCCCGCTGGATACCAATCAACAGC GGCAACTACACTCAAGGACTATGATATGACTACTGG GCCAGGGCACACAGGTGACAGTTTCTATCCGAGCCCAA TCTTCTGACAAAACCTCACACATGCCACCGTCCCGAGCA CCTGAACCTCTGGGGGACCGTCAAGTCTTCTCTTCCCC CCAAAACCCAGGACACCTCATGATCTCCCGGACCCCC GAGTTCACATGGCTGGTGGTGGAGCTGAGCCAGGAGAC	

	AAAGGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGAGCCCGGAGAACAATAC AAGHCAAGCCCTCCCGTGTGGACTCCGACGGC TCCCTCTCTCTGTGAGCAAGCTCACCGTGGAC AAGACAGGTGGCAGGAGGGAAGCTCTTCTCA TGTCCGTGATGATGAGGCTCTGCACAACCCGG TTCCGCGAGAAAGAGCCTCTCCCTGTCTCCGGT AAAGTCCCGAACCCGTGGAGGACAATGTGATC AATTTTGTGGCTATGAAGTTTATTGATAACAAC CTCTACTTTATCGCGAAGATGAGAAAATGGA GGCGGGGCAAGCCTCTGTGGCCTGCAGGCTAGA GTGGTTGGCGGAGGAGGTACATCTTTGGCAAA CTGGAGTCCAAGCTCTCTGTGATTCGGAACCTG AATGATCAGGTCTGTTCATCGATCAGGGAAT CGGCTTTGTTGAAGATATGACCGACTCCGAC GTGGAGATAACGCCCAAGGACCATTTCATC ATCTCCAAATATGGTGACTCCAGCCTCGGGGA CTCGAGTCAACATTCAGTGAAGTGGAGAAG ATTCTACCTTGTCTGTGTGAGAAATAAATTATC TCATTCAAGAGATGAATCCTCCAGATAATATT AAGACACAAAATCAGACATCATTTCTTCCAG CGGTCTGTCCCTGGCCACGACATAAAGTGCAG TTCCGAATCCTCTCTTATGAGGGTACTTCCCTG GCTGTGAGAGGAAGGAAGGACCTGTTTAAAGCTG ATTCTGAAGAAAGAGGATGAGTTGGGTGACCGA AGCAATTATGTTTACCGTCCAGAATGAAGAT (SEQ ID NO:127)	CCTGAGGTCAAGTTCAACTGGTAAGTGGACGGCGTGGAG GTGCATATATGCAAGACAAGCCGCGGAGAGCATAC AACAGCACTGACCTGTGTGTCAAGCTCTCACCGTCTCTG CACAGGACTGCTGAATGGCAAGGAGTACAGTGCAG GTCTCCAAAGAGCCCTCCAGCCCTCATCGAGAAAAC ATCTCCAAAGCAAGGCAAGCCCGAGAGATGACCAAGTG TACACCTGTCCCTCATCCGGGAGGAGATGACCAAGAAC CAGGTCAAGCTGTGTGTGCTTGTCTCAAGGCTTCTATCCC AGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCGG GAGAACAACTACAAGACACAGCCTCCCGTGTGGACTCC GACGGCTCCTTCTTCTCTTACAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGCAGGGGAACGTTCTCTCATGTCTCC GTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG AGCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:154)	
F U S E - 6 6 0	GAGCCCAAATCTCTGACAAAACTCACACATGC CCACCGTCCCAGCACCTGAACCTCTGGGGGA CCGTCAGTCTTCTCTCTTCCCCCAAAACCCCAAG GACACCTCATGATCTCCCGGACCCCGGAGGTC ACATCGGTGGTGGGACGTGAGTCACGAAGAC CCTGAGGTCAAGTTCAACTGTTACGTGGAGCGC GTGGAGGTGCATAATGCCAAGACAAGCCCGGG GAGGAGCAGTACACAGCACGTACCGTGTGTGTC AGCGTCTCAACCGTCTGCACCGAGACTGGCTG AATGCAAGGAGTACAAGTGCAGGCTCTCCAAC	GAAAGTCAGCTGCTGGAAGCGGAGGAGATTGGTGCAG GCAGGAGGAAGTCTGAGGCTGAGTTGTCCGCTAGCGGT AGAACATTTAGTAGTTATGCTATGGGGTGGTTAGGCAG GCTCTGGAAGAGAGAGGAGTCTGTTGGTGGTATCAAC TGGAGCAGCGGCTCTACATACTACGCTGATTCCTGGAAG GGAAGGTTCAATATCTCCAGGACAAATGCTAAGAACACA ATGTATCTGCAGATGAACAGCCTCAAGCCTGAGGACACOC GCCGTTTACTATTGCCCGCTGGATACCAATCAACAGC GGCAACTACACTTCAAGGACTATGATGATGACTACTGG GCCAGGGCACACAGGTGACAGTTTCATCCGAGCCCAAA	

AAAGCCCTCCAGGCCCCATCGAGAAAACCATC TCCAAAGCCAAAGGCGAGCCCCGAGAACACAG GIGTACACCTGCCCCCATCCCGGAGGAGATG ACCAAGAACACAGTCAGCCTGAGCTGCGCGCTC AAAGGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGCGAGCCCGGAGAACAACTAC AAGACCAAGCTCCCGTGTGGACTCCGACGGC TCCITCTTCTCTGTGAGCAAGCTACCGTGGAC AAGAGCAGGTGGCAGCAGGGGAAGCTTCTCA TGTCCGTAATGCAATGAGGCTCTGCACAACCG TTCACGCAGAAAGACCTCTCCCTGTCTCCGGGT AAAGCGCCGAGCCCGTCGAAGATAACGTGATC AACTTCGTGGCCATGAAATTCATCGATAATACA CTCTACTTTATTGCGAGGATGACGAGAACATC GAGCAGGATGGCGTCCATCGGCAACAGAAGT GGCGCGGAGGCAAGCCCTTGGGACTGCAGGCC AGGGTTGTCGGAGGTGGGGTACTATTGAGCAG GATTACTTTGGGAAGTTGGAATCCAAGCTCAGT GTGATCCGCAATCTGAATGATCAGTGTCTTTC ATCGACCAAGGGGAATCGGCCCTGTTCGAAGAT ATGACCGACTCCGATGTTAGGGATAACGCTCCT AGACTATCTTTATCATTTAGCAAGTATGGGAC TCTCAGCCCAAGAGGCTGGCCGTGACCATCTCC GTCAAAGTCGAAAAGATTTCCACTCTCTCTGTG GAAATAAGATCATCAGCTTTAAAGAGATGAAT CCCCGTGACAAACATCAAGGATACAAAATCTGAT ATCATCTTTTCCAGCGCTCTGTCCCGACAT GACACAAAGGTGCAGTTTGATCTACAGCTAC GAGGGTATTTCCCTCGCTGTTGAAAAGGAACGA GATCTCTTAAATTGATTTTGACAAGGAAGAT GAGCTGGGAGACAGGTCAATCATGTTCACCGTT CAGACCAAGAT (SEQ ID No:128)	TCTTCTGACAAAACCTCACATGCCACCCGTGCCAGCA CCTGAACCTCTGGGGGACCGTCAGTCTTCTCTTCCCC CTAAAACCCAAAGACACCCCTCATGATCTCCCGAACCCCC GAGGTACATGCGTGTGTGACGTGAGCCACGAAGAC CCTGAGGTCAAGTCAACTGGTACGTGGACGGCTGGAG GTGCATATATGCCAAGACAAAGCCCGGGAGAGCAGTAC AACAGCAGCTACCGTGTGGTCAAGCTCTCACCGTCTCTG CACCAAGACTGGTGAATGGCAAGGAGTACAGTGAAG GTCTCCAACAAGCCCTCCAGCCCCCATCGAGAAAAC ATCTCCAAGCAAAAGGGCAGCCCCGAGAACACAGGIG TACACCTGTCCCCATCCCGGAGGAGATGACCAAGAAC CAGGTACGCTGTGGTGCTTGGTCAAGGCTTCTATCCC AGCGACATCGCGTGGAGTGGGAGAGCAATGGCGAGCCG GAGAACAACTACAAGACCAAGCCCTCCGTGTGGACTCC GACGGCTCTTCTTCTCTCTACAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGCAGGGGAACGTTCTTCTCATGCTCC GTGATGCAATGAGGCTCTGCACAACCACTACACGCAAG AGCCTCTCCCTGTCTCCGGGTAAA (SEQ ID No:154)
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F	GAGCCCAAATCTTCTGTGACAAAACTCACACATGC	GAAGTGCAGCTGGTGGAAAGCGGAGGAGGATTGGTGCAG
U	CCACCGTGCCCAAGCACTGAACCTCTGGGGGA	GGAGGAGGAAGTCTGAGGCTGAGTTGTGCCCTAGCGGT
S	CCGTCAGTCTTCTCTTCCCCCAAAACCAAG	AGAACAATTTAGTAGTTATGCTATGGGTTGGTTAGGCAG
E	GACACCCCTCATGATCTCCCGGACCCCGAGETC	GCTCCTGGAAAGAGAGAGGAGTTCGTGGTGCATCAAC
-	ACATGGGTGGTGGTGGACGTGAGCCACGAAGAC	TGGAGCAGCGGCTCTACATACTACCTGCTGATTCCGTGAAG
6	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC	GGAGGTTCACAACTCCAGGGACAAATGCTAAGAACACA
8	GTGGAGGTGCATATAGCCCAAGACAAGCCGGG	ATGTATCTGAGATGAACAGGCTCAAGCCTGAGGACACC
6	GAGGAGCAGTACAACAGCACGTAACCGTGTGGTC	GGCGTTTACTATTGCCCGCTGGATACCAATCAACAGC
	AGCGTCTCACCGTCCGTGCAACAGACTGGCTG	GGCAACTACAACCTCAAGGACTATGATGATGACTACTGG
	AATGGCAAGGAGTACAAGTGAAGTCTCCAAC	GGCCAGGGCACACAGGTGACAGTTTCATCCGAGCCCCAA
	AAAGCCCTCCAGCCCCATCGAGAAAACCATC	TCCTCTGACAAAACCTCACATATGCCACCCTGCCCCAGCA
	TCCAAGCCCAAGGGCAGCCCCGGGAAACCAACAG	CCTGAACCTCTGGGGGACCGTCAGTCTTCTCTTCCCC
	GTGTACACCTGCCCCCATCCCCGGGAGGAGATG	CCAAAACCCAAAGACACCTCATGATCTCCCGGACCCCC
	ACCAGAACCAGGTCAGCCTGAGCTGCGCGGTC	GAGGTCACTGGGTGGTGGACGTGAGCCACGAAGAC
	AAAGGCTCTATCCAGCGACATCGCCGTGGAG	CCTGAGGTCAAGTCAACTGGTACGTGGAGCGGCTGGAG
	TGGGAGAGCAATGGCAGCCCGGAGAACAACTAC	GTGCATATAGCAAGACAAAAGCCGGGGAGGAGCAAGTAC
	AAGACCAAGCCTCCCGTGTCTGGACTCCGACGGC	AACAGCACGTACCGTGTGGTACAGTCTCTCACCGTCCTG
	TCCTTCTTCTCTGTGAGCAAGCTACCGTGGAC	CACAGGACTGGGTGAATGGCAAGGAGTACAGTGAAG
	AAGAGCAGGTGGCAGGAGGGGAAGCTTTCTCA	GTCTCCAAACAAGCCCTCCAGCCTCCATCGAGAAAAC
	TGTCGCGTGATGATGAGGCTCTGCAACAACCGG	ATCTCAAAGCAAAAGGCGAGCCCCGAGAACACACAGGTG
	TTACGCGAGAAGCCTCTCCCTGTCTCCGGGT	TACACCTGCCCCCATCCCGGAGGAGATGACCAAGAAC
	AAA (SEQ ID NO:114)	CAGGTCAGCCTGTGGTGCCTGGTCAAGGCTTCTATCC
		AGCGACATGCGCTGGAGTGGGAGAGCAATGGGCAGCGG
		GAGAACAACTACAGACCCACGCTCCCGTGGACTCC
		GACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGAC
		AAGAGCAGGTGGCAGCAGGGAACGTCTTCTCATGCTCC
		GTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG
		AGCCTCTCCCTGTCTCCGGTAAAGCTGCTGAACCTGTG
		GAGATAAATTCATTAATTTCTGGCCCATGAAATTCATC
		GATAATACCTGTACTTTCATCGCCGAAAATGATGAAAAC
		CAGGACATTTGATACCTTTGGAAAACCTGGAATCCAAATTG
		AGTGTGATCCGCAACCTGAACGATCAGGTGCTGTTCATC
		GACCAGGGCAATGCCCTGTTCCGAGGATATGACCGAC
		TCCGACTCCAGGACAAACGCACTAGGACCATCTTCTATC
		ATCTCTAAGTACGGCGATTCCAGCCCCAGGGCTTGGCT
		GTACCACTCTCCGTTAAGTCCGAGAGATTTCACCCCTG
		TCCTCCGAGAACAAAATCATCTCTCTCAAGAAATGAAC

		CCCCCGACACATCAAGGACACCAAAAGCGATATCATC TTCTTCCAGAGTCCGTGCCCGGCCACGATAACAAGTG CAGTTCGAGTCCAGCTCCACGAGGGCTACTTCCTGGCC TCCGAAAAGGAACCGGACCTGTTCAGCTGATCCTGAAG AAGGAGGACGAGCTGGGGACAGATCCATTATGTTCAOC GTTCAGAACGAGGAC (SEQ ID NO:168)	
F U S E - 6 9 1	CAGTTTCAGCTCGTCAGTCAAGCGGAGGAGTC GTTACGCCAGGAAGGAGTCTCAGGTGGACTGC AAGGATCAGGCATCACATTCTCCAACTCGGC ATGCATGGGTGAGCAGGCACTGGAAAGGA TTGGAGTGGGTGGCAGTGATCTGTACGATGGA AGCAAAAGATACTACGCCGACAGGCTCAAGGC AGTTACCATCAGCAGGACAAATAGCAAGAAC ACCTGTCTTTCAGATGAATAGTTGAGGCC GAGACACCGCGTATTACTGCGCTACCAAC GACGACTACTGGGCGAGGGAACCTGGTTACC GTGATAGCGCTAGCACCAAGGGCCCATCGGTC TTCCCGCTGGACCCCTCTCCAGAGCACTCT GGGGCACAGCGGCCCTGGCTGCTGGTCAAG GACTACTTCCCGAACCGGTGACGGTGTGTGG AACTCAGGCGCCCTGACCAAGCGGCTGCACAC TTCCCGCTGTCTTACAGTCCCTCAGGACTCTAC TCCCTCAGCAGCGTGGTGACCGTGGCCTCCAGC AGTTGGGCACCCAGACCTACATCTGCAACGTG AATCAAGCCCGACCAACACCAAGTGGACAAG AAAGTTAGCCCAATCTTGTACAAAATCTAC ACATGCCACCGTGCACAGCACTGAAGCCGCA GGGGACCGTCACTCTCTTCCCCCAAAA CCCAAGGACACCTCATGATCTCCCGGACCCCC GAGGTACATGCGTGGTGGACCTGAGCCAC		GAAATCGTGTGACCCAGTCCCC CGCTACCTTGAGTCTGTCCCTTG GAGAGAGAGCAACCTGTCTGT AGGGCTAGTCAGTCCGTGAGCAG CTATCTGGCTGTGTATCAGCAGA AGCCCGCCAGGCTCCTAGGTTG TTGATTTACGATGCCCTCCACAG AGCCACCGGATCCCTGCACGGT TCTCCGGTTCCGGTCTGTGTACA GACTTCACCTGACTATCAGCAG TCTGGAGCCCGAGGATTTCCGGC TTTACTACTGCGCAGCAGTCCCTC AACTGGCCCGAGACATTCGGTCA GGGCACCAAGTGGAGATCAAGC GTACGGTGGCTGCACCATCTGTC TTCATCTTCCCGCCATCTGATGA GCAGTTGAATCTGGAACCTGCT CTGTGTGTGCTGTGCTGATAAC TTCTATCCACAGAGGCCCCAAGT ACAGTGGAGGTGGATAACGCC TCCAAATCGGTAACTCCAGGAG AGTGTCAACAGCAGGACAGCAAA GGACAGCACCTACAGCTCAGCA GCAACCTGACGCTGAGCAAAAGCA

	GAAGACCCCTGAGGTCAAGTTCAACTGGTACGTG GACGGCGTGGAGGTGCATAATGCCAAGACAAAG CCGCGGGAGGAGCAGTACAAACAGCACGTACCGT GTGGTCAGCGTCTCACCGTCTCTGCAACCAGCAC TGGCTGAATGGCAAGAGTACAAAGTGCAGAGTCT TCCAAACAAAGCCCTCCCAGCCCCCATCGAGAAA ACCATCTCCAAAGCCAAAGGCAGCCCCGAGAAA CCACAGGTGTACACCCCTGCCCCCATGCCGGGAG GAGATGAACCAAGAACCCAGGTCAGCCCTGACCTGC CTGGTCAAAGGCTTCTATCCACAGCACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAAC AACTACAAGACACACGCCCTCCCGTGTGGACTCC GAGGCTCCTTCTTCTCTTACAGCAAGCTCACCC GTGGACAAGCAGAGGTGGCAGCAGGGGAAGCTC TTCTCATGCTCCGTGATGCATCAGGCTCTGCAAC AACCACTACACGCAAGAGCCCTCTCCCTGTCT CCGGGTAAA (SEQ ID NO:129)	CAGGTTCAAGTCTGTCGAAAGCGGAGGAGTCTGTCAG CCAGGAAGATCCCTCAGGCTCGACTGTAAAGCCCTCCGGA ATCACCTTCTCAACTCCGGAATGCATGGGTACAGGCAG GCTCTGGAAGAAGGACTGGAGTGGGTGGCTGTGATTTGG TACGACGGCTCCAAGAGATATACGCGGACTCTGTGAAG GGCGGTTCACTATCTCCAGGACAACTCCAAGAACACA CTGTTCTGCAGATGAATCCCTGCGGCTGAGGATACT GCCGTTTATTACTGCGCCACCAACGATGACTACTGGGGA CAGGGAACCTTGGTGACCGTGAAGTAGCGCTAGCACCAAG GGCCCATCGGTCTTCCCGCTGGCAACCTCTCCAGAGC ACCTCTGGGGGCACAGCGCCCTGGGCTGCCTGGTCAAG GACTACTTCCCGAACCCTGACGGTGTCTGTGAACCTCA GGCGCCCTGACCAAGCGGGGTGCACACCTTCCCGGCTGTC CTACAGTCTCCAGGACTCTACTCCCTCAGCAGCGTGGTG ACCGTGCCCTCCAGCAGCTTGGGCAACCCAGACCTACATC TGCAAAGTGAATCACAAAGCCAGCACCAACCAAGGTGAC AAGAAAGTTGAGCCCCAATCTTGTGACAAAATCTACACA TGCCTACCGCTGCCAGACCTGAAGCCGAGGGGACCG TCAGTCTTCTCTTCCCGCCAAACCAACAGGACACCCCTC ATGATCTCCCGGACCCCGAGGTCACTGCTGTGGTGGTG	GAAATCGTCTGACCCAGTCCCC CGCTACCTTGAGTCTGTCCCGTG GAGAGAGAGCCACCCCTGTCTTGT AGGGCTAGTCACTCCGTGAGCAG CTATCTGGCCTGGTATCAGCAGA AGCCCGCCAGGCTCCTTAGGTTG TTGATTTACGATGCTTCCCAACAG AGCCACCGGAATCCCTGCACGGT TCTCCGGTTCCGGTCTGTGTACA GACTTCACCCCTGACTATCAGCAG TCTGGAGCCCGAGGATTTCCGCG TTTACTACTGCCAGCAGTCCCTC AACTGGCCCGAGGACATTCGGTCA GGGCAACCAAGTGGAGATCAAGC GTACGGTGGCTGCACCATCTGTCT TTCATCTTCCCGCCATCTGATGA GCAGTTGAAATCTGGAATGCGCT CTGTTGTGTGCTGCTGAATATAC TTCTATCCAGAGAGGCCCAAGT ACAGTGGAAAGTGGATACACGCC
F U S E - 6 9 4			

ACATGCCACCGTGGCCAGCACCTGAAGCCGCA GGGGACCGTCAGTCTTCTTCCGCCCAAAA CCCAGGACACCCTCATGATCTCCCGAACCCC GAGTCACATGCGTGGTGGTGGACGTAGCCAC GAAGACCCCTGAGGTCAAGTTCAACTGGTACGTG CAGGCGTGGAGGTGCATATGCCAAGACAAAG CCGCGGGAGGAGGTACAAACAGCAAGTACCGT GTGTCAGCGTCTTCACCGTCCCTGCACCAAGGAC TGGCTGAATGGCAAGGAGTACAAGTCAAGGTC TCCAAACAAAGCCCTCCAGCCGCCCATCGAGAAA ACCATCTCCAAAGCCAAAGGGCAGCCCGAGAA CCACAGGTGTACACCTGCCCCCATCCCGGGAG GAGTGAACCAAGAACAGGTACGCTGAGCTGC GCCGTCAAAGGCTTCTATCCACAGGACATCGCC GTGGAGTGGAGAGCAATGGCAGCCGGAGAAC AATACAAGACCCAGCCCTCCCGTGTGGACTCC GAGGCTCCTTCTTCTCGTGACCAAGCTCACC GTGGACAAGAGCAGGTGGCAGCAGGGAAAGTC TTCCTATGTCCTCGTATGATGATGAGCTCTGCAC AACAGGTTCACACAGAAGAGCTTGAAGCTTGAGC CCCGGGGAGGGGGGATCTGGGGGAGGAGGT AGTGAGGCGGAGGATCCGCGGTGGAGGTTCT GGTGGTGGGGCAGTGGGGTGGGGATCAGCT GCTGAACCTGTGGAAGATAATCTATTAATTC GTGGCATGAAGTTCATCGATAATACTCTGTAC TTCTATCGCCGAAGATGATGAAAATATCGAGCAG GATTACTTCGGCAACTGGAAAGCAAACTGAGC GTGATCAGGAACCTCAAGCAGCAGCTGCTGTTT ATCGATCAGGGCAACAGGCCCTCTTTGAGGAC ATGACCGACAGCGATAGCAGGCAACGCACTT AGGACAATCTTCATCATCTCCAGTACGGCGAC TCCAGCCAGAGGATGGCTGTGACAATTTCC GTGAAATCCGAGAAGATCTCCACCTGTCCAGC GAGAACAGATCATCTCTTCAAGGACATGAAC CCCCCGACACATCAAGGACACAAAGTCCGAC ATCATCTTCTCCAGGCTCCGTCGCCGGTCAAT GATACAAGGTCCAGTTCGAGTCCAGCTCCTAC	GAGCTGAGCCACGAAGACCCCTGAGGTCAAGTCAACTGG TACGTGGACGGGTGGAGTGGATATATGCCAAGACAAAG CCCGGGAGGAGCAGTACAAAGCACGTAACGTGTGTTC AGCGTCTCAACCTCCTGCAACAGGACTGGCTGAATGGC AAGGAGTACAAGTCAAGGTCTCCAAACAAGCCCTCCCA GGCCCCATCGAAGAAACCATCTCCAAAGCCAAAGGGCAG CCCGAGAACACACAGGTGTACACCCCTGCCCATCCCGG GAGGAGATGACCAAGAACACAGGTACGCTGTGTGCCCTG GTCAAAGGCTTCTATCCAGCGACATGCGCTGGAGTGG GAGAGCAATGGCAGCCGGAGAACAACTACAAGACCAAG CCTCCCGTGTGGACTCCGACGGCTCCTTCTTCTCTAC AGCAAGCTCACCGTGGACAAAGACAGGTGGCAGCAGGG AACGTCTTCTCATGCTCCGTGATGATGAGGCTCTGCAC AACCACTACACGAGAGAGGCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:169)	TCCAAATCGGGTAACCTCCAGGAG ACTGTACAGAGCAGGACAGCAA GGACAGCACTACAGCCTCAGCA GCACCCCTGACGCTGAGCAAGCA GACTACGAGAAACACAAGTCTA CGCTGGGAAGTCAACCATCAGG GCCTGAGTTCGGCCCGTCAACAAG AGCTTCAACAGGGGAGAGTGT (SEQ ID NO:188)
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	GAGGATACCTTTCTGGCCCTCAGAGAAGGAAAGG GACCTGTTCAAACATCATCTGAGAGAGGAGGAC GAGCTGGGGACAGAAGCATCACTTCAACCGTC CAGAAATGAGGAC (SEQ ID NO:130)	
F	GAGCCCAAAATCTCTGACAAAACATCACACATGC	GGAGCGGGGGATCTGGGGAGGAGGTAGTGGAGCGGA
U	CCACGTGCCCCAGCACTGAACCTCTGGGGGA	GGATCCGGCGGTGGAGGTTCTGGTGGTGGGGCAGTGGG
S	CCGTGAGTCTTCTCTTCTCCCCCAAAACCCAAAG	GGTGGCGGATCAGGAATTGACGAGGACTACTTTGGAAAG
E	GACACCCCTCATGATCTCCCGGACCCCGAGGTC	CTGGAGAGCAAGCTGAGCGTGATCAGGAACCTGAACGAT
-	ACATGGGTGGTGGTGGACGTGAGCCACGAAGAC	CAGGTGCTGTTTCATCGATCAGGAAACAGGGCTCTGTTT
7	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC	GAGGACATGACAGACAGCGCTCAGGGACACACGCCCC
5	GTGGAGGTGCATATATGCCAAGACAAAGCCGGG	AGAACCATCTTCATCATCTCCATGTACAGGACTCCAG
6	GAGGACAGTACACAGCACGTACCGTGTGTC	CCCAGGGGAATGGCCGTTACAAATTCGGTGAAGTGGAG
	AGCGTCTCACCCGTCCTGCACCCAGCACTGGCTG	AAGATCTCCACACTGAGCCTGAGAACACAGATCATCTCC
	AATGGCAAGGAGTACAAAGTCAAGTCTCCAAC	TTCAAGGAGATGAACCCCCCGCACACATCAAGGACAAC
	AAAGCCCTCCAGCCCCCATCGAGAAAACCATC	AAATCCGACATCATCTTCTCCAGCGTCCGTCGCCGGG
	TCCAAGCCAAAGGGCAGCCCCCGAGAACCAACAG	CATGATAACAGATGCAGTTCGAAAGCTCTCTCTACGAA
	GTGTACACCTGCCCCCATCCCGGGAGGAGATG	GGCTACTTCTCTCGCCGTCGAAAGGAAGAGGACCTGTTC
	ACCAGAACCCAGTCAAGCCTGAGCTGCGGCGCTC	AAGCTCATCTCTCAAGAAGAGGACGAGCTGGGGACAGA
	AAAGGCTTCTATCCAGCGACATCGCCGTGGAG	AGCATCATGTTCAACCGTGCAGAACGAAGACGAACCTAAA
	TGGGAGAGCAATGGCAGCCCGGAGAACAACTAC	TCTCCGACAAAACTCACACATGCCCCACCGTGCACGAA
	AAGACCAAGCCTCCCGTCTGGACTCCGACGGC	CCTGAACCTCTGGGGGACCGTCAGTCTTCTCTCTCCCC
	TCCTTCTTCTCTGAGCAAGTCAACCGTGGAC	CCAAAACCCAGGACACCCCTCATGATCTCCCGACCCCC
	AAGAGCAGGTGGCAGCAGGGGAACCTCTCTCA	GAGGTACATGCTGGTGGTGGTGGACGTGAGCCAGGAGAC
	TGCTCCGCTGATGCATGAGGCTCTGCACAAACCG	CGTGAGGTCAAGTCAACTGTTACGTGGACGGCGGTGGAG
	TTACCGCAGAGAGCCTCTCCCTGTCTCCCGGTT	GTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTAC
	AAA (SEQ ID NO:114)	AACAGCACTGCTGCTGCTGCTGCTGCTGCTGCTGCTG
		CACGAGGACTGGTGAATGGCAAGGAGTACAGTGCAG
		GTCTCCAAACAAAGCCCTCCCGAGCCCCCATCGAGAAAC

		ATCTCCAAAGCCAAAGGCGAGCCCGAGAACACACAGGTG TACACCCCTGCCCCCATCCCGGGAGAGATGACCAAGAAC CAGGTACGCTGTGTGCTGGTCAAGAGGCTTCTATCCC AGCGACATCGCCGCTGGAGTGGGAGAGCAATGGGCAGCGG GAGAACAACTACAAGACCACGCTCCCGTGTGTGACTCC GACGGCTCCTTCTTCTCTACAGCAAGTCAACCGTGGAC AAGAGCAGGTGGCAGCGGGGAACGTCTTCTCATGCTCC GTGATGCAATGAGGCTCTGCACACCACTACACGACAGAAG AGCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:170)	
F U S E - 7 5 7	GAGCCCAATCTTCTGACAAAACATCACACATGC CCACCGTGCCCCAGCACTGAATCTCTGGGGGA CCGTGAGTCTTCTCTTCCCCCAAAACCCAAAG GACACCTCAATGATCTCCCGGACCCCGAGGTC ACATGGTGGTGGTGGACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGGTGGACGGC GTGGAGGTGCATTAATGCCAAGACAAAGCCGGG GAGGACAGTACACAGCACGATACCGTGTGTC AGCGTCTCACCGTCTGTGACCCAGACTGGCTG AATGGCAAGGAGTAAAGTGCAGGTCTCCAAC AAAGCCTCCAGCCCCCATCGAGAAAACCATC TCCAAGCCAAAGGGCAGCCCCGAGAACCAAG GTGTACACCTGCCCCCATCCCGGGAGGAGATG ACCAGAACCCAGTCAAGCTGAGCTGGCGCTC AAAGGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGCAGCCCGGAGAACAACTAC AAGACCAACGCTCCCGTGTGCACTCCGACGGC TCCTTCTTCTCTGTGAGCAAGTCAACGTGGAC AAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA TGCTCCGTGATGATGAGGCTCTGCACAAACCGG TTACGCGCAGAGAGCCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	GGTGGAGGAGGTCTGTGAGGTGGTGGATCAGGAATTGAG CAGGACTACTTTGGAAGCTGGAGAGCAAGCTGAGCGTG ATCAGGAACCTGAACGATCAGGTCTGTTCATCGATCAG GGAAACAGGCTCTGTGTGAGGACATGACAGACAGCGAC GTCAAGGACAAAGCACCCAGAACCATCTTCATCATCTCC ATGTACAAGGACTCCAGCCAGGGGAATGGCCGTTACA ATTTCCGTGAATGTGGAGAGATCTCCACACTGAGCGTG GAGAACAGATCATCTCTTCAAGGAGATGAACCCGCC GACAACTCAAGGACACCAATCCGACATCATCTTCTTC CAGCGCTCCGTGCCCGGCATGATACACAGATGCACTTC GAAAGCTCTCTACGAAGGCTACTTCTCGCCGTGAA AAGGAAGGACCTGTTCAGCTCATCTCAAGAGGAG GACGAGCTGGGGACAGAGCATCATGTTCACCGTGCAG AAGGAAGCAACCTAAATCTCCGACAAAACTCACACA TGCCACCGTGGCCAGCACCTGAACCTCTGGGGGACCG TCAGTCTTCTCTTCCCCCAAAACCCAGGACACCTC ATGATCTCCCGAACCCCGAGGTACATGGGTGGTGGTG GACGTGAGCCACGAAGACCTGAGGTCAAGTTCAACTGG TACGTGGACGGCTGGAGTGCATATATGCCAAGACAAAG CCCGGGGAGGAGTACACAGCACGATACCGTGTGGTC AGCGTCTCACCGTCTTGCACACGAGGACTGGTGAATGGC AAGGAGTACAGTGCAGGCTCTCCCAACAAGCCCTCCA GCCCCATCGAGAAAACCATCTCCAAGCCAAAGGCGAG CCCCGAGAACACAGGTGTACACCTGCCCCCATCCCGG	

		GAGGAGATGACCAAGAACCCAGGTCAGCCTGTGGTGCCTG GTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGG GAGAGCAATGGGCAGCCGGAGAACAACTACAGAACCAAG CCTCCCGTGTGACTCCGACGCTCCTTCTTCTCTCTAC AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG AAGCTTCTCTCATGCTCCGTGATGCATGAGGCTCTGCAC AACCACACAGCAGAGAGCCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:171)	
F	GAGCCAAATCTTCTGACAAAACCTCACACATGC	TTCCAGGCTCGTCTTGTGGGGCTGCTGCTACTATTGAG	
U	CCACCGTCCCAGCACTGAACCTCTGGGGGA	CAGACTACTTTGGGAAGCTGAGAGCAAGTTGAGCGTT	
S	CCGTGAGTCTTCTCTTCCCTCCCAAAACCCAAAG	ATTAGAAATCTGAACGACCAGCTTTGTTTATCGACCAG	
E	GACACCTCATGATCTCCCGGACCCCGGAGGTC	GGGAACCGTCTTTGTTTGGAGACATGACAGACAGGAC	
-	ACATCGGTGTTGGTGGACGTGAGCCACGAAGAC	GTCAAGGACACGCTCCAAGGACAATCTTCTATCATCTCC	
7	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC	ATGTACAAGGACTCCAGCCAGGGGAATGCCCGTTACA	
5	GTGAGGTGCATATGCCAAGACAAAGCCCGGG	ATCAGCGTGAAGTGGAGAAATCAGCACACTGAGCGTG	
8	GAGGACAGTACACAGCACGTACCGTGTGGTC	GACAACAATCATCATCAGCTTCAAGCAATGAACCCCCC	
	AGGTCTCTCAACGTCCTGCACCCAGGACTGGCTG	GACAACATCAGGACACCAATCCGACATCATCTTTTTC	
	AATGCCAAGGAGTACAAGTGCAGGTCTCCAAC	CAGAGGAGTGTCCCGGACACGACACAAATGCAGTTC	
	AAAGCCCTCCAGCCCCATCGAGAAAACCATC	GAATCCAGCTCTACGAGGGTACTTCTCTGGCCGTCGAA	
	TCCAAAGCCAAAGGGCAGCCCCGAGAACCCACAG	AAGAAAGGGACCTGTTCAAGCTGATCTGAGAAAGGAG	
	GTGTACACCCCTGCCCCCATCCCGGAGGAGATG	GATGAGCTGGGGACAGGTCATCATGTTCAACGTGCAG	
	ACCAGAACCCAGTCAAGCTGAGCTGGCCGCTC	AACGAGGACGAACCTAATCTCCGACACAAACTCACACA	
	AAAGCTTCTATCCAGCGACATCCCGTGGAG	TGCCCAACGTTGCCAGCACTGAACTCTCTGGGGGACCG	
	TGGGAGAGCAATGGGCAGCCCGGAGAACAACTAC	TCAGTCTTCTCTTCCCCCAAAACCCAGGACACCCCTC	
	AAGACCAACGCTCCCGTGTGGACTCCGACGGC	ATGATCTCCCGACCCCGAGGTCACATGCGTGGTGGTG	
	TCCTTCTTCTCTGTGAGCAAGCTCACCGTGGAC	GACGTGAGCCACGAAGACCCCTGAGGTCAAGTTCAACTGG	
	AAGACAGGTGGCAGCAGGGGAGCTTCTCTCA	TACGTGGACGGCTGGAGTGCATATGCCAAGACAAAG	
	TGCTCCGTGATGCATGAGGCTCTGCACAAACCGG	CCCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC	
	TTTACGACAGAGAGCCTCTCCCTGTCTCCCGGT	AGCGTCTCAACGCTCTGCACAGGACTGGGTGAATGGC	
	AAA (SEQ ID NO:114)	AAGGAGTACAAGTGCAGGTCCTCCCAACAAAGCCCTCCCA	
		GCCTCCATCGAGAAACCAATCTCCAAAGCCAAAGGGCAG	
		CCCCGAGAACCCAGGTGTACACCTGCCCCCATCCCGG	
		GAGGAGATGACCAAGAACCCAGGTCAAGCTGTGGTGCCTG	
		GTCAAAGGCTTCTATCCAGGACATCGCCGTGGAGTGG	
		GAGAGCAATGGCAGCCCGGAGAACAACTACAGAACCAAG	
		CCTCCCGTGTGAGCTCCGACGGCTCTTCTCTCTCTAC	
		AGCAAGCTCACCGTGGACAACAGCAGGTGGCAGCAGGGG	

		AACGCTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC AACCACTACAGCAGAGAGCCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:172)	
F	GAGCCAAATCTTGACAAAACTCACACATGC	GAAGTCAGCTGCTGGAGAGCGGAGGAGATTGGTCAG	
U	CCACGTCGCCAGCACCTGAACCTCTGGGGGA	GGAGGAGGAAGCCTGAGCTGAGTTGTCCGCTAGTGG	
S	CGTCAGTCTTCTCTCTCCGCCCAAACCCAAAG	AGCACATTTAGTTCCTATGCAATGGGGTGGTTCAGGCAG	
E	GACACCTCATGATCTCCCGGACCCCGGAGGTC	GGCCAGGAAGAAAGAGGATTTGTGGTGCCCATCAAC	
-	ACATGGGTGGTGGACGTGAGCCACGAAGAC	TGGAGTAGCGGATCTACATACTACGCTGATTCTGTGAAG	
7	CCTGAGCTCAAGTTCAACTGCTACCTGGACGGC	GGCAGGTTCAACATCAGCCGCGACAAATGCTAACAACACC	
7	GTGGAGGTGCATAATGCCAAGACAAGCCGGG	ATGTACCTGCAGATGCTCCTCAAGCCTGAAGATACT	
5	GAGGACAGTACAAAGACACGTACCGTGTGGTC	GGTGTACTACTGCGCGCGCGCTATCAGATCAATTCC	
	AGCGTCTCACCGTCTGTCACACGAGACTGGCTG	GGAAACTACAACCTTCAAAGATTACGAGTATGACTACTGG	
	AATGGCAAGGATACAAAGTGCAGGTCTCCAAC	GGCCAGGTTACCCAGGTGACAGTGAGTTCGGAACCTAAA	
	AAAGCCCTCCAGCCGCCATCGAGAAAAACCATC	TCTCCGACAAAACTCACACATGCCACCGTGCCAGCA	
	TCCAAGCCCAAAGGCAGCCCGGAGAACCCACAG	CCTGAACCTCTGGGGGACCGTCAGTCTTCTCTTCCOC	
	GTGTACACCTGCCCCCATCCCGGAGGAGATG	CCAAACCCAAAGACACCCCTCATGATCTCCCGACCCCC	
	ACCAAGAACCCAGGTCAGCCTGAGCTGGCGCGTC	GAGTTCACATGCTGTGGTGGACGTGAGCCACGAAGAC	
	AAAGCTTCTATCCAGCGACATCGCCGTGGAG	CCTGAGTCAAGTTCAACTGCTGACGTGGACGGGTGGAG	
	TGGGAGAGCAATGGGCAGCCCGGAGAACAACTAC	GTGCATAATGCCAAGACAAAGCCGCGGAGGAGCAGTAC	
	AAGACACGCCCTCCGTGCTGGACTCCGACGGC	AACAGCAGTACCGTGTGGTACGCTCTCACCGTCTCTG	
	TCCTTCTTCTCGTGAGCAAGCTCAACCGTGGAC	CACAGGACTGGGTGAATGGCAAGGAGTACAAGTGCAG	
	AAGACAGGTGGACAGGGGAACTCTTCTCA	GTCTCCAACAAGCCCTCCAGCCCCCATCGAGAAACC	
	TGCTCGGTGATGCATGAGGCTCTGCACAACCGG	ATCTCCAAGCCAAAGGCGAGCCCGAGAACCCACAGGTG	
	TTCACGCAGAGAGCCTCTCCCTGTCTCCGGGT	TACACCTTGCCCCCATCCCGGAGGAGATGACCAAGAAC	
	AAA (SEQ ID NO:114)	CAGGTCAGCCTGTGGTGCCTGGTCAAAGGCTTCTATCCC	
		AGGACATCGCCGTGGAGTGGAGAGCAATGGGCAGCCG	
		GAGAACAATAAGAACCCAGCCTCCCGTGTGGACTCC	
		GACGGTCTCTTCTCTCTACAGCAAGCTCACCGTGGAC	
		AAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCC	
		GTGATGCATGAGGCTCTGCACAACCACTACAGGCAGAAG	
		AGCCTCTCCCTGTCTCCGGTAAAGCTGCTGAACCTGTG	
		GAAGATAATGTGATCAATTTGTGGCCCATGAATTTATT	
		GACAACACCCCTGTATTTCAATCCCGGAAACGATGAAAC	
		GGCGGAGGATCTTATTTTGGAAAGCTGGAATCCAAATTG	
		AGCGTGATCAGGAACCTGAACGATCAGGTGCTGTTTATC	
		GACCAGGGCAACAGGCCCTGTTCGAGGATATGACCGGAC	
		AGTGACGTGAGGACACACGCTCCCGGAACCATCTTCATC	

	ATCAGTAAGTATGGAGACTCCAGCCCAAGGGACTGGCC GTTACAATTAGCGTAAAGTCGAGAAGATTTCACATTG AGCGTGGAGACAAGATCACTCTCTTCAAGGAGATGAAC CCCCCGACAAACATTAAGGACACCAAAAGCGATATCATC TTCTTCCAGAGTCCTGCTGGCACGACATAAAGTG CAGTTCGAGTCCAGTCTCTACAGGGCTACTTCTGGCA GTGGAGAAGAAAGGACCTGTTCAAGCTGATCCTGAAG AAGGAGGACGAGTGGGGACAGGTCCATCATGTTCACC GTCCAGAATGAGGAC (SEQ ID NO:173)	ATCAGTAAGTATGGAGACTCCAGCCCAAGGGACTGGCC GTTACAATTAGCGTAAAGTCGAGAAGATTTCACATTG AGCGTGGAGACAAGATCACTCTCTTCAAGGAGATGAAC CCCCCGACAAACATTAAGGACACCAAAAGCGATATCATC TTCTTCCAGAGTCCTGCTGGCACGACATAAAGTG CAGTTCGAGTCCAGTCTCTACAGGGCTACTTCTGGCA GTGGAGAAGAAAGGACCTGTTCAAGCTGATCCTGAAG AAGGAGGACGAGTGGGGACAGGTCCATCATGTTCACC GTCCAGAATGAGGAC (SEQ ID NO:173)
F	CAGGTTCAAGTCTGAGTCAAGCGGAGGAGTCTCAA	CAGGTTCAAGTCTGAGTCAAGCGGAGGAGTCTCAA
U	GTTCAGCCAGGAAGATCCCTCAGGCTCGACTGT	CCAGGAAGAAAGCTCAGACTCGACTGCAAGCAAGCGC
S	AAGGCTCCGGAATCAGCTTCTCCAACTCCGGA	ATCACCTTCAGCAACAGCGGAAATGCACTGGGTGAGACAA
E	ATGCACTGGTCAAGCAGGCTCCTGGAAAGGA	GCCCCGAAAGGCCCTGGAGTGGTTCCTGTGATTTGG
-	CTGGAGTGGTGGCTGTGATTTGGTACGACGGC	TACGAGGGCAGCAAAAGATATTACGCCGACAGTGTGAAA
7	TCCAGAGATACTACGCCGACTCTGTGAAGGC	GGCAGATTTACAATCTCAAGGCACAACAGCAGAACACA
8	CGTTCACTATCTCCAGGGACAACCTCCAAAGAAC	CTCTTCTCAGATGACAGGCTCAGAGCCGACGATACT
2	ACACTGTTCTGCAGATGAGCAGTTTGAGGGCC	GGAGTGTATTACTGCGCCACCAAGCAAGCACTACTGGGA
	GAGGACACCGCTGTTTACTACTACGCGCAACCAAC	CAAGGAAACCTTGGTACCGTGAAGTAGCGCTAGCACCAAG
	GATGACTACTGGGGCAGGGAACCTGGTTACA	GGCCCATCGGTCTTCCCTCGCACCTCTCTCAAGAGC
	GTGAGTAGCGCTAGCACCAAGGGCCATCGGTC	ACCTCTGGGGCAGCAGCGGCTGGCTGCTGCTCAAG
	TTCCCTCTGGACCTCTCTCCAAAGACAACCTCT	GACTACTTCCCGAAACCGTGAAGGTGCTGTGGAACCTCA
	GGGGCACAGCGGCCCTGGCTGCTGCTGCTCAAG	GGCGCCTGACAGCGCGCTGCACACCTTCCCGCTGTC
	GACTACTTCCCGGAACCGTGACGCTGTGTGTG	CTACAGTCTCTCAGGACTCTACTCTCTCAGCAGCGTGTG
	AACTCAGGGCCCTGACCAAGCGGCTGCACACC	ACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATC
	TTCCGGCTGTCTTACAGTCTCTCAGGACTCTAC	TGCAACGTGAATCACAAAGCCAGCAACCAAGGTGGAC
	TCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGC	AGAAAGTTGAGCCCAAATCTTGTGACAAATCACACA
	AGCTTGGGCACCCAGACCTACATCTGCAACGTG	TGCCCCACCGTGGCCAGCACTGAAGCCGAGGGGACCG
	AATCACAAGCCCCAGCAACACCAAGGTGGACAAG	TCAGTCTTCTCTTCTCCCCCAAAACCAAGCACCCCTC
	AAAGTTGAGCCCCAATCTTGTGACAAAACCTCAC	ATCATCTCCCGACCCCGAGGTCCATGCGTGGTGTG
	ACATGCCCCACCGTGCCAGCACTGAAGCCGCA	GAGGTGAGCCAGAAAGACCCCTGAGTCAAGTTCAACTGG
	GGGGACCGTCAGTCTTCTCTTCCCCCCCCAAA	TAGGTGAGCGGCTGGAGTGGATTAATGCCAAGACAAAG
	CCCAGGACACCCCTCATGATCTCTCGGACCCCC	CCCGGGAGGAGCAGTACAACAGCACGTACCGTGTGCTC
	GAGTCACATGCGTGGTGGTGAACCTGAGCCAC	AGCGTCTCAACCTCTCTGACACAGGACTGGCTGAATGSC
	GAAGACCTGAGGTCAAGTTCACACTGGTACGTG	AAGGAGTACAAGTCAAGTCTCCCAACAAAGCCCTCCCA
	GACGGCTGGAGGTGCATTAATGCCAAGACAAAG	GGCCCCATCGAATAAACCATCTCCAAAGCCAAAGGGCAG
	CCGGGGAGGAGTACACAGCAGCTACCGT	CCCGGAGAACACAGGTGTACACCTTGCCCCCATCCCCGG
	GTGTACGCTCTCAACCGTCTCTGACCCAGGAC	GAGGAGATGACCAAGAACCAAGTCAAGCTCAGCTGTGGTGCCTG

	TGGCTGAATGGCAAGGAGTACAAGTGAAGGTC TCCAAACAAGCCCTCCAGAGCCCATCGAGAAA ACCHTCTCCAAAGCCAAAGGGCAGCCCGAGAA CCACAGGTGTACACCCCTGCCCCCATCCCGGGAG GAGATGACCAAGAACAGGTGAGCTGAGCTGC GCCGTCAAAGGCTTCTATCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGAGCGCGGAGAAC AATACAGACACCGCTCCCGTGTCTGGACTCC GACGGCTCCTTCTCTCTCGTGGAGAGCTCAAC GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC TTCTCATGTCTCCGTGATGATGAGCTCTGAC AACAGGTTCACGCAAGAGCCCTCTCCCTGTCT CCGGGTAAA (SEQ ID NO:131)	GTCAAAGGCTTCTATCCAGGACATCGCCGTGGAGTGG GAGAGCAATGGGAGCCGGAGAACAACTACAGACCAAG CCTCCCGTGTGGACTCCGACGGCTCCTTCTCTCTAC AGCAAGCTCACCGTGGACAAGAGCAGGTGGAGCAGGG AACGCTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC AACCTACACAGAGAGAGGCTCTCCCTGTCTCCGGGT GGTGGCGGAGGCTCTGGTGGAGGATCCGGGGGAGGA GGTTCAGGAGCGGGGAGTGTCTGAACCTGTGGAA GATAATTTCTAATACTTCGTGGCCATGAAGTTCATCGAT AACTACTGTGACTTCATCGCCGAAACGATGAGAACGGA GGAGGATCTTACTTTGGAAAACGTGGAAAGCAAGCTGAGC GTGATCCGGAACCTGAACGATCAAGTGTCTGTTTATCGAC CAGGCAACAGGCCCTGTTCGAGGATATGACCGACAGC GACAGCAGGACAAAGCTCTCTAGAACAATCTTCATCATC TCCAAGTACGGGACAGCCAGCCAGAGGACTGGCTGTG AOCATAAGCGTGAAGAGAGAAAATAGCACCCCTGAGC AGCAGACAACAGATCATATCTCTCAAAGAGATGAACCCC CCCGACAACATTAAGACACCCAAAGCGATATCATCTTC TTCCAGAGAGGCTGCCCGCCACGATAACAAAGTGCAA TTCCGAAAGCAGAGCTACGAGGCTACTTCCCTGGCTTCC GAAAAGGAGAGGACCTGTTCAGCTGATCCTGTGAAGAAG GAGGACGAGCTGGGGACAGATCAATAATGTTCAACCGTG CAGAAGGAGGAC (SEQ ID NO:174)	AGCTTCAACAGGGAGAGTGT (SEQ ID NO:188)
F U S E - 7 8 3	CAGGTTCAAGTCTGTGAAAGCGGAGGAGGATC GTTCAAGCCAGGAAGATCCCTCAGGCTCGACTGT AAGGCTCCGGAATCAGCTTCTCCAACTCCGGA ATGCACTGGGTCAGGAGGCTCCTGGAAAGGA CTGGAGTGGTGGCTGTGATTTGGTACGACGGC TCCAGAGATATCTACGCCGACTCTGTGAAGGGC CGGTTCACTATCTCCAGGACAACTCCAGAAC ACACTGTTCTCTGAGATGAGCAGTTTGAGGGCC GAGGACACCGCTGTTTACTACGTGCAACCAAC GATGACTACTGGGGCAGGGAACCTGGTTACA GTGAGTAGCGCTAGCACCAAGGGCCATCGGTC TTCCCCCTGGCACCTCTCTCCAGAGCACTCT GGGGCACAGGGCCCTGGGCTGCTGGTCAAG GACTACTTCCCGAACCGGTGACGCTGTGGTGG	CAGGTTCAAGTCTGTGAGTCAAGCGGAGGAGTGTCAA CCAGGAAGAAGCTCAGACTCGACTGCAAGCAAGCGGC ATCAGCTTCAGCAACAGCGGAATGCATGGGTGAGACAA GCCCTGGAAGAAGGCTGGAGTGGGTGTCTGTGATTGG TACGACGGCAGCAAAAGATATTACGCCGACAGTGTGAAA GGCAGATTTACAAATCTCAAGGACACACAGCAAGAACACA CTGTTCTCTGAGATGAGCAGCTGAGAGCCGAGGATACT GAGTGTATTACTGGCCCAACAGCAAGACTACTGGGGA CAGGAACCCCTGGTGAACCTGAGTAGCGTACGACCAAG GGCCATCGGTCTTCCCTCCCTGCCAACCCTCTCCAGAGC ACCTCTGGGGCAGCAGCGCCCTGGGTGCTGTGGTCAAG GACTACTTCCCGAACCCGTTGAGGCTGTCTGGAACTCA GGGCCCTGACAGCGGGGTGACACCTCTCCCGGCTGTG CTACAGTCTCTCAGGACTCTACTCCCTCAGCAGGCTGTG	GAAATCGTGTGACCCAGTCCC CGCTACCTTGAGTCTGTCCCCTG GAGAGAGACCAACCCTGTCTGT AGGGCTAGTCACTCCGTGAGCAG CTATCTGGCCCTGGTATCAGCAGA AGCCCGGCCAGGCTCCTAGGTTG TTGATTTACGATGCCCTCCAACAG AGCCACCGGAATCCCTGCAAGGT TCTCCGGTTCGGTTCGTGTACA GACTTCACCCCTGACTATCAGCAG TCTGGAGCCGAGGATTTCCGCCG TTTACTACTGCCAGCAGTCTCTCC AACTGGCCAGGACATTCGGTCA GGGCAACCAAGGTGGAGATCAAGC

AATCAGGCGCCCTGACCAAGCGGGTGCACACC TTCCGGGTGTCTACAGTCCACAGGACTCTAC TCCCTCAGCAGCGTGGTGAOCCTGACCTCCAGC AGCTTGGGCAOCCAGACCTACATCTGCAACGTG AATCACAAGCCCAAGCAACACCAAGTGGACAAG AAAGTTAGCCCAATCTTGTGACAAAATCTCAC ACATGCCCAOCCGTCAGCACTTGAAGCCGCA GGGGACCGTCACTCTCTCTTCCOCCCAAAA CCCAAGGACACCCCTCATGATCTCCCGAACCCO GAGTCAACATGCGTGGTGGAGCGAGCCAC GAAGCCCTGAGGTCAAGTTCAACTGGTACGTG GACGGGTGGAGTGCATAATGCCAAGACAAAG CCCGGGAGGAGCAGTACACAGCAGCTACCGT GTGFTCAGCGTCTCTACCGTCTCTGCAACGAGC TGGTGAATGGCAAGGAGTCAAGTGCACAGGTC TCCAAACAAGCCCTCCAGCCOCCATCGAGAAA ACCTCTCCAAAGCCAAAGGCGAGCCCGGAGAA CCACAGGTGTACACCTGCCOCCCATCCCGGGAG GAGATGACCAAGAACAGGTCAAGCTGAGCTGC GCCGTCAAAGGCTTCTATCCAGCGACATCGOC GTGGAGTGGAGAGCAATGGCGAGCCGGAGAAC AACTACAAGACCAAGCTCCCGTCTGGACTCC GACGGTCTCTCTCTCTGAGCAAGCTCAAC GTGGACAAGAGCAGGTGGCAGCAGGGGACGTC TTCTCATGCTCCGTGATGCATGAGGCTCTGCAC AAGAGTTCAAGCAAGAGCCCTCTCCCTGTCT CCGGGTAAA (SEQ ID NO:131)	AGCGTGCCCTCCAGCAGCTTGGCACCCAGACCTACATC TCCAAAGTGAATCACAAGCCAGCAACACCAAGGTGGAC AAGAAAGTTGACCCCAAATCTTGTGACAAAATCACACA TGCCCAOCCGTGCCAGCACCTGAAGCCGAGGGGACCG TCAGTCTTCTCTCTCCOCCCAAAACCCAGCACACCTC ATGATCTCCCGAACCCCGAGTTCACATGCGTGGTGTG GAGCTGAGCCAGCAGACCTCAGGTCAAGTTCAACTGG TACGTGGACGGCGTGGAGTGCATATGCCAAGACAAAG CCCGGGAGGAGCAGTACAACAGCACGTACCGTGTGTC AGCTCTCTACCGTCTGCAACAGGACTGGTGAATGGC AAGAGTACAAGTCAAGTCAAGTCTCCAAACAAGCCCTCCCA GCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG CCCGAGAACCAAGTGTACACCTGCCOCCATCCCGG GAGGAGATGACCAAGAACCCAGTCAAGCTGTGTTGCCGTG GTCAAAGGCTTCTATCCAGCGACATCGCGTGGAGTGG GAGACCAATGGCAGCCCGAGCAACAACCTACAAGACCACG CTTCCGTGCTGGACTCCGACGGTCTCTCTCTCTCTCTAC AGCAAGTCAACCGTGGACCAAGCAGGTGGCAGCAGGGG AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC AACCACTACAGCAGAAAGAGCTCTCCCTGTCTCCGGGT GGTGGCGGAGGTCTGTGTGGAGGATCCGGGGGAGGA GGTTCAGGAGCGGGGAGAGTCTGTGAOCTGTGGAA GATAATGTGATAAACTCTCTGCGCATGAAGTTCATGAC AATACCTGTATTTCTATGCGCGAGATGATGAAAACGGA GGAGGATCTTACTTCGGAACAACTGGAAAGCAAACTGAGC GTGATAAGAAACCTGAACGATCAAGTGTGTCTCATCGAC CAGGCAACCCCTCTGTTCGAAGATATGACCGACAGC GACGTGAGGACCAACGCTCTTAGAACATCTTCATCATC AGCAATAGCGGACTCCAGCCAGGGGACTGGCTGTG ACCATCAGCGTGAAGTGGAGAGATAAGCACACTGAGC GTGGAGAACAGATCATCTTTTAAAGGATGAACCCC CCCGACAACATCAAGACACCAAAAGCGATATCATCTTC TTCCAGAGAAGCGTCCCTGGCAGCAGCAACAAGTGCAG TTCCAGTCAAGCAGCTACGAGGCTACTTCTCTCGCCGT GAAAGCAAGACACTTGTCAAGCTGATCTCTGAAGAAG GAGGACGAGCTGGGGACAGAGCATAATGTTACCCGTT CAGACGAGGAC (SEQ ID NO:175)	GTACGGTGGTGCACCATCTGTCTC TTCATCTTCCCGCCATCTGATGA GCAGTTGAAATCTGGAATGCTCT CTGTTGTGCTGCTGCTGAATAAC TTCATCCAGAGAGGCCAAAGT ACAGTGGAAAGTGGATACCGCC TCCATCGGGTAACTCCAGGAG AGTGTCAACAGCAGGACAGCA GGACAGCACTACAGCTCAGCA GCACCCCTGAGCTGAGCAAGCA GACTACGAGAAACACAAAGTCTA CGCTGCGAAGTCAACCATCAGG GCCTGAGTTCGCCCCGTCAAAAG AGCTTCAACAGGGGAGAGTGT (SEQ ID NO:188)
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F	GAGCCCAAAATCTAGCGACAAAACCTACACATGC	GAGCCTAAAAGAGCGGACAAGACCCACACCTGCCCCCT
U	CCACCGTGCCCGAGCACTGAAGCCGAGGGGGA	TGCCCCGCTCTGAAGCTGCTGGAGGCCCCCTCAGTGTTC
S	CCGTCAGTCTTCTCTTCCCCCAAAACCCAAAG	CTGTTTCTCCCAAGCCCAAGACACACIGATGATTTCC
E	GACACCCCTCATGATCTCCCGGACCCCGAGETC	AGAAACCCCGAGTGACATGCTGTGTGTGTGACGTGAGC
-	ACATGGTGTGTGTGGACGTGAGCCACGAAGAC	CACGAAGATCCGAGGTGAAGTTAATTGGTACGTGGAC
8	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC	GGCGTGAAGTGCACAAACGCCAAGACCAAACCCCGGAG
7	GTGGAGGTGCATATATGCCAAGACAAGCCGCGG	GGCAGTATATATAGACACCTCAGAGTGGTGTGAGCGTGTG
2	GAGGAGCAGTACAACAGCACGTACCGTGTGGTC	ACCGTGTCTCAGTACAGGATGGCTGAACGGCAGGAATAC
7	AGCGTCTCACCGTCCGTGCAACAGACTGGCTG	AAATGCAAGTGAACAACAAGCCCTGCTGCCCTATC
	AAUGGCAAGGAGTACAAGTGCAGGTCTCCAAC	GAGAAGACCAATCAGCAAAAGCCAAGGGACAGCCAAGAGAA
	AAAGCCCTCCAGCCCCATCGAGAAAACCATC	CCCCAGGTGTACACCTTGCCCCCAGCAGAGAAGAAATG
	TCCAAGCCCAAGGGCAGCCCCGGGAAACCAAG	AGCAAGAACCCAGGTGAGCTGTGTGGTGCCTGGTGAAGGC
	GTGTACACCTGCCCCCATCCCGGGAGGAGATG	TTCTACCCCAGGACATCGCCCTGGAGTGGGAGAGCAAC
	ACCAGAACCAGGTCAGCCTGAGCTGCGCGGTC	GGCCAGCCAGAGAAACAATAAGACAAACACCCCCGCTG
	AAAGGCTTCTATCCAGCGACATCGCCGTGGAG	CTGGACAGCGAGGCTCTTTCTCTCTGTACAGTAAACTG
	TGGGAGAGCAATGGCGAGCCCGGAGAAACAATAC	ACCGTGGACAATCAAGTGGCGAGCAGGCAACGCTGTTTC
	AAGACCAACGCTCCCGTGTCTGGACTCCGACGGC	AGCTGTCCGGTGAACGACAGAGGCCCTGCACACCACTAT
	TCTTCTTCTCTGTGAGCAAGCTACCGTGGAC	ACCCAGAAAGGCTGTCCCTGAGCCCCGGCAGCGAGGA
	AAGAGCAGGTGGCGAGGGGGAAGCTTCTCTCA	GGAGGAGCTGTGAACCTGTGGAAAGATAATTCTATTAAAC
	TGTCGGGTGATGATGAGGCTCTGCAACAACCGG	TTCTGTGGCCATGAAGTTTCATCGATATAACTCTGTACTTC
	TTACCGCAGAAAGCCCTCTCCCTGTCTCCGGGT	ATCGCCGAAAACGATGAGAACGGAGGAGGATCTTACTTT
	AAA (SEQ ID NO:132)	GGAAAACTGGAAGCAAGCTGAGCGTGATCCGGAACTTG
		AACGATCAAGTCTGTTTATCGACCAAGGCAACAGGCC
		CTGTTGAGGATATGACCGACAGCGACAGCGAGGCAAC
		GCTCCTAGAACAAATCTTCATCATCTCCAAGTACGGCGAC
		AGCCAGCCCGAGGACTGGCTGTGACCATAGCGTGAAA
		AGCGAGAAAATTAGCAACCTGAGCAGCGAGAGACAAGATC
		ATATCCTTCAACAGATGAACCCCGACACATTAATAA
		GACACCAAAAGCGATATCATCTTCTTCCAGAGAAGCGTG
		CCCGCCCAAGATAACAAAGTGCATTCGAATTCGAAGCAGC
		TACGAGGGCTACTTCCCTGGCTTCCGAAAAGGAGAGGGAC
		CTGTTCAAGCTGATCCTGAAGAGGAGGACGAGCTGGGG
		GACAGATCAATAATGTTTCAACCGTGCAGAACGAGGAC
		(SEQ ID NO:176)
F	GAGCCCAAAATCTTGTGACAAAACCTACACATGC	TCCTACTTCGGCAAGCTCGAATCCAAGCTTCGGTCAATC
U	CCACCGTGCCCGAGCACTGAACCTCTGGGGGA	CCGAACCTCAACGACCAAGTCTCTTTATCGACCAAGGC
S	CCGTCAGTCTTCTCTTCCCCCAAAACCCAAAG	AACCGCCCTCTCTTCGAGATATGACCGACTCCGACGTC

E	GACACCTCATGATCTCCCGACCCCGAGGTC	CGGACACAGCTCCTAGGACCATTTTCATCATCTCCATG
-	ACATGGGTGGTGGACGTGAGCCACGAAGAC	TACAAGGACTCCAGCCCGGTGGAATGGCTTTACAAAT
8	CTTGAGGTCAAGTCAACTGGTAGTGGACGGC	TTCTGTAAGGTGAGAGAAATCTCCACCCGTCCGTGGAG
7	GTGGAGGTGCATAATGCCAAGACAAAGCCGGG	AACAAGATCATTTCTTTCAAGGAGATGAACCCCGGAC
4	GAGGACAGTACACAGCACGTAACCGTGTGGTC	AACATCAAGGACACCAAGAGGACATCATCTCTCCAG
	AGGTCTCTACCGTCTGCAACGAGACTGGCTG	CGTCCGTGCCCGGACATGATAACAAATGCAATTCGAG
	AATGGCAAGGAGTACAAAGTGCAAGGTCTCCAAC	TTCTCTCTCTAGGAGGCTACTTCTCTGCGAGTCGAAAAG
	AAAGCCCTCCAGCCCCCATCGAGAAAACCATC	GRAAGGACCTGTTCAGTTCATCTTGAAGAGGAGGAC
	TCCAAAGCCAAAGGCGAGCCCGAGAACCCACAG	GAGCTGGTGACAGGTCCATCATGTTCAOCCGCCAGAAC
	GTGTACACCCCTGCCCCCATCCCGGAGGAGATG	GAGGACGAGCTAAATCTCCGACAAAACTCACACATGC
	ACCAGAACCAAGTCAAGCTGAGCTGCGCCGTC	CTACCGTGCCAGCACTGAACCTCTGGGGGACCCGTCA
	AAAGGTCTCTATCCAGCGACATCGCCGTGGAG	GTCTTCTCTTCCCCCAAACCCCAAGGACCCCTCATG
	TGGGAGAGCAATGGGCGAGCCGAGAGAACACTAC	ATCTCCCGGACCCCGAGTCAATGGTGGTGGTGGAC
	AAGACACGCTCCCGTGTGGACTCCGAGCGGC	GTGAGCCACGAAGACCTGAGGTCAAGTTCAACTGGTAC
	TCCTTCTCTCTGAGCAAGCTACCCGTGGAC	GTGGACGGGTGGAGGTGCATATGCCAAGACAAAGCCG
	AAGCAGGTGGTAGCAGGGGAACTCTTCTCA	CGGAGGAGAGTACAAACAGCAAGTACCGTGGTTCAGC
	TGCTCCGTGATGCATGAGGCTCTGCACACACCGG	GTCTTCACTCTCTGCACCAAGACTGGCTGATGGCAAG
	TTTACGCAGAGAGGCTCTCCCTGTCTCCGGGT	GACTACAAGTCAAGGTCTCCAAACAAGCCCTCCAGCC
	AAA (SEQ ID NO:114)	CCCATCGAGAAACCATCTCCAAAGCCAAAGGGCAGCC
		CGAGAACCAAGGTGTACACCTGCCCTGCCCTCCCGGAG
		GGATGACCAAGAACCAAGGTGAGCTGTGGTGGCTGGTC
		AAAGGCTTCTATCCCGAGCATCGCGTGGAGTGGAG
		AGCAATGGGACCGGAGAACCACTACAAGACCAAGCCT
		CCGTGCTGGACTCCGAGCGCTCTCTTCTCTACAGC
		AAGCTACCGTGGACAAAGAGAGGTGGCAGAGGGGAAC
		GTCTTCTCATGTCCGTGATGCATGAGGCTGTGCACAAC
		CACTACACGCAAGAGCCCTCTCCCTGTCTCCGGGTAAA
		(SEQ ID NO:177)

F	GAGCCCAAATCTTCTGACAAAACATCACACATGC	GGAGGAGGAGGAGTACTTCTGGCAAGCTGGAGTCCAAG
U	CCACCGTGCCCAAGCACTGAACCTCTGGGGGA	CTGTCCGTGATCCGGAAACCTGAACGACCAAGTCTGTTC
S	CCGTGAGTCTTCTCTTCCCCCAAAACCAAG	ATCGAACAGGCAACAGGCTCTCTTCGAGGATATGACC
E	GACACCCATCATGATCTCCCGGACCCCGAGGTC	GACTCCGACGTGAGGATACCGTCCAGGACAATCTTC
-	ACATGGTGGTGGTGGACGTGAGCCACGAAGAC	ATCATCTCATGTACAAAGGACTCCAGCCAGGGGAATG
8	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC	GCTTTACAAATTTCCGTGAAGTGGAGAAATCTCCACC
7	GTGGAGTGCATATATGCCAAGACAAGCCGGG	CTGTCCGTGGAAAACAAGATCATCAGTTTCAAAAGAGATG
5	GAGGACAGTACAACAGCACGTAACGTTGTGTC	AACCCCCCGACAACATCAAGACACCAATCCGACATC
	AGGTTCTCACCGTCCGTGCAACAGGACTGGCTG	ATCTTCTTCCAGCGCTCTGTGCCGGCCATGATAACAA
	AATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC	ATCCAGTTGGAAGCTCTCTACGAAGGTACTTCCIG
	AAAGCCCTCCAGCCCCATCGAGAAAACCATC	GGCGTCGAAAAGAAACGCACTCTTCAAGTCAATCCTG
	TCCAAGCCAAAGGCAAGCCCGGAGAACCAAG	AAGAAGGAGGAGAACTGGGGACAGGAGCATCATGTTT
	GTGTACACCTGCCCCATCCCGGAGGAGATG	ACCGTTTCAAGAACGAGACGAGCTAATCTCCGACAAA
	ACCAGAACCAGTCAAGCTGAGTGGCGGTC	ACTCACACATGCCACCGTGGCCAGCACCTGAACTCCIG
	AAAGGTTCTATCCAGCGACATCGCCGTGGAG	GGGGACCGTCACTCTCTCTTCCCCCAAAACCCAAG
	TGGAGAGCAATGGCAGCCCGGAGAACAACTAC	GACACCTTATGATCTCCCGACCCCGAGTCAATGC
	AAGCCACGCTCCCGTCTGGACTCCGACGGC	GTGTGGTGGAGCTGAGCCACGAAGACCTTGAGTTCAAG
	TCTTCTTCTCTGTGAGCAAGTCAACGTGGAC	TTCAACTGTGTACTGGACGGCTGGAGTTGCATTAATGCC
	AAGAGCAGGTGGCAGAGGGGAAGCTTTCTCA	AAGACAAAGCCGGGAGGAGAGTACAACAGCACGTAC
	TGTCGGTGATGATGAGGCTCTGACAAACCGG	CGTGTGTAGGCTCTCACCGTCTGCACAGGACTGG
	TTACGCCAGAGAGCTCTCCCTGTCTCCGGGT	CTGAATGGCAAGAGTACAAGTGCAAGTCTCCAAACAA
	AAA (SEQ ID NO:114)	GGCTCCCAAGCCCAATCGAGAAAACCATCTCCAAAGCC
		AAAGGGCAGCCCGAGAACACAGGTTACACCTGCC
		CCATCCGGGAGGAGATGACCAAGAACCCAGGTCAGCCTG
		TGTTGCCCTGGTCAAGGCTTCTATCCAGGACATCGCC
		GTGGAGTGGGAGACCAATGGGAGCCCGGAGAACAACTAC
		AAGACCACGCTCCCGTCTGGACTCCGACGGTCTCTTC
		TTCTCTACAGCAAGCTCACCGTGGACAAAGACAGGTGG
		CAGCAGGGGAAGTCTTCTCATGCTCCGTGATGATGAG
		GCTCTGCACAAACCACTACACGCAAGAGAGCTCTCCCTG
		TTCTCCGGGTAAA (SEQ ID NO:178)
F	GAGCCCAAATCTTCTGACAAAACATCACACATGC	GGTGGAGGAGTCTTGGAGGTGGTGGATCACTTCCGGC
U	CCACCGTGCCCAAGCACTGAACCTCTGGGGGA	AAGCTGGATCCAAAGCTGTCCGTGATCCGGAACCTGAAC
S	CCGTGAGTCTTCTCTTCCCCCAAAACCAAG	GACACGTTGCTGTCTCATCGACAGGGCAACAGGCTCTC
E	GACACCCATCATGATCTCCCGGACCCCGAGGTC	TTCTGAGGATATGACCCGACTCCGACGTGAGGATTAACGCT
-	ACATGGTGGTGGTGGACGTGAGCCACGAAGAC	CCAAGGACAATCTTCACTCATCTCCATGTACAGGACTCC
8	CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC	CAGCCCAAGGGATGGCTGTACAAATTTCCGTGAAAGTG

7	GTGGAGGTGCATTAATGCCAAGACAAAGCCGGG	GAGAAAATCTCACCCCTGTCCGTGGAAAACAAGATCATC
6	GAGGAGCAGTACACAGCACGTAACGGTGTGGTC AGCGTCCCTCACCGTCCCTGCAACAGGACTGGCTG AATGGCAAGGAGTACAAGTGCAGGCTCCCAAC AAAGCCCTCCAGCCCATCGAGAAAACCATC TCCAAGCCAAAGGCAAGCCCGGAGAACCAACAG GTGTACACCCCTGCCCCATCCCGGGAGGAGATG ACCAAGAACCCAGGTGAGCCTGAGCTGCGCGGTC AAAGGCTTCTATCCAGAGGACATCGCCGTGGAG TGGGAGAGCAATGGCAGCCCGGAGAACAACTAC AAGACACGCCCTCCCGTGTGGACTCCGACGGC TCCTTCTTCTCTGTGAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGCAGGGGAAGCTCTCTCA TGCTCCGTGATGCATGAGGCTCTGCACAAACCGG TTCAGCAGAGAGCCCTCTCCCTGTCTCCCGGT AAA (SEQ ID NO:114)	AGCTTCAAAGAGATGAACCCCCCGACACAATCAAAGAC ACCAAATCCGACATCATCTTCTCCAGCGCTCTGTGCC GSCCATGATAACAAAATGAGTTCGAAAGCTCCTCTAC GAAGGCTACTTCTCGCCGCTGAAAAGGAAACGCGACCTC TTCAAGCTCATCTCTGAAGAGGAGCAACTGTGGGGAC AGGAGCATCATGTTTCAACCTTCAGAACGAGACGAGCCT AAATCTCCGACAAAACCTCACACATGCCACCGTGCCCA GCACTGAATCTCTGGGGGACCGTCACTCTCTCTCTC CCCCAAAACCAAGGACACCTCATGATCTCCCGAAC CCGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAA GACCTGAGTCAAGTTCACTGGTACGTGGACGGCTG GAGGTGCATATGCCAAGACAAAGCCCGGGAGGAGCAG TACAACAGCACGTACCGTGTGTGTCAGCGTCTCACCGTC CTGCACAGGACTGGCTGAATGGCAAGGAGTACAAGTGC AAGGTCTCAACAAAGCCCTCCAGCCCGCCATCGAGAAA ACCATCTCCAAAGCCAAAGGGCAGCCCGGAAACACACAG GTGTACACCCCTGCCCATCCCGGAGGAGTACCAAG AACAGGTCAAGCTGTGTGGTGGTCAAGGCTCTAT CCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG CCGGAGAACAACTACAGACACCGCTCCCGTGGTGGAC TCCGACGGCTCTTCTTCTCTACAGCAAGCTCACCGTG GACAAGAGCAGTGGCAGCAGGGGAAGCTCTTCTCATGC TCCGTGATGCATGAGGCTCTGCACAAACCTACACGCAG AAGAGCCCTCTCCCTGTCTCCGGGTAAA (SEQ ID NO:1179)
F	GAGCCCAATCTTCTGACAAAACCTCACACATGC	GRACCTAAATCTCCGACAAAACCTCACACATGCCACCG
U	CCACCGTCCCCAGACCTGAACCTCTGGGGGA	TGCCAGCACCTGAACCTCTGGGGGACCGTCACTCTTC
S	CCGTAGTCTTCTCTTCCCCCAAAACCCAAAG	CTCTTCCCCCAAAACCCAAAGCACCCCTCATGATCTCC
E	GACACCTCATGATCTCCCGGACCCCGAGGTC	CGACCCCGAGTCAATGCGTGGTGGTGGACGTGAGC
-	ACATGGGTGGTGGACGTGAGCCACGAGAC	CACGAAGACCTGAGGTCAAGTTCACTGGTACGTGGAC
8	CTGAGGTCAAGTTCAACTGGTACGTGGACGGC	GGCGTGGAGTGCATATGCCAAGACAAAGCCCGGGAG
8	GTGAGGTGCATTAATGCCAAGACAAAGCCGGG	GACAGTACAACAGCAAGTACCGTGTGGTCAAGGTCCTC
7	GAGGAGCAGTACACAGCACGTACCGTGTGGTC	ACCGTCTGCACAGGACTGGCTGAATGGCAAGGAGTAC
	AGGTCTCACCGTCTGCACAGGACTGGCTG	AAGTCAAGGTCTCCAAACAAAGCCCTCCAGCCCGCATC
	AATGGCAAGGAGTACAAGTGCAGGCTCTCCAA	GAGAAAACCATCTCCAAAGCCCAAGGGCAGCCCGGAGAA
	AAAGCCCTCCAGCCCATCGAGAAAACCATC	CTACAGGTGTACACCTTCCCCCATCCCCGGGAGGAGATG

	TCCAAAGCCAAAGGGCAGCCCGGAGAACACAG GTGTACACCCCTGCCCCATCCCGGAGGAGATG ACCAAGAACCAGGTACGCCCTGAGCTGGCGCGTC AAAGGCTTCTATCCAGCGACATCCCGTGGAG TGGGAGAGCAATGGGCAGCCGGAGAACAACTAC AAGBCCACGCCCTCCGCTGCTGGACTCCGACGGC TCCCTTCTTCCCTGGTGGCAAGCTCAACCGTGGAC AAGAGCAGGTGGCAGCAGGGGAAGCTCTTCTCA TGGTCCGTGATGCATGAGGCTCTGCACAAACCGG TTCACGCAGAGAGGCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	ACCAAGAACCAGGTACGCTGTGGTGCCCTGTTCAAAGGC TTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGCGAGCGGAGAACAACTACAAGACCAACGCTCCCGTGG CTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTC ACCGTGGACAGAGCAGGTGGCAGCAGGGGACAACTCTTC TCACTGCTCCGTGATGCATGAGGCTCTGCACAAACCACTAC ACGCAGAAGAGCCTCTCCCTGTCTCCGGTAAAGCTGCT GAACTGTGGAAGATAATACTATTAAATTTCTGTGGCCATG AAATTCATCGATAATACTCTGTACTTTCATTCGCCGAAGAT GATGAAATCTGGAAAGTGAATTACTTTTGGAAAGCTGGAA AGCAAACTGAGCGGTATCCGCAACCTCAACGATCAGGTG CTGTTTCATCGACCGAGGCAATAGGCCCTGTTCGAGGAC ATGACCGACTCTGACTCCAGGGACAAACGCCCTCTCGAACC ATTTCATCATCTCCATGTACAAGGACTCCAGCCCAAGG GGCATGGCGGTACAAATTTCCGTGAAGTCCGAGAAATC TCCACCTTGAGCAGCGGAAAACAAAATCATCTCTCTCAA GAGATGAACCCCCCGACACATCAAGGACACCAAAATCC GACATCATCTTCTTCCAGAGTCCGTGCCCGGCCACGAT AACAAATGCAGTTCCGAGAGCAGCTCCTACGAGGGGTAC TTCTTGGCCTCCGAAAAGGAAAAGGACCTGTTCAAGCTG ATCCTGAAGAAGGAGGACGAGCTGGGGACACAGAGCATC ATGTTCAACCGTGCAGAACGAGGAC (SEQ ID NO:180)	GAACCTAATCTCCGACAAAACCTCACACATGCCACCG TGCCCAGCACCTGAACCTCCTGGGGGACCGTCACTCTTC CTCTTCCCCCAAACCAAGGACACCTCATGATCTCC CGGACCCCGAGGTACATGCGGTGGTGGACGTGAGC CACGAAGACCCCTGAGGTCAAGTTCAACTGTTACGTGGAC GGCGTGGAGTGCATATGCCAAGACAAAGCCGGGAG GAGCAGTACAAACAGCACGCTACCGTGTGTGTCAGCGTCTC ACCGTCTGTACACAGGACTGGCTGAATGGCAAGGAGTAC AAGTGCAGGTCTCCACAAAGCCCTCCAGCCCCCATC GAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAA CCACAGGTGTACACCTTGCCCCCATCCCGGGAGGAGATG ACCAAGAACAGGTACGCTGTGGTGCCCTGTTCAAAGGC TTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGCGACCGGAGAACAACTACAAGACCAACGCTCCCGTGG
F U S E - 8 8 8	GAGCCCAAATCTTCTGACAAAACCTCACACATGC CCACCGTGCCCGAGCACCTGAACCTCTGGGGGA CCGTACAGTCTTCTTCTTCCCCCAAACCCAAAG GACACCTCATGATCTCCCGGACCCCGGAGGTC ACATCGGTGGTGTGGACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGAGGTGCATAATGCCAAGACAAAGCCCGGG GAGGACGAGTACAAACAGCACGCTACCGTGTGTGTC AGCGTCTTACCGTCTGACACCGACTGGGTG AATGGCAAGGAGTACAAGTGAAGGTCTTCCAAAC AAAGCCCTCCAGCCCCCATCGAGAAAACCATC TCCAAAGCCAAAGGCGAGCCCGGAGAACACAG GTGTACACCTTGCCCCCATCCCGGGAGGAGATG ACCAAGAACCAGGTACGCTGAGCTGGCGCGTC		

	AAAGGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGAGCCGGAGAACAACTAC AAGACCAACGCTCCCGTCTGGACTCCGACGGC TCCCTCTTCCGTGTGAGCAAGCTCACCGTGGAC AAGCAGGTGGCAGGGAAGCTCTTCTCA TGTCCGTGATGATGAGGCTCTGCACAACCGG TTTCAGCGAGAAGACCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	CTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGGAGCAGGGGAACGTCTTC TCAATGCTCCGTGATGCAATGAGGCTCTGCACAACCACTAC ACCCAGAAAGCCTCTCCCTGTCTCCGGTAAAGCTGCT GAACCTGTGGAGATAATCAGATTAATTTTGGCCATG AAATTCATTCACAATACCTGTATTTTCATCGCCGAAGAT GATGAAAACCTGGAATCTGATTAATTTTGGAAAACCTGAA AGCAAACTGAGCGGTATCAGGAACCTGAACGATCAGGTG CTGTTTATCGACAGGGCAACAGGCCCTCTTTGAGGAC ATGACCGACTCTGACTCTAGGGACAACGCCGCCAGGAOC ATCTTCATCATCTCCATGTACAAGGACTCCAGCCAAAGG GGAATGGCGGTGACAATTTCCGTGAAATCCGAGAAGATC TCCACCTGTCTCCGAGAACAAAATCATCTCCTTCAAA GAGATGAACCCCGGACAACATCAAGACACACAAAATCC GACATCATCTTCTCCGAGAGTCCGTGCCCGGTCAAGAC AACAAATGCAATTCGAGAGCAGCAGCTACGAGGGCTAC TTCTCGCTCCGAAAGGAAGGACCTGTTCAAGCTG ATCCTGAAGAGGAGGACGAGCTGGGGACAGGTCTATC ATGTTCAACCGTCCAGAACGAGGAC (SEQ ID NO:181)	
F U S E - 8 8 9	GAGCCCAATCTTCTGACAAAACCTACACATGC CCACCGTGCCAGCACTGAATCTCTGGGGGA CCGTGAGTCTTCTCTTCCCCCAAAACCCAAAG GACACCTCAATGATCTCCCGGACCCCGAGGTG ACATGGTGGTGGACGTGAGCCACGAAAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGGAGGTGCATATGCCAAGACAAGCCCGGG GAGGACAGTACAAACAGCACGTACCGTGTGCTG AGCTTCTCACCTCTCTGCACCCAGGACTGGCTG AATGGCAAGGAGTACAAGTGCAAGGTCTCCAAAC AAAGCCCTCCAGCCCTCATCGAGAAAACCATC TCCAAAGCCAAAGGGCAGCCCGGAGAACCCACAG GTGTACACCTTGCCTCCATCCCGGAGGAGATG ACCAAGAACCCAGGTACGCTGAGCTGCGCCCTC AAAGGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGAGCCCGGAGAACAACTAC AAGACCAACGCTTCCCGTCTGGACTCCGACGGC	GAACCTAAATCTCCGACAAAACCTACACATGCCACCG TGCCAGCACCTGAATCTCTGGGGGACCGTCACTCTTC CTCTTCCCCCAAAACCCAGACACCTCATGATCTCC CGGACCCCGAGGTCAATGCGTGTGGTGGACGTGAGC CAGGAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATATATGCCAAGACAAGCCCGGGAG GAGCAGTACAAACAGCACTACCGTGTGGTCAAGCTCTC ACCGTCTGCACCCAGGACTGGCTGAATGGCAAGGAGTAC AAGTGCAAGTCTCCAAAGACCCCTCCAGCCCTCCAGCCCTATC GAGAAAACCATCTCCAAAGCCAAAGGCGAGCCCGGAGAA CCACAGGTGTACACCTTGCCTCCCCCATCCCGGGAGGAGATG ACCAAGAACCCAGGTACGCTGTGGTGCCTGTCTCAAGGC TTCTATCCAGGACATCGCCGTGGAGTGGGAGAGCAAT GGGACGCCGAGAACAACTACAAGACCAAGCCCTCCCGTG CTGGACTCCAGCGCTCCTCTCTTCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTC TCAATGCTCCGTGATGCAATGAGGCTCTGCACAACCACTAC	

	TCCCTTCTTCTCTCGTGAGCAAGCTCACCCGTGGAC AAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA TGCTCCGTGATGCATGAGGCTCTGCACAAACCGG TTCCAGCAGAAAGAGCCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	ATGACAGACTCCGACGCCCGGACAAAGCTCCTAGAACAA ATCTTCATCACTCTATGTACAAGGACTCCAGCCCCAGG GGAATGGCCGTACAAATTCCTGTGAAGGCGCAGAGATC TCCACCTGTCCGCCGAAACAAAGATCATCTCTCAAA GAGATGAACCCCCCGACAAATCAAGGACACCAATCC GACATCATCTTCTCCAGCGCTCCGTGCCCGCCATGAT AACAAATGCAGTTCCGAAAGCTCCTCTACGAGGGATAC TTTCTGGCCGCGAAAGAAAGGGAACCTGTTCAGCTG ATCCTGAAGAGGAGGACGAGCTGGGGACAGATCCATC ATGTTCAACCGTTCCAGAAACGAGGAC (SEQ ID NO:182)	AGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAAAGCTGCT GAACTGTGGAGATAATGATATTATTTCTGTGGCCCATG AAATTCATCGATAATACCTCTCTACTTCAATCCCGAAGAT GATGAAACCTCGAATCCGATTATTTTGGAAAACCTGGAA TCCAAACTGAGGTGATCAGGAACCTCAACGACCAGGTG CTGTTCATTTGACCCAGGCAACAGGCCCTGTTCGAGGAT ATGACAGACTCCGACGCCCGGACAAAGCTCCTAGAACAA ATCTTCATCACTCTATGTACAAGGACTCCAGCCCCAGG GGAATGGCCGTACAAATTCCTGTGAAGGCGCAGAGATC TCCACCTGTCCGCCGAAACAAAGATCATCTCTCAAA GAGATGAACCCCCCGACAAATCAAGGACACCAATCC GACATCATCTTCTCCAGCGCTCCGTGCCCGCCATGAT AACAAATGCAGTTCCGAAAGCTCCTCTACGAGGGATAC TTTCTGGCCGCGAAAGAAAGGGAACCTGTTCAGCTG ATCCTGAAGAGGAGGACGAGCTGGGGACAGATCCATC ATGTTCAACCGTTCCAGAAACGAGGAC (SEQ ID NO:182)
F U S E - 8 9 0	GAGCCCAATCTTGACAAAACCTCACACATGC CCACCGTCCCCAGCACCTGAACCTCTGGGGGA CCGTGAGTCTTCTCTTCCCCCAAAACCCAAAG GACACCTCATGATCTCCCGGACCCCGGAGGTC ACATGGTGGTGGTGGACGTGAGCCACGAGAC CCTGAGGTCAAGTTCAACTGTTAGTGGACGGC GTGGAGGTGCATAATGCCAAGACAAAGCCGGG GAGGACAGTACACACAGCACGTACCGTGTGTC AGGTCTCTACCGTCTGCACCCAGGACTGGCTG AATGGCAAGGAGTACAGTGCAGGTCTCCAAAC AAAGCCCTCCAGCCCATCCGAGAAAACCATC TCCAAAGCCAAAGGGCAGCCCCGAGAACCCACAG GTGTACACCTTGCCCCCATCCCGGAGGAGATG ACCRAGAACCAGGTGAGCTGAGCTGGCCCGTC AAAGCTTCTTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGGCAGCCCGGAGAACAACTAC AAGACACGCCCTCCGTGCTGGACTCCGACGGC TCCCTCTTCTCGTGAGCAAGTCAACCCGTGGAC AAGACAGGTGGCAGCAGGGGAACGTCTTCTCA TGCTCCGTGATGCATGAGGCTCTGCACAAACCGG	GRACCTAATCTCCGACAAAACCTCACACATGCCACCG TGCCACGACACCTGAACCTCTGGGGGACCGTCAGTCTTC CTCTCCCCCAAAACCCAAAGGACACCCCTCATGATCTCC CGACCCCCGAGGTGCATGCGTGGTGGTGGACGTGAGC CACGAAGACCCCTGAGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCCGGAG GAGCAGTACAAACAGCACGTACCGTGTGTGAGGTCTC ACCGTCTCTGCACCCAGGACTGGCTGAATGGCAAGGAGTAC AAGTGCAAGTCTCCAAAGCCCTCCAGCCCCCATC GAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAA CCACAGGTGTACACCCCTGCCCCCATCCCGGAGGAGATG ACCAAGAACCAGGTGAGCCTGTGGTGCCTGGTCAAAAGGC TTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGCAGCCGGAGAACAACTACAAGACCAACGCTCCCGTG CTGGACTCCGACGGCTCTTCTCTCTCTACAGCAAGCTC ACCGTGGACAAAGACAGGTGGCAGCAGGGGAACGTCTTC TCTATGCTCCGTGATGATGAGGTCTGCACACCACTAC ACCGAGAAGAGCTCTCCCTGTCTCCGGGTAAAGCTGCT GAACTGTGGAGATAATTTTCATCAATTTTGTGGCCCATG AAATTCATTTGATAACACCCCTGTATTTTCATCCCGAAGAT	

	TTCACGCAGAGAAGAGCCTCTCCCTGTCTCCGGGT AAA (SEQ ID No:114)	GATGAAAAACCTGGAGTCTGATTACTTTTGGAAAGCTGGAA AGCAAACTGAGCGTGATCCGCAACCTCAACGATCAGGTG CTGTTTATCGACACAGGGCAACAGGCCACCTGTTGAGGAC ATGACCGACAGCGACGCCAGGGATAACGCCCTAGAACAA ATCTTCATTATCTCCATGTACAAGGACTCCAGCCCCAGG GGAATGGCAGTGACAAATCTCCGTGAAGGCCGAGAGAATC AGCAACCTGAGCGCCGAAAACAAGATCATCTCTTCAAG GAGATGAACCCCCCGACACATCAAGGACACCAAAATCC GACATCATCTTCTTCCAGAGGTCCGTGCCGCCACGAT AACAAAAATGCAATTTGAATCTCTCTACGAAGGTAC TTTCTGGCCGCCGAAAAGGAAGAGACTTGTTCAGCTG ATCCTGAAGAAGGAGGACGAGCTGGGGGACAGATCCATC ATCTTCACCGTTCAGAACGAGGAC (SEQ ID No:183)
F	GAGCCCAAAATCTTCTGACAAAACTCACATGTC	GAACCTAAATCTCCGACAAAAACTCACATGCCCCACCG
U	CCACGTGCCCAGACCTGAACCTCTGTGGGGGA	TGCCAGACCTGAACCTCTGTGGGGACCCGTAGTCTTC
S	CCGTCAGTCTTCTCTTCCCCCAAAACCCAAAG	CTCTTCCCCCAAAACCCAAAGACACCTCATGATCTCC
E	GACACCTCATGATCTCCCGGACCCCGAGGTC	CSGACCCCGAGGTACATGCGTGGTGGACGTGAGC
-	ACATGGTGGTGGTGGAGCTGAGCCACGAAGAC	CACGAAGACCTGAGGTCAAGTTCAACTGTTACGTGGAC
8	CCTGAGGTCAAGTTCAACTGGTGGACGGC	GGGTGGAGGTGATAATGCCAAGACAAAGCCGCGGAG
9	GTGAGGTGCATATGCCAAGACAAAGCCCGGG	GAGCAGTACAACAGCACGTACCGTGTGTGAGCTCTC
1	GAGGACAGTACACAGCACGTACCGTGTGCTC	ACCGTCTGCACAGGACTGGGTGAATGGCAAGGAGTAC
	AGCGTCTCACCGTCTGCACCGAGGACTGGCTG	AAGTCAAGGTCTCCAAACAAGCCCTCCAGCCCCCATC
	AATGGCAAGGAGTACAAGTGAAGGTCTCCAAC	GAGAAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAA
	AAAGCCCTCCAGCCCCCATCGAAGAAAACCATC	CCACAGGTGTACACCTGCCCCCATCCCGGAGGAGATG
	TCCAAGCCAAAGGCAGCCCGGAGAACCCACAG	ACCAGAACCAGGTACGCTGTGGTGCCTGCTCAAAGGC
	GTGTACACCTGCCCCCATCCCGGAGGAGATG	TTCTATCCAGGACATCGCCGTGGAGTGGGAGAGCAAT
	ACCAGAACCAGGTACGCTGAGCTGCGCGTC	GGCAGCCGGAGAACAACTACAAGACCACGCTCCCGTG
	AAAGGCTTCTATCCAGCGACATCGCCGTGGAG	CTGGACTCCGAGCGCTCCTTCTTCTCTACAGCAAGCTC
	TGGGAGAGCAATGGGCAGCCGGAGAACAACTAC	ACCGTGGACAGAGCAGGTGGCAGCAGGGGACGTCTTC
	AAGACACGCTCCCGTGTGGACTCCGACGGC	TCATGCTCCGTAATGCAATGAGGTCTGCAACAACCACTAC
	TCCCTTCTCTCTGTGAGCAAGCTCACCGTGGAC	ACCCAGAAGAGCTCTCCCTGTCTCCGGTAAAGCTGCT
	AAGAGCAGGTGGCAGCAGGGGAACCTCTCTCA	GAACTGTGGAGATATCTGATTAATTTTGTGGCCATG
	TGCTCCGTGATGCATGAGGCTCTGCACAAACCGG	AAATTCATCGATTAACACCTTGTACTTTATCGCTGAAGAT
	TTCACGCAGAGAAGCCTCTCCCTGTCTCCGGGT	GATGAAAAATCTGAAAAGTGAATCTTCGGAAAACTGGAA
	AAA (SEQ ID No:114)	AGCAAAATGAGCGTGATCAGGAATCTGAACGATCAGGTG CTGTTTCATCGACACAGGGCAACGCCCTCTGTTTCAGGAT

		ATGACCGACTCTGACGTGAGGGACACGCCCAAGGACA ATCTTTCATCATCTCTATGTACAAGGATTCAGAGCCAGG GGCATGGCCGTTACAATTTCCGTGAAGGTGGAGAAGATC TCCACACTGAGCGTGGAGAACAAAGATCATCTCCTCAAG GAGATGAACCCCCCGGACAAACATCAAGGACACCAATCC GACATCATCTTTTCCAGAGGAGTGTGCCGGTCAAGAC AACAAAGATGACGTTCCGAATCCAGTCTCTACGAAGGTAC TTCTCTGGCGTTCGAAAAGGAAAGGACCTGTTCAAGCTG ATCCTGAAGAAGGAGGACGAGTTGGGGGACAGGAGCATC ATGTTCAACGTCACAGAACGAGGAC (SEQ ID NO:184)	
F U S E - 8 9 2	GAGCCAAATCTTCTGACAAAACTCACACATGC CCACCGTGCCCAGACCTGAACCTCTGTGGGGGA CCGTGAGTCTTCTCTTCCCCCAGAAACCCAAAG GACACCTCAATGATCTCCCGGACCCCGAGGTC ACATGGTGGTGGTGGACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGC GTGGAGGTGCATTAATGCCAAGACAAAGCCGGGG GAGGACAGTACACAGCACGTACCGTGTGGTC AGCTCTCTACCTCTGTCAACAGGACTGGCTG AATGGCAAGGAGTACAAGTGAAGTCTCCAAC AAAGCCCTCCAGCCCCATCGAGAAAACCATC TCCAAGCCAAAGGGCAGCCCGGAGAACCAAG GTGTACACCTGCCCCCATCCCGGGAGGAGATG ACCAGAACCCAGTCAAGCTGAGCTGGCGCTC AAAGGCTTCTATCCAGCGACATCGCCGTGGAG TGGGAGAGCAATGGCAGCCCGGAGAACAACTAC AAGACCAAGCCCTCCCGTGTGCACTCCGACGGC TCCTTCTTCTCTGTGAGCAAGTCAACGTGGAC AAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCA TGCTCCGTGATGATGAGGCTCTGCACAACCGG TTCAACGACAGAGCCCTCTCCCTGTCTCCGGGT AAA (SEQ ID NO:114)	GAACCTAAATCTCCGACAAAACCTCACACATGCCG TGCCAGACCTGAACCTCTGTGGGGAGCCGTGAGTCTTC CTCTTCCCCCAGAAACCCAAAGACACCTCATGATCTCC CGGACCCCGAGGTCAATGCTGTGGTGGACGTGAGC CACGAAGACCTGAGTCAAGTTCAACTGTTACGTGGAC GGCGTGGAGGTGCATATATGCCAAGACAAAGCCGGGAG GAGCAGTACAAAGACAGTACCGTGTGGTCAAGGTCTTC ACCGTCTGCACAGGACTGGCTGAATGGCAAGGAGTAC AAGTCAAGTCTCCAAACAAAGCCCTCCAGCCCCCATC GAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGAGAA CCACAGGTGTACACCTTGCCTCCATCCCGGGAGGAGATG ACCAAGAACAGGTCAAGCTGTGGTGCCTGGTCAAGGC TTCTATCCAGGACATCGCCGTGGAGTGGGAGAGCAAT GGCAGCGGAGAGAACAACTACAAGACACGCCCTCCCGTG CTGGACTCCGACGGCTCCTTCTCTCTACAGCAAGCTC ACCGTGGACAAAGACAGTGGCAGCAGGGGAACGTCTTC TCATGTCCTGATGCATGAGGCTCTGCACAACCACTAC ACCCAGAGAGCCCTCTCCCTGTCTCCGGTAAAGCTGCT GAACTGTGGAGATATCATATTAATTTCTGTGGCCATG AAATTCATCGATAATCTGTACTTTCATCGCCGAAGAT GATGAAATCTGGAAGTGTATTACTTTTGGAAAGCTGGA AGCAAACTGAGCGTGTACAGCAATCTCAACCATCAGGTG CTGTTTCATCGACAGGCAATAGGCCCTGTTCGAGGAC ATGACCGACTCCGACGTGGGATACGCCCTTAGAACA	

	ATCTTCATCATCTCCATGTACAGGACTCCAGCCAAAGG GGCATGGCAGTGAACAATCAGCGTGAAGTGGAGAGATC TCCACACTGTCCGTGGAGAACAAAGATCACTCCTCAAG GAGATGAACCCCCCGACACATCAAGGACACAAAGAGC GATATCATTTTCTTCCAGAGGAGCGTCCCGGCACGAT AACAAAATGCAGTTCGAATCCAGCTCCTACGAAGGTAC TTCCTGCCCGTCGAAAGGAAGGGACCTGTTCAGTTG ATCCTGAAGAGGAGGACGAAATGGGGACAGGTCCATC ATGTTCACCGTCAGAGACGAGGAC (SEQ ID NO:185)	
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Table 3. Yields of exemplary fusion proteins.

	Yield		Yield		Yield		Yield
FUSE-422	191 mg/L	FUSE-501	147 mg/L	FUSE-583	86 mg/L	FUSE-775	79 mg/L
FUSE-423	214 mg/L	FUSE-502	159 mg/L	FUSE-584	124 mg/L	FUSE-782	41 mg/L
FUSE-424	198 mg/L	FUSE-503	44 mg/L	FUSE-585	136 mg/L	FUSE-783	99 mg/L
FUSE-441	386 mg/L	FUSE-504	135 mg/L	FUSE-586	107 mg/L	FUSE-827	207 mg/L
FUSE-442	197 mg/L	FUSE-505	162 mg/L	FUSE-587	228 mg/L	FUSE-874	246 mg/L
FUSE-462	304 mg/L	FUSE-507	557 mg/L	FUSE-599	76 mg/L	FUSE-875	137 mg/L
FUSE-480	130 mg/L	FUSE-508	34 mg/L	FUSE-600	79 mg/L	FUSE-876	216 mg/L
FUSE-481	199 mg/L	FUSE-509	537 mg/L	FUSE-601	86 mg/L	FUSE-887	155 mg/L
FUSE-484	164 mg/L	FUSE-510	32 mg/L	FUSE-602	64 mg/L	FUSE-888	149 mg/L
FUSE-485	348 mg/L	FUSE-516	215 mg/L	FUSE-691	69 mg/L	FUSE-889	223 mg/L
FUSE-486	400 mg/L	FUSE-517	150 mg/L	FUSE-694	67 mg/L	FUSE-890	190 mg/L
FUSE-487	205 mg/L	FUSE-545	144 mg/L	FUSE-756	46 mg/L	FUSE-891	181 mg/L
FUSE-499	410 mg/L	FUSE-546	143 mg/L	FUSE-757	96 mg/L	FUSE-892	371 mg/L
FUSE-500	253 mg/L	FUSE-547	135 mg/L	FUSE-758	64 mg/L		

Table 4. Amino acid sequences for Fc heterodimerization including different versions of knobs-into-holes of respective polypeptide arms, forming (part of) the protein capable of translocating to the ER, for exemplary fusion proteins.

	First Polypeptide Arm	Second Polypeptide Arm
7.8.60	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTDNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTTPVIMSDGSFFLASK LTVDKSRWQOGNMFSCSVMEALHNHYTQKSLSLSPGK (SEQ ID NO:189)	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTDNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTTPVIMSDGSFFLASK LTVDKSRWQOGNMFSCSVMEALHNHYTQKSLSLSPGK (SEQ ID NO:190)
7.8.60 CH3	GQPREPQVYTLPPSRDELTDNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTTPVIMSDGSFFLASKLTVDKSRWQOGNMFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:191)	GQPREPQVYTLPPSRDELTDNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTTPVIMSDGSFFLASKLTVDKSRWQOGNMFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:192)
A107	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTDNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTTPVIMSDGSFFLASK LTVDKSRWQOGNMFSCSVMEALHNHYTQKSLSLSPGK (SEQ ID NO:193)	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTDNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTTPVIMSDGSFFLASK LTVDKSRWQOGNMFSCSVMEALHNHYTQKSLSLSPGK (SEQ ID NO:194)
A107 CH3	GQPREPQVYTLPPSRDELTDNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTTPVIMSDGSFFLASKLTVDKSRWQOGNMFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:195)	GQPREPQVYTLPPSRDELTDNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTTPVIMSDGSFFLASKLTVDKSRWQOGNMFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:196)
DD-KK	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTDNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTTPVIMSDGSFFLASK LTVDKSRWQOGNMFSCSVMEALHNHYTQKSLSLSPGK (SEQ ID NO:197)	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTIISKAKGQPREPQVYTLPPSRDELTDNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTTPVIMSDGSFFLASK LTVDKSRWQOGNMFSCSVMEALHNHYTQKSLSLSPGK (SEQ ID NO:198)
DD-KK CH3	GQPREPQVYTLPPSRDELTDNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTTPVIMSDGSFFLASKLTVDKSRWQOGNMFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:199)	GQPREPQVYTLPPSRDELTDNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTTPVIMSDGSFFLASKLTVDKSRWQOGNMFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:200)

Ducbody	PSVFLFPPKPKDTLMSRTEPVTCTVVDVSHEDPEVKFNWYVD GVEVHNARTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELYSR LTVDKSRWQOQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:201)	PSVFLFPPKPKDTLMSRTEPVTCTVVDVSHEDPEVKFNWYVD GVEVHNARTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELYSK LTVDKSRWQOQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:202)
Ducbody CH3	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFPYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFELYSLTVLHQDWLNGKEYKCKV VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:203)	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFPYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFELYSLTVLHQDWLNGKEYKCKV VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:204)
Electrost atic Steering CH3	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFPYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFELYSLTVLHQDWLNGKEYKCKV VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:205)	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFPYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFELYSLTVLHQDWLNGKEYKCKV VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:206)
Electrost atic Steering	PSVFLFPPKPKDTLMSRTEPVTCTVVDVSHEDPEVKFNWYVD GVEVHNARTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELYSN LTVDKSRWQOQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:207)	PSVFLFPPKPKDTLMSRTEPVTCTVVDVSHEDPEVKFNWYVD GVEVHNARTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELYSK LTVDKSRWQOQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:208)
EW-RVT	PSVFLFPPKPKDTLMSRTEPVTCTVVDVSHEDPEVKFNWYVD GVEVHNARTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELYSW LTVDKSRWQOQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:193)	PSVFLFPPKPKDTLMSRTEPVTCTVVDVSHEDPEVKFNWYVD GVEVHNARTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELYSK LTVDKSRWQOQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:209)
EW-RVT (2)	PSVFLFPPKPKDTLMSRTEPVTCTVVDVSHEDPEVKFNWYVD GVEVHNARTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELYSW LTVDKSRWQOQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:210)	PSVFLFPPKPKDTLMSRTEPVTCTVVDVSHEDPEVKFNWYVD GVEVHNARTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFPYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFELYSK LTVDKSRWQOQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:211)
EW-RVT (2) CH3	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFPYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFELYSLTVLHQDWLNGKEYKCKV VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:212)	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFPYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFELYSLTVLHQDWLNGKEYKCKV VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:213)

EW-RVT CH3	GQPREPVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSWLTVDKSRWQOGNVSFCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:195)	GQPREPVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQOGNVSFCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:214)
HA-TF (1)	PSVLEFPKPKDPTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQOGNVSFCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:215)	PSVLEFPKPKDPTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQOGNVSFCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:216)
HA-TF (1) CH3	GQPREPVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQOGNVSFCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:217)	GQPREPVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQOGNVSFCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:218)
Knob-in- hole (1)	PSVLEFPKPKDPTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLW CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQOGNVSFCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:219)	PSVLEFPKPKDPTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLW CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQOGNVSFCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:220)
Knob-in- hole (1) CH3	GQPREPVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQOGNVSFCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:221)	GQPREPVYTLPPSRDELTKNQVSLCAVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQOGNVSFCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:222)
Knob-in- hole (2)	PSVLEFPKPKDPTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLW CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQOGNVSFCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:223)	PSVLEFPKPKDPTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLW CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQOGNVSFCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:224)
Knob-in- hole (2) CH3	GQPREPVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQOGNVSFCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:225)	GQPREPVYTLPPSRDELTKNQVSLCAVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQOGNVSFCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:226)

XmAb	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNARTKPEREEQYNSTYRVVSVLTVHLQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CDVSGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:227)	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNARTKPEREEQYNSTYRVVSVLTVHLQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:228)
XmAb CH3	GQPREPQVYTLPPSRDELTKNQVSLTCDVSGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:229)	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:230)
ZW1	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNARTKPEREEQYNSTYRVVSVLTVHLQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYVPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFALVSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:231)	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNARTKPEREEQYNSTYRVVSVLTVHLQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYVLPSPRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYLTWPEPVLDSGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:232)
ZW1 CH3	GQPREPQVYVYFPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFALVSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:233)	GQPREPQVYVLPSPRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYLTWPEPVLDSGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO:234)

Table 5. Table 5. The sequences, antibodies and fragments thereof (e.g., VHH, Fab regions, or scFv) in the references, publications, patent documents, webpages contained in this table are hereby incorporated by reference as though fully set forth.

Name	Alternative names	Description
Anti-CD3		
muromonab	OKT3 (Ortho Kung T3)	First monoclonal murine antibody to become available for therapy in humans - mouse IgG2a is directed against the CD3 epsilon chain of the CD3/TCR complex
Teplizumab	hOKT3γ1 (Ala-Ala) and MGA031	CDRs grafted onto human IgG backbone with two mutations (L234/A, L235/A)
Otelixizumab	CbAglyCD3, TRX4, GSK2136525	chimeric and humanized IgG1 bears a single mutation in the γ1 Fc portion (N297/A) to avoid glycosylation and thus inhibit FcR binding
Visilizumab	Nuvion, HuM291	humanized IgG2 antibody rendered non mitogenic by two point mutations in its Fc region (V234/A, V237/A)

Foralumab	28F11-AE; NI-0401	entirely human anti-CD3 mAb whose Fc portion of this human IgG1 was mutated (L234/A, V235E) such that the mAb is non FcR binding in vitro and exhibits only minor cytokine release
Bispecific		
Blinatumomab	AMG 103	linked scFv(s) against CD19 on tumor cells and CD3 on T cells; no Fc domain; Anti-CD3 comes from murine mAb: L2K-07; published sequences encoding scFv addressing CD3ε (dilL2K, the de-immunized version of the mouse monoclonal antibody L2K)
flotetuzumab	MGD006	DART targeting CD3 and CD123
Cibisatamab		1 binding site for CD3ε chain and 2 CEA binding sites for cancer cells
Catumaxomab		consists of mouse IgG2 and rat IgG2b and targets CD3 on T cells and EpCAM on tumor cells
Mesunetuzumab		CD20×CD3 T-cell engaging bsAb
		All candidates shared the same CD3-specific singlechain antibody derived from mouse monoclonal antibody L2K, which is distinct from monoclonal antibodies TR66 and OKT3. L2K was subjected to a procedure that identifies human T helper cell epitopes and removes by point mutations MHC class II anchor amino acids within potential epitopes (Jones et al., 2004). This resulted in "de-immunized" L2K (dilL2K) (sequence encoding scFv addressing CD3ε is disclosed in K. Brischwein et al. / Molecular Immunology 43 (2006) 1129–1143)
TR66		monoclonal anti-human CD3 epsilon antibody
PIT565		Trispecific: CD19 X CD3 X CD2
Four CD3 mAb-based binders: OKT3, L2K, h38E4.v1 and TRX4		
OKT3		
TRX4		
h38E4.v1		Binds N-terminal portion of CD3ε extracellular domain
L2K		L2K, for instance shares over 90% sequence identity with OKT3 and recognizes the same epitope on CD3ε but differs in affinity by about 100-fold
Anti-CD16		
3G8		monoclonal anti-human CD16
US9035026		
HRS-3/A9		A9 is anti-CD16 mouse IgG1/λ Mab

Humanization of anti-CD16 Fab	Protein Engineering, Design and Selection, Volume 22, Issue 3, March 2009, Pages 175–188, the CDRs of the anti-CD16 mouse IgG1/λ. MAb A9 were grafted onto human Ig sequences (CDRs were transplanted onto a human κ light chain + Affinity maturation via radon mutation in the humanized VH and Vk domains)
AFM13	Tetravalent bispecific CD30/CD16 (binds CD16A on NK cell surface, thus activating and recruiting NK cells to CD30+ tumor cell)
GTB-3550	Trispecific CD16/IL-15/CD33 (anti-CD16 nanobody, or 1st generation uses scFv anti-CD16)
IPH6501	Antibody-based tetraspecific against NKp46, CD16a, CD122 or IL-2R, and CD20
AFM13: anti-CD16A binder is variable domains from human scFv clone LSV21	
Other human scFv anti-CD16A clones: LSV14, LSV49, LBH16, LBH15, LBH13, 50NI	
Cite: Reusch et al., mAbs 6:3, 727-738, May/June 2014	
Binders for V gamma 9, V delta 2 gene, V delta 1 gene segments in TCR	
LAVA-051	Lava Therapeutics: bispecific gamma delta T cell engagers (bsTCEs). Vγ9Vδ2 T cell receptor occupancy of LAVA-051 increased with LAVA-051 dose increases and peripheral blood Vγ9Vδ2 T cells also expressed higher levels of activation markers after LAVA-051 dosing LAVA-051 consists of two humanized single domain antibodies (VHH) linked via a short five a.a. G-S linker, wherein one domain antibody recognizes the Vδ2 chain of the Vγ9Vδ2 T cell receptor, and the other domain antibody is specific for CD1d.
LAVA-1207	Binds: the Vδ2 chain of Vγ9Vδ2-T cells and prostate specific membrane antigen (PSMA)
Bruin et al., Clinical Immunology, v. 169, 128-138, August 2016	set of Vγ9Vδ2-T cell specific VHH (or nanobody)
Clones: 5C1, 5D3, 5E3, 5G3, 5F5, 5C7, 5D7, 5E7, 5C8, 5B11, 6A1, 6C1, 6H1, 6E3, 6G3, 6H3, 6C4, 6E4, 6H4, 6F6	
US Pat. Nos. 10,501,540 & 11384145	
clone 7A5: the variable regions of the Vγ9gd T-cell-specific antibody (	Construct: Vγ9 TCR x Her2/neu; that is, (Her2) ₂ xVγ9 bispecific antibody
GDX012	allogeneic, non-engineered, variable delta 1 (Vδ1) gamma-delta (γδ) T cell therapy
See Pat. Appl. pub.: US20220403025; US20220290101;	

Anti-CD137 (4- 1BB/TNFRSF9)			
AGEN2373			by Agerus Inc; mAb IgG1 ; US Patent # 11,098,117 & 11,242,385
utomilumab	PF-05082566		Humanized IgG2 mAb; binding site: cysteine-rich domain (CRD)s III and IV
Urelumab	BMS-663513		Human IgG4 mAb; binding site: CRD I; trial by BMS
CTX-471	by Compass Therapeutics		fully human IgG4 mAb
ADG106	by Adagene Suzhou		fully human ligand-blocking, agonistic IgG4
LVGN6051	by Lyvgen Biopharma/Merck Sharp & Dohme		IgG1, improved FcγRIIB binding
ATOR-1017	by Alligator Bioscience AB		IgG4
HOT-1030	by Shanghai Huabo Biopharmaceutical (Huatao)/Eutilex		IgG1, abrogated FcγRIIB binding
EU101	by Eutilex/Zhejiang Huahai Pharmaceutical		IgG
YH004	by Eucure (Beijing) Biopharma		IgG1
ADG206	by Adagene Suzhou		IgG1, enhanced IgG1 binding, 4- 1BB binding sites are masked
PE0116	by Shanghai Hyamab Biotech		IgG4
FS120	by F-Star Therapeutics Inc.		OX40/CD137 mAb ² dual agonist bispecific antibody
cinrebafusp alfa	PRS-343		bispecific 4-1BB (Anticalin®) X HER2
RG7827	RO 712290		FAP x 4-1BBL antibody fusion protein
INBRX-105	ES101		humanized, bispecific IgG1 targeting PD-L1 X 4-1BB

Acasunlimab	GEN 1046, BNT 311	Fc-silenced IgG1 bispecific PD-L1 X 4-1BB
MCLA-145		bispecific CD137 X PD-L1
Englumafusp alfa	RG6076, RO7227166	CD19 X CD137
Additional bi/multispecific in MAbs, 2023; 15(1): 2167189		
Anti-CD28		
Theralizumab	TGN1412, CD28-SuperMAB,	CYTOKINE storm failed human safety trial; humanised monoclonal antibody directed against the human CD28
	> Renamed as TAB08	Trial for rheumatoid arthritis
Anti-DNAM-1 (CD226 or PTA1)		
LY3435151		agonistic anti-CD226; NCT04099277 by Eli Lilly; US Pat. # 11,440,959
Anti-NKp46 (NCRL, CD335)		
IPH6501		NKp46-Targeting Tetraspecific Antibody-Based Natural Killer Cell Engager Therapeutic Armed with a Non-Alpha IL-2 Variant (by Innate Pharma)
Trifunctional NKCE		Targeting NKp46, CD16, and a tumor antigen (Cell 177, 1701-1713, June 13, 2019), US Pat # 10,519,234 (by Innate Pharma)
Anti-NKp30		Other Innate Pharma owned NKp46 binder patents: 11,001,629, 11,377,492, and 11,267,897
	Compass Therapeutics	US20200109195, US2020079867, particularly SEQ ID NOs: 14 and 18
Anti-NKG2D		
	NCT05213195 by Zhejiang Univ.	US20200360437 by Asko (Suzhou)
		NCT05213195, NCT05247957, NCT04324996, NCT04623944, NCT03415100

Anti-OX40 (CD134; TNFRSF4)			human IgG1
INCAGN1949			Anti-OX40 patents : US Patent # 11,472,883, 11,447,557, 11,359,028, 11,332,536, 11,136,404, 10,626,181, 10,259,882
HFB301001			2nd gen. fully human IgG1 OX40 agonist antibody by HiFiBio
GSK3174998			anti-OX40 mAb
INBRX 106			hexavalent OX40 agonist, active ingredient: hexavalent IgG antibody that targets the human OX40 receptor (TNFRSF4)
FS120	by F-Star Therapeutics Inc.		OX40/CD137 mAb ² dual agonist bispecific antibody
Ixuxolimab	PF-04518600 or PF 8600		humanized agonistic IgG2 monoclonal antibodies against OX40
BGB-A445			does not block the OX40-OX40L interaction;
MOXR0916	by Genentech		humanized effector-competent agonist IgG1 mAb, completely blocked OX40 binding to OX40L
BMS-986178			fully human IgG1 agonist mAb
Anti-ICOS (CD278, A2IM, CVID1)			
Izoralimab	XmAb23104 by Xencor		bispecific PD1 X ICOS
MEDI-570	by AstraZeneca		
BMS-986226			
KY 1044	by Kymab		fully human anti-ICOS IgG1
feladilimab	GSK3359609, INDUCE-1		humanized IgG4 anti-ICOS monoclonal
vopratelimab	JTX-2011 by Jounce Therapeutics		
Acazicolcept			ICOS X CD28

Anti-CD2			
Sipilizumab	TCD601, MEDI-507, Hu-BTI-322 by Novartis	humanized monoclonal anti-CD2 IgG1 (humanized form of BTI-322 below)	
PIT565		Trispecific CD19 X CD3 X CD2 (NCT05397496)	
Alefacept		fusion protein composed of the first extracellular domain of LFA-3 (natural ligand of CD2) fused to the human IgG1 hinge, CH2, and CH3 domains	
BTI-322	Lo-CD2a	rat anti-human CD2 IgG2b mAb	
Anti-CD40L (CD154)			
raplizumab	BG 9588, hu5c8	humanized IgG1k	
Dazodalibep	HZN-4920 by CDP7657	antagonistic	
Dapirolizumab pegol		anti-CD40L antibody fragment with the Fc moiety substituted by polyethylene glycol	
Tegoprunbart	AT-1501	humanized mAb	
Frexalimab	SAR441344	2nd gen. mAb engineered to lack the domain that activated FcγRIIA	
Lu AG22515	APB-A1; by Lundbeck	differentiated anti-CD40L antibody	
Letolizumab	BMS 986004	humanized mAb (a dimeric fusion protein composed of the C-terminus of the domain antibody (dAb) BMS2h-572-633 targeting CD40L linked to a modified Fc fragment of IgG1)	
BIIB063		high affinity MAb, engineered to reduce Fc effector function and avoid half antibody formation in vivo (IgG4P)	
Anti-CD40 (TNFRSF5)			
CDX-1140		fully human IgG2 agonistic mAb	
Sotigalimab	APX005M	humanized IgG1 agonistic mAb	
2141-V11		human anti-CD40 antibody with modified Fc domain (IgG1), which may induce durable anti-tumor immunity	
solirelumab	RO7009789 by Roche, or CP-870893	human IgG2 agonistic mAb, CP-870,893	
dalnicastobart	LVGN7409	humanized IgG1 mAb	

Isalizumab	CFZ533	fully human IgG1 mAb
Dacetuzumab	SGN-40	humanized IgG1 form of S2C6 (a murine anti-human CD40)
BI 655064	by Boehringer Ingelheim	humanised, nondepleting, antagonistic anti-CD40
Bleselumab	ASKP1240	fully human IgG4 mAb
YH003		humanized agonistic CD40 IgG2 mAb
SL-172154	SIRPa-Fc-CD40L	Bifunctional CD47 X CD40
Giloralinab	ABBV-927	agonistic mAb
Lucatumumab	CHIR 12.12 or HCD122	fully human mAb
Mitazalimab	ADC-1013	agonistic human IgG1 mAb
GEN1042		agonistic bispecific CD40 X 4-1BB
FFP104	PG102	humanised
KPL-404		humanized IgG4 antibody engineered to bind CD40 without triggering Fc effector functions
Cifutrilimab	SEA-CD40	humanized IgG1 mAb
Ravagalimab	ABBV-323	antagonistic
ABBV-428		Bispecific CD40 X MSLN
BMS-986090	INX-189	a dimeric anti-human CD40 VH antagonist domain antibody formatted with a human IgG4 Fc
BSI-038		agonistic mAb
MEDI5083		by MedImmune, now AstraZeneca, hexameric CD40L-Fc fusion
RG6189		a FAP-targeted CD40 agonistic bispecific antibody
Inezetanab	AMG 994	an immunoglobulin G1-scFv_L-lambda2 dimer

EXAMPLES

[0158] The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art may develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention.

Example 1

[0159] The N-terminal of pro-IL-18 was fused to the C-terminal of an IgG1 CH3 domain so as to engineer a variant of IL-18 expressible in mammalian cells. Pro-IL-18 was fused to the knob of a knob into hole heterodimeric IgG1 protein. Further modification was made to pro-IL-18 to reduce aggregation of the molecule such that each cysteine residue in both the pro-peptide and mature IL-18 was substituted with serine ("IL-18AS", as in FUSE-480), alanine ("IL-18AA", as in FUSE-481), or valine ("IL-18AV", as in FUSE-442). Illustrations of the three variants are shown in panel A of figure 1.

[0160] Transient transfection in the ExpiCHO system resulted in titers of 191, 214, and 198 mg/L, for FUSE-480, FUSE-481, and FUSE-442, respectively. These Fc-pro-IL-18 fusion proteins were hypothesized as harboring a "masked" version of IL-18, where the biological activity of the fused IL-18 would be reduced until the propeptide is cleaved off. To evaluate cleavage of the propeptide, a cleavage site specific for the enterokinase (EK) was inserted within the propeptide ("pp") upstream of mature IL-18 sequence in the location of the endogenous Caspase 1 site. EK was chosen because of its robust protease activity and activity in phosphate buffered saline. To evaluate the biological activity of the Fc-pro-IL-18 fusion proteins before and after treatment with EK, a reporter system was used. Here, HEK-Blue-IL-18 cells were used to quantify IL-18 activity. HEK-Blue IL-18 cells are made from HEK-293 engineered to express the human IL-18 receptor complex (IL-18R α / β) and an NF- κ B/AP-1-inducible secreted embryonic alkaline phosphatase (SEAP) reporter gene. The cells are also engineered not to respond to human TNF- α and IL-1 β . Upon exposure to IL-18, HEK-Blue IL-18 produce SEAP in a dose dependent manner, which can be quantified via a colorimetric assay. We observed that compared to recombinant human mature IL-18, all three mutants induced lower biological activity greater than 1000 fold and up to 100,000 fold. Upon demasking (enzymatic cleavage) by treatment with EK, the biological activity of the released protein from the alanine-substituted mutant (FUSE-480) and the valine-substituted mutant (FUSE-442) was not substantially different from recombinant human mature IL-18. Following release of the serine mutant with EK (1B), however, although biological activity was restored by >30,000 fold, it was ~50 fold less potent than recombinant human mature IL-18. Potency was measured as the concentration of test article that induced have maximal SEAP production (EC50-SEAP).

[0161] As shown in figure 2, pro-IL-18mut2 was fused to the knob of a knob into hole heterodimeric IgG1 protein. IL-18mut2 incorporates four amino acid substitutions hypothesized to reduce binding to IL-18BP while maintaining wild type binding to the IL-18 receptor complex. Further modification was made to pro-IL-

IL-18mut2 to reduce aggregation of the molecule such that each cysteine residue in both the pro-peptide and mature IL-18mut2 was substituted with serine (IL-18mut2AS), alanine (IL-18mut2AA), or valine (IL-18mut2AV). Illustrations of the three variants are shown in panel A of figure 2. As in figure 1, the biological activity was assessed using HEK-Blue. Compared to recombinant human mature IL-18, all three mutants induced lower biological activity of at least 100,000 fold. Upon demasking (enzymatic cleavage) by treatment with EK, the biological activity of the released protein from the alanine-substituted mutant (FUSE-423) and the valine-substituted mutant (FUSE-424) was not substantially different from recombinant human mature IL-18. Following release of the serine mutant with (FUSE422), however, although biological activity was restored by about 100,000 fold, it was about 100 fold less potent than recombinant human mature IL-18. Potency was measured as the concentration of test article that induced have maximal SEAP production (EC50-SEAP).

[0162] As shown in figure 3, we examined the impact of a propeptide on masking of IL-18AV biological activity in the context of Fc fusions variants incorporating IL-18AV on the C-terminal of the Fc with (panel A, FUSE-442; Fc-EKpp-IL-18AV) or without (panel B, FUSE-505; Fc-EK-IL-18AV) the propeptide. For the fusion in which the propeptide was removed, the EK cleavage site that replaced the Caspase 1 site was moved to a position directly in between the CH2 domain of the knob and mature IL-18AV without the addition of a flexible linker. Using the HEK-Blue IL-18AV reporter cell assay as a readout, we exposed these cells to a titration of FUSE-442 or FUSE-505 with or without treatment with EK. The biological activity, measured as the EC50-SEAP, of FUSE-442 and -505 were attenuated compared to human recombinant IL-18AV at the orders of ~150 fold and ~15,000 fold, respectively (panel C) such that incorporation of the propeptide contributed to ~100-fold additional attenuation compared to the Fc fusion alone. Treatment with EK, designed to cleave off the IL-18AV fragment from FUSE-505 and FUSE-442 led to restoration of biological activity. In the case of FUSE-442, treatment with EK resulted in biological activity that was not substantially different from recombinant human mature IL-18AV. For FUSE-505, however, although biological activity was restored following treatment with EK, potency remained reduced by ~30 fold compared to recombinant human mature IL-18AV. The EC50-SEAP for each compound is shown in panel D. Given that FUSE-505 and FUSE-442 both harbor the same IL-18AV, the difference in activity after demasking with EK could not be explained by any difference in IL-18AV variant. Rather, we observed that EK was far less efficient at releasing IL-18AV from FUSE-505 (<10% cleavage efficiency) than FUSE-442 (>95% cleavage efficiency). Hence, the reduced biological activity observed from EK cleaved FUSE-505 versus EK cleaved 442 was the result of less IL-18AV being released by the former compared to the latter. We hypothesize that the lack of a flexible linker between the CH3 domain of the knob and IL-18AV in FUSE-505 resulted in a mostly inaccessible EK cleavage site. In contrast, the propeptide incorporated into FUSE-442 allowed for sufficient access of EK to its cleavage site for efficient release of IL-18AV. The data indicates strongly that in the context of an IL-18AV Fc fusion protein, the propeptide is not required but contributes to masking of IL-18AV biological activity. In the absence of the propeptide, masking is likely the consequence of steric hindrance mediated by the protein fused to the N-terminal of IL-18AV

[0163] As shown in figure 4, as in figure 3 with IL-18AV, we examined the impact of a propeptide on masking of IL-18mut2AV biological activity in the context of Fc fusions variants incorporating IL-18AVmut2 on the C-terminal of the Fc with (panel A of figure 4, FUSE-424; Fc-EKpp-IL-18mut2AV) or without (panel B, FUSE-441, Fc-EK-IL-18mut2AV) the propeptide. The biological activity of FUSE-441 and FUSE424 were highly attenuated compared to human recombinant IL-18 at the orders of >100,000 fold (panel C). Treatment with EK led to restoration of biological activity. In the case of FUSE-424, treatment with EK resulted in biological activity that was not substantially different from recombinant human mature IL-18. For FUSE-441, however, although the vast majority of biological activity was restored following treatment with EK, potency remained reduced by ~10 fold compared to recombinant human mature IL-18. The EC50-SEAP for each compound is shown in panel D. Given that FUSE-441 and FUSE-442 both harbor the same IL-18mut2AV, the difference in activity after demasking with EK could not be explained by any difference in IL-18 variant. Rather, we observed that EK was far less efficient at releasing IL-18mut2AV from FUSE-441 (<20% cleavage efficiency) than FUSE-424 (>95% cleavage efficiency). Hence, the reduced biological activity observed from EK cleaved FUSE-441 versus EK cleaved FUSE-424 was likely the result of less IL-18mut2AV being released by the former compared to the latter. We hypothesize that the lack of a flexible linker between the CH3 domain of the knob and IL-18mut2AV in FUSE-441 resulted in a mostly inaccessible EK cleavage site. For example, a flexible linker can be the propeptide; or the propeptide behaves as a flexible linker. In contrast, the propeptide incorporated into FUSE-424 allowed for sufficient access of EK to its cleavage site for efficient release of IL-18mut2AV. The data indicates strongly that in the context of an IL-18mut2AV Fc fusion protein, the propeptide is not required for masking of IL-18mut2AV biological activity but is rather the consequence of steric hindrance mediated by the protein fused to the N-terminal of IL-18mut2AV. As such, we hypothesize that any N-terminal protein of sufficient size (e.g., about 4 kDa or larger, e.g., the propeptide is about 4 kDa, Fc is about 28 kDa as a monomer, HSA is about 66 kDa, VHH is about 14 kDa) would be capable of masking the biological activity of IL-18mut2AV; and that an EK cleavage site containing linker of sufficient size (e.g., 25 amino acid or longer) to allow access to EK, when incorporated between the Fc or other N-terminal protein mask and IL-18mut2AV, would substitute for the EK containing propeptide. Further, should such N-terminal masking protein or fragment thereof be engineered or naturally be transported through the Endoplasmic Reticulum (ER), this would result in expression yields from transient transfection of mammalian cells such as Expi-CHO acceptable for therapeutic development.

[0164] As shown in figure 5, we examined the impact of fusing the propeptide-IL-18AV fusion to the C-terminus of wild type IgG1 (FUSE-507, panel A) and wild type IgG4 (FUSE-509, panel B). In both formats, one molecule of the propeptide-IL-18AV fusion are linked to each Fc-CH3 domain, resulting in two molecules of the propeptide-IL-18AV fusion per IgG1 or IgG4 homodimer. As previously described, a cleavage site specific for EK was inserted between the propeptide and mature IL-18 sequence in the location of the endogenous Caspase-1 site. To evaluate the biological activity of the Fc-pro-IL-18 fusion proteins before and after treatment with EK, the HEK-Blue-IL-18 cell reporter system was used. Using this system as a readout, we exposed HEK-Blue-IL-18 cells to a

titration of FUSE-507 (IgG1Fc-EKpp-IL-18AV) or FUSE-509 (IgG4Fc-EKpp-IL-18AV) with or without treatment with EK. The biological activity, measured as the EC50-SEAP, of FUSE-507 and -509 were highly attenuated compared to human recombinant IL-18 at the orders of >10,000 fold (panel C). Treatment with EK, designed to cleave off the IL-18AV fragment from FUSE-507 and FUSE-509 led to restoration of biological activity that was approximately 2 fold greater than hrIL-18. This difference was likely the result of two molecules of IL-18AV being release per IgG1 or IgG4 fusion resulting in about a 2:1 molar ratio of IL-18AV to hrIL-18 when the IgG1 or IgG4 fusion proteins were fully cleaved by EK. The EC50-SEAP for each compound is shown in panel D. We also generated versions of FUSE-507 and FUSE-509 without the propeptide; IgG1Fc-EK-IL-18AV and IgG4Fc-EK-IL-18AV, respectively. These did not express well, likely due to the propensity of IL-18 to form homodimers and the absence of a flexible linker between the CH3 domain of IgG1 or IgG4 and mature IL-18AV (data not shown). The data indicate that the in the context of a propeptide-IL-182AV fusion, it is possible to obtain both expression exceeding 135 mg/L and masking/attenuation of IL-18AV biological activity as high or greater than 100,000 fold (compare Figure 5 to Figure 1 and 3) whether IL-18AV is fused to the C-terminus of wild type IgG1 or IgG4 (two molecules of IL-18AV) or an IgG1 knob into hole heterodimer (one molecule of IL-18AV). The formats utilizing wild type IgG1 or IgG4 indicate allowance for straightforward plug and play fusion of propeptide-IL-18 fusions, their variants and fragments thereof to an array of monoclonal antibodies including commercialized ones such as Avelumab (anti-PDL1), Cetuximab (anti-EGFR), Trastuzumab (anti-HER2/neu), etc.

[0165] As shown in figure 6, to address the universality of masking of IL-18 and its variants by a polypeptide fused to the N-terminus of IL-18's mature form, we examined the capacity of an N-terminal protein (mask) distinct from the Fc domain of IgG to attenuate the biological activity of IL-18-AV with or without the propeptide. The N-terminus of IL-18AV with (panel A, FUSE-501) or without (panel B, FUSE-503) the propeptide was fused to the C-terminus of Human Serum Albumin (HSA). For the fusion in which the propeptide was removed, the EK cleavage site that replaced the Caspase 1 site was moved to a position directly in between the C-terminus of HSA and mature IL-18AV without the addition of a flexible linker. Using the HEK-Blue IL-18 reporter cell assay as a readout, we exposed these cells to a titration of FUSE-501 (HSA-EKpp-IL-18AV) or FUSE-503 (HSA-EK-IL-18AV) with or without treatment with EK. The biological activity, measured as the EC50-SEAP of FUSE-501 (panel C) was highly attenuated compared to human recombinant IL-18 at the order of ~35,000 fold. FUSE-503 (panel D), which does not contain the propeptide, was also attenuated at the order of ~3,500 fold. Treatment with EK, designed to cleave off the IL-18AV fragment from FUSE-501 and FUSE-503 led to restoration of biological activity. In the case of FUSE-501, treatment with EK resulted in biological activity that was not substantially different from recombinant human mature IL-18. For FUSE-503, however, although biological activity was increased by treatment with EK, it remained ~40 fold weaker than human recombinant IL-18. The EC50-SEAP for each compound is shown in panel E. Given that FUSE-501 and FUSE-503 both harbor the same IL-18AV, the difference in activity after demasking with EK could not be explained by any difference in IL-18

variant. Rather, we observed that EK was far less efficient at releasing IL-18AV from FUSE-503 (<20% cleavage efficiency) than FUSE-501 (>95% cleavage efficiency). Hence, the reduced biological activity observed from EK cleaved FUSE-503 versus EK cleaved -501 was the result of less IL-18AV being released by the former compared to the latter. We hypothesize that the lack of a flexible linker between the C-terminus of HSA and IL-18AV in FUSE-503 resulted in a mostly inaccessible EK cleavage site. In contrast, the propeptide incorporated into FUSE-501 allowed for sufficient access of EK to its cleavage site for efficient release of IL-18AV. Taken together with data obtained from the Fc fusions, the results indicate strongly that in the context of an HSA-IL-18AV fusion protein, the propeptide is not required for masking of IL-18AV biological activity but may contribute to greater attenuation when present in HSA-IL-18 fusion proteins. For both FUSE-501 and -503, masking appears to be the consequence of steric hindrance mediated by the protein fused to the N-terminal of IL-18AV. As such, this data provides further support that any N-terminal protein of sufficient size would be capable of masking the biological activity of IL-18AV and that an EK cleavage site containing linker of sufficient size to allow access to EK, when incorporated between the Fc, HSA or other N-terminal protein mask and IL-18AV, would substitute for the EK containing propeptide. Further, should such N-terminal masking protein or fragment thereof be engineered or naturally be transported through the Endoplasmic Reticulum (ER), this would result in expression yields from transient transfection of mammalian cells such as Expi-CHO acceptable for therapeutic development.

[0166] As shown in figure 7, to address the universality of masking of IL-18 and its variants by a polypeptide fused to the N-terminus of IL-18's mature form, we examined the capacity of an N-terminal protein (mask) distinct from the Fc domain of IgG to attenuate the biological activity of IL-18-mut2AV with or without the propeptide. The N-terminus of IL-18mut2AV with (panel A, FUSE-502) or without (panel B, FUSE-504) the propeptide was fused to the C-terminus of Human Serum Albumin (HSA). For the fusion in which the propeptide was removed, the EK cleavage site that replaced the Caspase 1 site was moved to a position directly in between the C-terminus of HSA and mature IL-18AV without the addition of a flexible linker. Using the HEK-Blue IL-18 reporter cell assay as a readout, we exposed these cells to a titration of FUSE-502 (HSA-EKpp-IL-18mu2AV) or FUSE-504 (HSA-EK-IL-18mut2AV) with or without treatment with EK. The biological activity, measured as the EC50-SEAP, of FUSE-502 (panel C) and FUSE-504 (panel D) were highly attenuated compared to human recombinant IL-18 at the orders of at least ~30,000 fold and ~50,000 fold, respectively. Treatment with EK, designed to cleave off the IL-18mut2AV fragment from FUSE-504 and FUSE-502 led to restoration of biological activity. In the case of FUSE-502, treatment with EK resulted in biological activity that was not substantially different from recombinant human mature IL-18 (panel C). For FUSE-504, although the vast majority of biological activity was restored following treatment with EK, potency remained reduced by ~3 fold compared to recombinant human mature IL-18 (panel D). The EC50-SEAP for each compound is shown in panel E. Given that FUSE-504 and FUSE-502 both harbor the same IL-18mut2AV, the difference in activity after demasking with EK could not be explained by any difference in IL-18 variant. Rather, we observed that EK was far less efficient at releasing IL-18mut2AV from FUSE-504 (<20% cleavage efficiency) than FUSE-502 (>95% cleavage efficiency). Hence, the

reduced biological activity observed from EK cleaved FUSE-504 versus EK cleaved -502 was the result of less IL-18mut2AV being released by the former compared to the latter. We hypothesize that the lack of a flexible linker between the C-terminus of HAS and IL-18mut2AV in FUSE-504 resulted in a mostly inaccessible EK cleavage site. In contrast, the propeptide incorporated into FUSE-502 allowed for sufficient access of EK to its cleavage site for efficient release of IL-18mut2AV. Taken together with data obtained from the Fc fusions, the results indicate strongly that in the context of an HSA-IL-18mut2AV fusion protein, the propeptide is not required for masking of IL-18mut2AV biological activity but is rather the consequence of steric hindrance mediated by the protein fused to the N-terminal of IL-18mut2AV. As such, this data provides further support that any N-terminal protein of sufficient size would be capable of masking the biological activity of IL-18mut2AV and that an EK cleavage site containing linker of sufficient size to allow access to EK, when incorporated between the Fc, HAS or other N-terminal protein mask and IL-18mut2AV, would substitute for the EK containing propeptide. Further, should such N-terminal masking protein or fragment thereof be engineered or naturally be transported through the Endoplasmic Reticulum (ER), this would result in expression yields from transient transfection of mammalian cells such as Expi-CHO acceptable for therapeutic development.

[0167] As shown in figure 8, we examined the impact of the propeptide on the biological activity of a single IL-18AV fused to the N-terminus of IgG1 Fc. Panels A and B are exemplary illustrations of IL-18AV fused on the knob of a knob into hole IgG1-Fc domain with the propeptide (FUSE-499; Fc-pp-IL-18AV; panel A) or without the propeptide (FUSE-500; Fc-IL-18AV; panel B). In this case, we used a wild type propeptide in which all cysteine residues were substituted for valine but the Caspase 1 site was maintained. To allow for translocation of both constructs into the Endoplasmic Reticulum (ER) of mammalian cells and hence expression/secretion, the signal peptide from the Ig Kappa chain (IgK leader) was encoded upstream of either the propeptide of FUSE-499 or the IL-18AV of FUSE-500. Using the HEK-Blue IL-18 reporter cell assay as a readout, we examined the capacity of our C→V (AV) propeptide to mask IL-18AV (FUSE-499) and the ability of Caspase 1 to demask/restore biological activity. The biological activity, measured as the EC₅₀-SEAP, of FUSE499 was highly attenuated compared to human recombinant IL-18 at the order of >50,000 fold (panel C). In contrast, in the absence of the propeptide in FUSE-500, there was no reduction in biological activity compared to human recombinant IL-18, indicating that in the absence of a the propeptide (or another polypeptide) attached to the N-terminus of mature IL-18, the IL-18-Fc fusion protein is fully functional. Importantly, de-masking of FUSE-499 with Caspase 1 resulted in restoration of biological activity that was not appreciably different from to human recombinant IL-18. Treatment of FUSE-500, which did not contain a masking domain nor Caspase 1 cleavage site, with Caspase 1 served as a negative control and indeed had no effect on biological activity. This data indicates that in the configuration whereby IL-18AV is linked to the N-terminus of an IgG, the propeptide is required for attenuation. Taken together with our previous data that a CH3 domain or HSA attenuated the biological activity of IL-18AV and IL-18mut2AV when fused to the N-terminus of each IL-18 variant without the presence of a propeptide, we hypothesize that any polypeptide of sufficient size fused to the N-terminal of mature IL-18 and/or its variants and

fragments thereof would be capable of masking the biological activity of IL-18. While the smallest polypeptide tested was the propeptide (~6 kDa), polypeptides as small as 2 kDa would also be of sufficient size. In various embodiments, the short polypeptide or protein being about 2 kDa or no greater than 250 kDa. Further, the propeptide in FUSE-499 is not naturally transported through the ER but was engineered to do so via addition of an IgK leader sequence upstream to it. This indicates that any polypeptide of sufficient size fused to the N-terminus of mature IL-18 and/or its variants and fragments thereof would be expected to attenuate the biological activity of IL-18. That is, the N-terminal polypeptide might naturally translocate into the Endoplasmic Reticulum (ER) or it may be engineered to do so. In both cases, transport through the ER is important for obtaining expression yields from transient transfection of mammalian cells such as Expi-CHO acceptable for therapeutic development.

[0168] As shown in figures 9A-9I, we examined whether proteases other than the proof of concept EK could be used to demask/activate pro-IL-18. As such, we chose (a) the matrix metalloproteinase (MMP), MMP2, reported to be preferentially over-expressed in the tumor microenvironment and (b) Granzyme B, which is released by cytotoxic lymphocytes including NK cells and CD8+ T cells and may therefore accumulate in inflamed tumors. For MMP2, we replaced the EK cleavage site within the propeptide (pp) of FUSE-442 (Fc-EKpp-IL-18AV) with the (a) the MMP2/9 cleavage sequence (GPLGVR (SEQ ID NO:89)) to generate FUSE-486 (Fc-MMP2pp-IL-18AV) and (b) the MMP9/2 cleavage sequence (VHMPGLGFLGP (SEQ ID NO:90)) to generate FUSE-487 (Fc-MMP2/9pp-IL-18AV). (Desnoyers et al., *Sci Transl Med.* 2013 Oct 16;5(207):207ra144.) In each case, the MMP to the left of the forward slash preferentially cleaves the aforementioned peptide sequence. For Granzyme B, we substituted the EK cleavage site within the propeptide (pp) of both FUSE-442 (Fc-EKpp-IL-18AV) and FUSE-424 (Fc-EKpp-IL-18mut2AV) with a prototypical cleavage site for Granzyme B (IEQD (SEQ ID NO:88)); thus, generating FUSE-485 (Fc-GzmBpp-IL-18AV) and FUSE-462 (Fc-GzmBpp-IL-18mut2AV). FUSE-486, FUSE-487, FUSE-485 and FUSE-462 are illustrated in FIGs. 9A and 9D. Using the HEK-Blue IL-18 reporter cell assay as a readout, we exposed these cells to a titration of (a) FUSE-486 or FUSE-487 (9B) with or without treatment with recombinant human MMP2 or (b) FUSE-485 or FUSE-462 with or without recombinant human Granzyme B (FUSE-485 and FUSE-462) (see FIG. 9D). The biological activity, measured as the EC50-SEAP, of the MMP produg fusions, FUSE486 and FUSE487, were greatly attenuated at the orders of up to approximately 5000-fold compared to rhIL18. Following treatment of FUSE-486 with MMP2, the biological activity of the demasked IL-18AV fragment was restored to within 3-fold that of rhIL-18. Next, we added a Granzyme B cleavage site immediately C-terminal to the MMP site in FUSE486 to create FUSE587 (black triangle). As seen in FIG. 9C, FUSE587 was about 3,000-fold attenuated relative to recombinant human IL-18.

[0169] Interestingly, we observed that cleavage of FUSE587 with MMP2 released an IL-18AV variant that was still about 100-fold attenuated relative to recombinant IL-18. In contrast, cleavage with Granzyme B released an IL-18AV variant with activity similar activity as recombinant IL-18. Cleavage with Granzyme B results in release of mature IL-18AV without any N-terminal residues constituting an overhang, whereas 11 and 15 amino acid N-terminal polypeptide overhangs remain after cleavage of FUSE486 and FUSE587, respectively, with

MMP2. We speculated that these overhangs might be attenuating IL-18AV activity, albeit to a lesser degree than the full size variant propeptide. This phenomenon was further investigated in FIG. 11 and FIG. 13.

[0170] FUSE-485 and FUSE-462 were also highly attenuated compared to human recombinant IL-18 at the orders of >15,000-fold (9E and 9F). Treatment with recombinant human Granzyme B (rhGb), designed to cleave off the IL-18AV fragment and the IL-18mut2AV fragment from FUSE-485 and FUSE-462, respectively, led to restoration of biological activity. In both cases, the masked IL-18 variants displayed nearly identical attenuation and the restored biological activity was about 2-fold weaker than recombinant human mature IL-18. Further, we did not observe an appreciable difference between the activity of the demasked IL-18AV and IL-18mut2AV.

[0171] Summary tables of the potencies (EC50-SEAP) for each of the test articles is shown below FIGs 9A-9B and in FIG. 9F.

[0172] We next examined whether our finding could form the basis for a plug and play masked IL-18 platform for targeting pro-IL-18 variants to cell surface proteins including but not limited to tumor associated antigens (TAA). As such, we used Cetuximab as our proof-of-concept TAA targeting protein for pro-IL-18 fusion. Cetuximab is an EGFR targeting monoclonal antibody that is commercially used for the treatment of multiple cancer indications including colorectal and head and neck cancer. First, we fused a Granzyme B cleavable pp-IL-18AV onto the C-terminus of Cetuximab's Fc domain. We found that fusion of pp-Gb-IL-18AV onto the CH3 domain of Cetuximab, that forms a natural homodimer, expressed poorly. This was presumably due to the presence of two fabs because a knob into hole IgG1 format in which ppGb-IL-18AV was fused to the C-terminus knob (or hole) and the EGR specific fab was fused to the N-terminal knob (or hole) expressed well. FUSE-517 (Cetuximab_KiH_ppGb-IL-18-AV), as illustrated in panel G consists of the fab from Cetuximab fused to the N-terminus of the Fc-knob and ppGb-IL-18AV fused to the C-terminus of the Fc-knob. Using the HEK-Blue IL-18 reporter cell assay as a readout, we exposed these cells to a titration of FUSE-517 (9H) with or without treatment with rhGb. Relative to rhIL-18, FUSE-517 was highly attenuated at the order of >250,000-fold. Treatment of FUSE-517 with rhGb, designed to cleave off IL-18AV, led to the restoration of biological activity within 2-fold that of rhIL-18.

[0173] FIG. 9I is summary tables of potencies (EC50-SEAP) related to the data shown in FIG. 9H. Overall, the data indicates strongly that both MMP2 and granzyme B are capable of demasking/activating IL-18AV (and IL-18mut2AV with Granzyme B) in the context of a pp mask fused in-between an IgG CH3 domain and the mature IL-18AV fragment. Given our ability to successfully use other polypeptides that translocate through the ER as masks when fused to the N-terminus of multiple variants of IL-18, our observation suggests strongly that masked fusion proteins of IL-18, its variants or fragments thereof can be engineered to be selectively activated by proteases found in tumors/inflamed tumors including MMPs and Granzymes. As shown in figure 10, we examined the susceptibility of select IL-18 variants to attenuation of biological activity by its natural antagonist, IL-18 BP. Panel A of figure 10 is an illustration of the IL-18 fusion proteins examined. That is, FUSE-442 (Fc-EKpp-IL-18AV)

and FUSE-424 (Fc-EKpp-IL-18mut2AV). Both variants contain the same cysteine to valine substitutions, however, FUSE-424 harbors a mature IL-18AV (termed IL-18mut2AV) downstream of the polypeptide (pp) that includes the following mutations: M51K, K53G, M60L and M113V. These four residues within the mature 18 kDa fragment of IL-18 were previously described as important to binding/masking of wild type IL-18. We therefore hypothesized that substitution of these residues would reduce binding of IL-18 BP such that IL-18AVmut2 would maintain biological activity in the presence of IL-18BP, which is often over-represented relative to IL-18 in the tumor microenvironment (TME). As in previous examples, HEK Blue IL-18 was used to assess biological activity via MYD88 driven SEAP and potency reported as the EC₅₀-SEAP. FUSE-442 (Fc-EKpp-IL-18AV) and FUSE-424 (Fc-EKpp-IL-18mut2AV) were treated with EK to release mature IL-18AV or IL-18mut2AV, respectively. Each cleavage product was then titrated from 1 pg/ml to 1 µg/ml in media alone or media containing 1.25 µg/ml human recombinant IL-18-BP (hrIL-18-BP). Human recombinant IL-18 (hrIL-18) was used as the reference molecule for wild type inhibition of HEK Blue IL-18 reporter activity mediated by rhIL-18BP. Panels B (rhIL-18), D (FUSE-442), and F (FUSE-424) are non-linear x-y plots of SEAP release (IL-18R reporter activity) on the y-axis versus the concentration of test article on the x-axis in the presence or absence of IL-18BP. A summary of biological potencies (EC₅₀-SEAP) relevant to each graph is shown as panels C, E, and G (beneath each x-y plot). As is well documented, we observed strong attenuation of rhIL-18 by rhIL-18BP in the order of at least 300-1000-fold. For IL-18AV released from FUSE442, we observed about 100 to 150-fold attenuation of biological activity (i.e., ~3-6 fold less than rhIL-18) suggesting that apparent affinity of IL-18AV for IL-18BP is weaker than that of rhIL-18 for IL-18BP. Importantly, the cleavage product of FUSE424, IL-18mut2AV, appeared resistant to biological attenuation by rhIL-18BP. As seen in panel F, we observed no appreciable difference in biological activity between IL-18mut2AV released from FUSE424 and the same molecule exposed to rhIL-18BP. This data suggests strongly that IL-18mut2AV binds with far weaker apparent affinity to rhIL-18BP compared to IL-18AV or rhIL-18. As such, a masked version of IL-18mut2AV designed to be released by proteases present in the TME including but not limited to MMP2, 9 and 14 and/or proteases released in inflamed tumors including but not limited to Granzymes A, B and M may be predicted to function in the presence of IL-18BP to promote anti-tumor activity via multiple pathways including but not limited to IFN γ mediated Th1 and Tc1 activity.

Example 2

[0174] As shown in figure 11, we examined the impact of the size of polypeptides fused to the N-terminus of mature IL-18 on the biological activity of a single IL-18AV fused to the N-terminus of IgG1 Fc. Panels A are exemplary illustrations of IL-18AV fused on the knob of a knob into hole IgG1-Fc domain with different size polypeptides ranging from a propeptide variant (FUSE-499; described in FIG. 18) to 35 amino acids (FUSE756) to 15 amino acids (FUSE757 and FUSE758). To allow for translocation of all constructs into the Endoplasmic Reticulum (ER) of mammalian cells and hence expression/secretion, the signal peptide from the Ig Kappa chain (IgK leader) was encoded upstream of the polypeptides (and cleaved off the signal peptidase in the

ER). The polypeptides of FUSE756 and FUSE757 are made up of a series of glycine and serine residues whereas that of FUSE758 is the sequence of the overhang generated by MMP2 mediated cleavage of the MMP cleavage site, KPLGLQARVVGGGG (SEQ ID NO:252). In these three cases, the C-terminus of the N-terminal polypeptides also incorporated the Granzyme B site, IEQD (SEQ ID NO:88). Using the HEK-Blue IL-18 reporter cell assay as a readout, we examined the capacity of the different size polypeptides to attenuate/mask IL-18AV-Fc (FUSE500; closed squares) or rhIL-18 (black cross hatches "X"). All polypeptides fused to the N-terminus of mature IL-18AV reduced biological activity, measured as EC50-SEAP, by at least 100-fold. FUSE499 (closed triangles) was the most attenuated (>10,000-fold). FUSE757 (closed diamonds) and 758 (open reverse triangle), both of which included 11 amino acid polypeptides fused to the N-terminus of mature IL-18AV, were about 250-fold less biologically active relative to FUSE500 or rhIL-18. FUSE756 (open triangles), which contained a polypeptide of 31 amino acids polypeptides fused to the N-terminus of mature IL-18AV was approximately 1000-fold less biologically active relative to FUSE500 or rhIL-18. Thus, all polypeptides tested and larger proteins including HSA and fragments of IgG from previous examples, fused to the N-terminus of mature IL-18AV, regardless of size or amino acid constitution, attenuated the biological activity of mature IL-18. The degree of attenuation appears to correlate positively with the size of the polypeptide/protein fused to the N-terminus of IL-18.

Example 3

Techniques and Procedures

HEK-Blue-IL-18 cell activation assay with IL-18 or FUSE proteins

[0175] HEK-BLUE™-IL-18 cells from Invivogen were maintained in culture medium (DMEM medium with 4.5 g/L glucose, 2 mM L-Glutamine, 10% (v/v) heat-inactivated fetal bovine serum, 100 U/mL penicillin, 100 µg/mL streptomycin, 100 µg/mL Normocin and 1× HEK-blue selection reagent). HEK-BLUE™ IL-18 cells are engineered from the human embryonic kidney 293 (HEK293) cell line to stably express genes encoding the IL-18 receptor (IL-18R) and IL-18 receptor accessory protein (IL-18RAP) and express an NF-Kb/AP-1-inducible secreted embryonic alkaline phosphatase (SEAP) reporter gene, therefore being useful for detection of bioactive IL-18 by monitoring the activation of the NF-Kb and AP-1 pathways via quantification in the supernatant of the SEAP level (which is produced upon activation of NF-Kb) with a solution such as QUANTI-BLUE™ Solution. In addition, the responses to human TNF-α and IL-1β have been blocked in HEK-BLUE™ IL-18 cells, and so the HEK-BLUE™ IL-18 cells are responsive specifically to IL-18.

[0176] On the day of experiment setup, HEK-BLUE-IL-18 cells were gently rinsed twice with pre-warmed phosphate buffered saline (PBS) and then detached in PBS by tapping the flask. Detached HEK-Blue-IL-18 cells were resuspended in pre-warmed testing medium (DMEM with 4.5 g/L glucose, 2 mM L-Glutamine, 10% (v/v) heat-inactivated FBS, 100 U/mL penicillin, and 100 µg/mL streptomycin) at the density of 5×10^5 cell per mL.

To seed the cells (50000 cells per well), 100 μ L of resuspended HEK-Blue-IL-18 cells were added to designated wells in 96-well plate.

[0177] For protein preparation, FUSE proteins were diluted in testing medium from 500000 pg/mL to 6.4 pg/mL ($2\times$ of final concentration) by 5-fold serial dilution. IL-18 was also diluted in testing medium from 800 pg/mL to 1.28 pg/mL ($2\times$ of final concentration) by 5-fold serial dilution. To treat HEK-Blue-IL-18 cells, 100 μ L of prepared IL-18 or FUSE proteins were added to the designated wells with 50000 cells in the 96-well plate, and then the proteins were gently mixed the cells. The 96-well plate was then incubated at 37°C with 5% CO₂ for 24 hours.

[0178] After 24-hour activation, HEK-Blue-IL-18 cells released secreted alkaline phosphatase in the supernatant. 20 μ L of HEK-Blue-IL-18 cell culture supernatant was transferred to a new 96-well plate. Meanwhile, QUANTI-Blue solution from Invivogen was prepared by adding 1 mL of QB reagent and 1 mL of QB buffer to 98 mL of sterile water. 180 μ L of prepared QUANTI-Blue solution was then added to the 96-well plate with 20 μ L of HEK-Blue-IL-18 cell culture supernatant and incubated at 37°C for 4 hours. The level of secreted alkaline phosphatase related to HEK-Blue-IL-18 cell activation was detected by measuring the OD at 630 nm using a spectrophotometer.

HEK-Blue-IL-18 cell activation assay with enterokinase (EK)-cleaved FUSE proteins

[0179] HEK-Blue-IL-18 cells from Invivogen were maintained in culture medium. On the day of experiment setup, HEK-Blue-IL-18 cells were gently rinsed twice with pre-warmed phosphate buffered saline (PBS) and then detached in PBS by tapping the flask. Detached HEK-Blue-IL-18 cells were resuspended in pre-warmed testing medium at the density of 5×10^5 cell per mL. To seed the cells (50000 cells per well), 100 μ L of resuspended HEK-Blue-IL-18 cells were added to designated wells in 96-well plate.

[0180] For FUSE protein cleavage, 4 μ g of FUSE protein was mixed with 80 ng of EK enzyme and 2 μ L of $10\times$ PBS in a tube. Sterile water was added to the tube to bring the total reaction volume to 20 μ L. The tube was then incubated at 25 °C for 40 minutes. After 40-minute incubation, cleaved FUSE proteins were diluted in testing medium from 500000 pg/mL to 6.4 pg/mL ($2\times$ of final concentration) by 5-fold serial dilution. IL-18 was also diluted in testing medium from 800 pg/mL to 1.28 pg/mL ($2\times$ of final concentration) by 5-fold serial dilution. To treat HEK-Blue-IL-18 cells, 100 μ L of prepared IL-18 or cleaved FUSE proteins were added to the designated wells with 50000 cells in the 96-well plate and then gently mixed the cells with proteins. The 96-well plate was then incubated at 37°C with 5% CO₂ for 24 hours.

[0181] After 24-hour activation, 20 μ L of HEK-Blue-IL-18 cell culture supernatant with secreted alkaline phosphatase was transferred to a new 96-well plate. Meanwhile, QUANTI-Blue solution was prepared by adding 1 mL of QB reagent and 1 mL of QB buffer to 98 mL of sterile water. 180 μ L of prepared QUANTI-Blue solution was then added to the 96-well plate with 20 μ L of HEK-Blue-IL-18 cell culture supernatant and incubated

at 37°C for 4 hours. The level of secreted alkaline phosphatase related to HEK-Blue-IL-18 cell activation was detected by measuring the OD at 630 nm using a spectrophotometer.

HEK-Blue-IL-18 cell activation assay with matrix metalloproteinase (MMP)-cleaved FUSE proteins

[0182] HEK-Blue-IL-18 cells from Invivogen were maintained in culture medium. On the day of experiment setup, HEK-Blue-IL-18 cells were gently rinsed twice with pre-warmed phosphate buffered saline (PBS) and then detached in PBS by tapping the flask. Detached HEK-Blue-IL-18 cells were resuspended in pre-warmed testing medium at the density of 5×10^5 cell per mL. To seed the cells (50000 cells per well), 100 μ L of resuspended HEK-Blue-IL-18 cells were added to designated wells in 96-well plate.

[0183] For FUSE protein cleavage, 1 μ g of FUSE protein was mixed with 280 ng of MMP2 or MMP9 enzyme and 2.8 μ L of $10\times$ assay buffer (500 mM Tris, 100 mM CaCl_2 , 1500 mM NaCl, 0.5% (w/v) Brij-35, pH 7.5,) in a tube. Sterile water was added to the tube to bring the total reaction volume to 28 μ L. The tube was then incubated at 37 °C for 2 hours. After 2-hour incubation, cleaved FUSE proteins were diluted in testing medium from 500000 pg/mL to 6.4 pg/mL ($2\times$ of final concentration) by 5-fold serial dilution. IL-18 was also diluted in testing medium from 800 pg/mL to 1.28 pg/mL ($2\times$ of final concentration) by 5-fold serial dilution. To treat HEK-Blue-IL-18 cells, 100 μ L of prepared IL-18 or cleaved FUSE proteins were added to the designated wells with 50000 cells in the 96-well plate and then gently mixed the cells with proteins. The 96-well plate was then incubated at 37°C with 5% CO_2 for 24 hours.

[0184] After 24-hour activation, 20 μ L of HEK-Blue-IL-18 cell culture supernatant with secreted alkaline phosphatase was transferred to a new 96-well plate. Meanwhile, QUANTI-Blue solution was prepared by adding 1 mL of QB reagent and 1 mL of QB buffer to 98 mL of sterile water. 180 μ L of prepared QUANTI-Blue solution was then added to the 96-well plate with 20 μ L of HEK-Blue-IL-18 cell culture supernatant and incubated at 37°C for 4 hours. The level of secreted alkaline phosphatase related to HEK-Blue-IL-18 cell activation was detected by measuring the OD at 630 nm using a spectrophotometer.

HEK-Blue-IL-18 cell activation assay with Caspase I-cleaved FUSE proteins

[0185] HEK-Blue-IL-18 cells from Invivogen were maintained in culture medium. On the day of experiment setup, HEK-Blue-IL-18 cells were gently rinsed twice with pre-warmed phosphate buffered saline (PBS) and then detached in PBS by tapping the flask. Detached HEK-Blue-IL-18 cells were resuspended in pre-warmed testing medium at the density of 5×10^5 cell per mL. To seed the cells (50000 cells per well), 100 μ L of resuspended HEK-Blue-IL-18 cells were added to designated wells in 96-well plate.

[0186] For FUSE protein cleavage, 14 μ g of FUSE protein was mixed with 0.5 unit of Caspase I enzyme and 2.8 μ L of $10\times$ assay buffer (500 mM Hepes, pH 7.2, 500 mM NaCl, 1% Chaps, 100 mM EDTA, 50% Glycerol, and 100 mM DTT) in a tube. Sterile water was added to the tube to bring the total reaction volume to 28 μ L. The tube was then incubated at 37 °C for 2 hours. After 2-hour incubation, cleaved FUSE proteins were diluted in testing medium from 500000 pg/mL to 6.4 pg/mL ($2\times$ of final concentration) by 5-fold serial dilution. IL-18 was

also diluted in testing medium from 800 pg/mL to 1.28 pg/mL ($2\times$ of final concentration) by 5-fold serial dilution. To treat HEK-Blue-IL-18 cells, 100 μ L of prepared IL-18 or cleaved FUSE proteins were added to the designated wells with 50000 cells in the 96-well plate and then gently mixed the cells with proteins. The 96-well plate was then incubated at 37°C with 5% CO₂ for 24 hours.

[0187] After 24-hour activation, 20 μ L of HEK-Blue-IL-18 cell culture supernatant with secreted alkaline phosphatase was transferred to a new 96-well plate. Meanwhile, QUANTI-Blue solution was prepared by adding 1 mL of QB reagent and 1 mL of QB buffer to 98 mL of sterile water. 180 μ L of prepared QUANTI-Blue solution was then added to the 96-well plate with 20 μ L of HEK-Blue-IL-18 cell culture supernatant and incubated at 37°C for 4 hours. The level of secreted alkaline phosphatase related to HEK-Blue-IL-18 cell activation was detected by measuring the OD at 630 nm using a spectrophotometer.

HEK-Blue-IL-18 cell activation assay with granzyme B-cleaved FUSE proteins

[0188] HEK-Blue-IL-18 cells from Invivogen were maintained in culture medium. On the day of experiment setup, HEK-Blue-IL-18 cells were gently rinsed twice with pre-warmed phosphate buffered saline (PBS) and then detached in PBS by tapping the flask. Detached HEK-Blue-IL-18 cells were resuspended in pre-warmed testing medium at the density of 5×10^5 cell per mL. To seed the cells (50000 cells per well), 100 μ L of resuspended HEK-Blue-IL-18 cells were added to designated wells in 96-well plate.

[0189] Mature active human granzyme B was generated by cleaving human pro-granzyme B using EK enzyme. In brief, 4 μ g of human pro-granzyme B was mixed with 40 ng of EK enzyme and 2 μ L of $10\times$ PBS in a tube. Sterile water was added to the tube to bring the total reaction volume to 20 μ L. The tube was then incubated at 25 °C for 40 minutes. After 40-minute incubation, activated human granzyme B was used to cleave FUSE proteins. In brief, 10 μ g of fuse proteins were mixed with 1 μ g of activated human granzyme B in assay buffer (50 mM HEPES (pH 7.4), 100 mM NaCl, 0.1% CHAPS, 1 mM EDTA, 10% Glycerol) and incubated for certain time indicated in each experiment at 37°C.

[0190] Granzyme B-cleaved fuse proteins were then diluted in testing medium from 500000 pg/mL to 6.4 pg/mL ($2\times$ of final concentration) by 5-fold serial dilution. IL-18 was also diluted in testing medium from 800 pg/mL to 1.28 pg/mL ($2\times$ of final concentration) by 5-fold serial dilution. To treat HEK-Blue-IL-18 cells, 100 μ L of prepared IL-18 or cleaved FUSE proteins were added to the designated wells with 50000 cells in the 96-well plate and then gently mixed the cells with proteins. The 96-well plate was then incubated at 37°C with 5% CO₂ for 24 hours.

[0191] After 24-hour activation, 20 μ L of HEK-Blue-IL-18 cell culture supernatant with secreted alkaline phosphatase was transferred to a new 96-well plate. Meanwhile, QUANTI-Blue solution was prepared by adding 1 mL of QB reagent and 1 mL of QB buffer to 98 mL of sterile water. 180 μ L of prepared QUANTI-Blue solution was then added to the 96-well plate with 20 μ L of HEK-Blue-IL-18 cell culture supernatant and incubated

at 37°C for 4 hours. The level of secreted alkaline phosphatase related to HEK-Blue-IL-18 cell activation was detected by measuring the OD at 630 nm using a spectrophotometer.

IL-18BP blockage of IL-18 or FUSE protein-induced HEK-Blue-IL-18 cell activation

[0192] HEK-Blue-IL-18 cells from Invivogen were maintained in culture medium. On the day of experiment setup, HEK-Blue-IL-18 cells were gently rinsed twice with pre-warmed phosphate buffered saline (PBS) and then detached in PBS by tapping the flask. Detached HEK-Blue-IL-18 cells were resuspended in pre-warmed testing medium at the density of 5×10^5 cell per mL. To seed the cells (50000 cells per well), 100 μ L of resuspended HEK-Blue-IL-18 cells were added to designated wells in 96-well plate.

[0193] Non-cleaved or cleaved FUSE proteins were prepared in testing medium from 1000000 pg/ml to 12.8 pg/ml ($4\times$ of final concentration) by 5-fold serial dilution. IL-18BP was diluted in testing medium at the concentration of 5,000,000 pg/ml ($4\times$ of final concentration). To treat HEK-Blue-IL-18 cells, 50 μ L of prepared non-cleaved or cleaved FUSE proteins and 50 μ L of prepared IL-18BP were mixed, incubated for 1 hour, and then added to the designated wells with 50000 cells in the 96-well plate and then gently mixed the cells with proteins. The 96-well plate was then incubated at 37°C with 5% CO₂ for 24 hours. Since our fusion proteins have attenuated binding to the IL-18R complex, we conceive that they will also have reduced binding to IL-18BP, compared to cleaved FUSE proteins, because both IL-18R and IL-18BP compete for binding to IL-18. The recent crystal structures of binary and ternary complexes of hIL-18 with its receptors have shown that IL-18BP competes directly with the hIL-18R α D3 domain for binding hIL-18, overlapping the previously identified hIL-18 binding site II (Krumm, et al., *Acta Crystallogr F Struct Biol Commun.* 2015 Jun 1; 71(Pt 6): 710–717).

[0194] After 24-hour activation, 20 μ L of HEK-Blue-IL-18 cell culture supernatant with secreted alkaline phosphatase was transferred to a new 96-well plate. Meanwhile, QUANTI-Blue solution was prepared by adding 1 mL of QB reagent and 1 mL of QB buffer to 98 mL of sterile water. 180 μ L of prepared QUANTI-Blue solution was then added to the 96-well plate with 20 μ L of HEK-Blue-IL-18 cell culture supernatant and incubated at 37°C for 4 hours. The level of secreted alkaline phosphatase related to HEK-Blue-IL-18 cell activation was detected by measuring the OD at 630 nm using a spectrophotometer.

Binding assay by Biolayer Interferometry

[0195] Coating proteins were prepared in 1 $\times$ PBS with 0.02% Tween-20 with the final concentration of 15 μ g/mL. Capturing protein were also prepared, and serial diluted (4-fold dilution ranging from 400 nM to 1.6 nM) in 1 $\times$ PBS with 0.02% Tween-20. The biosensors were pre-moistened in 200 μ L of 1 $\times$ PBS with 0.02% Tween-20 for 10 minutes. Meanwhile, Octet BLI system (ForteBio) was prewarmed for 30 minutes and the flow rate was set to 1000 rpm. The biosensors (Capture biosensor) were soaked in 250 μ L of 1 $\times$ PBS with 0.02% Tween-20 for 60 seconds at 30 °C to get an initial baseline reading. After the 60-second baseline reading, the biosensors were exposed to coating proteins for 300 seconds at 30 °C for the association between antibody and the biosensors (coupling coating proteins with biosensor). The biosensors with coating proteins were then exposed to capturing proteins in

250 uL of 1×PBS with 0.02% Tween-20 at 30 °C for 300 seconds for the association reaction between the coating proteins and capturing proteins (association curve). After 300-second association reaction between coating proteins and capturing proteins, the biosensors with coating proteins and capturing proteins were then exposed to 250 uL of 1×PBS with 0.02% Tween-20 at 30 °C for 300 seconds for the dissociation reaction between coating proteins and capturing proteins (dissociation curve). For binding to IL18BP, each IL18 mutant was coated onto AHC biosensor tips and probed with recombinant His tagged IL-18BP at concentrations ranging from 400 nM to 1.6 nM. For binding to IL18Rα, His tagged IL18Rα was coated into nickel biosensor tips and probed with recombinant each IL18 mutant at concentrations ranging from 400 nM to 1.6 nM. The binding affinity was calculated by the built-in data fitting algorithm.

Example 4

- [0196]

As shown in figure 12, we engineered eleven mutants of human IL-18 (IL-18AV shown) and measured their ability to bind recombinant human IL-18BP and recombinant human IL-18RA (also termed IL-18Rα). All test articles were generated as Fc fusion proteins with the IL-18 variant fused to the N-terminus of the Fc (see FIG. 11A). The locations and amino acid substitutions associated with each variant are depicted in FIG. 12A.
- [0197]

To assess binding to human IL18BP or human IL18Rα, kinetic binding graphs were generated via Bio-Layer Interferometry (BLI) using an Octet system (ForteBio). For binding to IL18BP, each IL18 mutant was coated onto AHC biosensor tips and probed with recombinant His tagged IL-18BP at concentrations ranging from 400 nM to 1.6 nM (FIG. 12B). For binding to IL18Rα, His tagged IL18Rα was coated into nickel biosensor tips and probed with recombinant each IL18 mutant at concentrations ranging from 400 nM to 1.6 nM (FIG. 12D). Summary tables for binding to IL-18BP and IL18-RA (binding affinity (KD), on rate (k-on) and off rate (k-dis)) are shown in FIGs 12C and 12E, respectively.
- [0198]

All eleven IL-18 mutants bound to IL18BP with weaker affinity than FUSE500 (wild type human IL-18-AV-Fc). Five mutants were associated with no appreciable binding. These are FUSE545, FUSE599, FUSE600, FUSE601 and FUSE602.
- [0199]

In contrast, all eleven mutants maintained appreciable binding to IL18RA. The affinities ranged from 11 nM to 30 nM, which was only between 1.5-fold and 4-fold weaker than the affinity of FUSE500 for IL-18RA (7.4 nM).

Example 5

- [0200]

As shown in the table below, we tabulated the binding affinities of eleven mutant variants of human IL-18 (IL-18AV shown) to human IL18BP and human IL18Rα. Each IL-18 protein was generated as an Fc fusion proteins whereby the IL-18 variant was fused to the N-terminus of the Fc (see FIG. 11A).

Protein	Mutant	IL-BP Kd (nM)	IL-18Rα Kd (nM)
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IL18		4E-10***	2E-08****
FUSE500	Wild type AV	7.28E-10*	7.4E-09**
FUSE 545	mut2	-	1.9E-08
FUSE 546	mut3	1.4E-07	1.8E-08
FUSE 547	mut4	4.0E-08	2.6E-08
FUSE 583	mut5	3.2E-09	1.2E-08
FUSE 584	mut6	4.0E-08	2.5E-08
FUSE 585	mut7	1.5E-07	2.0E-08
FUSE 586	mut8	2.6E-09	1.6E-08
FUSE 599	mut9	-	3.0E-08
FUSE 600	mut10	-	1.8E-08
FUSE 601	mut11	-	2.1E-08
FUSE 602	mut12	-	1.1E-08

*mean of 11 measurements, ** mean of 9 measurements

***www.pnas.org/doi/10.1073/pnas.97.3.1190

****arthritis-research.biomedcentral.com/articles/10.1186/ar3295

Example 6

[0201] As shown in figure 13, we examined the impact of the size of polypeptides fused to the N-terminus of mature IL-18 on the biological activity of a single IL-18AV fused to the N-terminus of IgG1 Fc.

[0202] A single N-terminal amino acid (FUSE874; downward open triangles) and different size polypeptides ranging from five amino acids (FUSE875) to the propeptide variant of FUSE-499 (upward closed triangles; see FIG. 11 for description) were investigated. FUSE500 was used as the fully active control without a N-terminal polypeptide.

[0203] To allow for translocation of all constructs into the Endoplasmic Reticulum (ER) of mammalian cells and hence expression/secretion, the signal peptide from the Ig Kappa chain (IgK leader) was encoded upstream of the polypeptides (and cleaved off the signal peptidase in the ER).

[0204] The polypeptides of FUSE875 (5 residues; closed stars), FUSE876 (10 residues; open diamonds), FUSE757 (15 residues; open circles), FUSE756 (35 residues; downward closed triangles) are made up of a series of glycine and serine residues. The N-terminal polypeptide associated with FUSE758 (open upward triangles) is the sequence of the overhang generated by MMP2 cleavage of FUSE486 (see FIG. 9). For FUSE756, FUSE757 and FUSE758, the final four amino acids of the N-terminal peptide consisted of the Granzyme B cleavage site, IEQD (SEQ ID NO:88) (see FIG. 11).

[0205] Using the HEK-Blue IL-18 reporter cell assay as a readout, we examined the capacity of the different size polypeptides to attenuate/mask IL-18AV-Fc (FUSE500; closed squares) or rhIL-18 (black crosses "X"). All polypeptides and the single amino acid (serine) fused to the N-terminus of mature IL-18AV reduced biological activity, measured as EC50-SEAP, by at least 10-fold.

[0206] The degree of attenuation increased as the size of the polypeptide increased, such that the rank order of attenuation was observed as FUSE499>FUSE756, FUSE757, FUSE758>FUSE876, FUSE875>FUSE874. A summary table of potencies (EC50-SEAP) is shown beneath the non-linear x-y graph.

Example 7

[0207] As shown in figure 14A-14H, we examined the impact of the substituting the cysteine residue in the pro-peptide and cysteine residues in the mature IL18, which were fused together to form the pro-IL-18 variant cassette, on the biological activity of each variant using the HEK Blue IL18 assay system. Unless otherwise stated, the proteins were generated such that the propeptide-IL-18 variant was fused to the C-terminal knob or hole of a knobs into holes human IgG1 Fc as previously depicted in FIG. 1A with a Granzyme B cleavage site added between the pro-peptide variant and the mature IL18 variant. The three variants assessed in FIG. 1 contained serine substitutions (FUSE480), alanine substitutions (FUSE481) or valine substitutions (FUSE442) at all the cysteine residues in pro-IL-18. Mature IL-18 variants released from FUSE442 and FUSE481 were about as active as recombinant human IL-18 whereas mature IL18 released from FUSE480 (serine substituted) was approximately 100-fold attenuated versus recombinant human IL-18 (see FIGs 1B-1D).

[0208] For this example, the variant of pro-IL-18 in which all the cysteines were substituted for valine included an N-terminus EGFR specific VHH (FUSE516; closed triangle) and the variant of pro-IL-18 in which all the cysteines were substituted for serine included an N-terminus PD-1 specific Fab (FUSE694; closed diamond). As in FIG. 1, biological activity of the pro-IL18 test articles were assessed using HEK Blue IL18. Each was tested as an intact untreated protein or following exposure to recombinant human Granzyme B.

[0209] FIG 14A shows the results with FUSE516 (closed triangle), in which the cysteine residue in its pro-peptide variant is replaced with valine and all the cysteines in its mature IL18 variant are replaced by valine. Intact FUSE516 is about 1000-fold attenuated relative to recombinant human IL18 and that the mature IL18 variant released from FUSE516 (open triangle) by Granzyme B is approximately as active as recombinant human IL18.

[0210] FIG 14B shows the results with FUSE694 (closed diamond), in which the cysteine residue in its pro-peptide variant is replaced with serine and all of the cysteines in its mature IL18 variant are replaced by serines. Intact FUSE694 is greater than 10,000-fold attenuated relative to recombinant human IL18 and that the mature IL18 variant released from FUSE694 (open diamond) by Granzyme B is approximately 60-fold less active than recombinant human IL18.

[0211] FIG 14C shows the results with FUSE887 (closed reverse triangle), in which the cysteine residue in its pro-peptide variant is replaced with threonine and all the cysteines in its mature IL18 variant are replaced by serines. Intact FUSE887 is greater than 10,000-fold attenuated relative to recombinant human IL18 and that the mature IL18 variant released from FUSE887 by Granzyme B (open reverse triangle) is approximately 100-fold less active than recombinant human IL18.

[0212] FIG 14D shows the results with FUSE888 (closed triangle), in which the cysteine residue in its pro-peptide variant is replaced with glutamine and all the cysteines in its mature IL18 variant are replaced by serines. Intact FUSE888 is greater than 10,000-fold attenuated relative to recombinant human IL18 and that the mature IL18 variant released from FUSE888 (open triangle) by Granzyme B is approximately 100-fold less active than recombinant human IL18.

[0213] FIG 14E shows the results with FUSE889 (closed square), in which the cysteine residue in its pro-peptide variant is replaced with aspartic acid and all the cysteines in its mature IL18 variant are replaced by alanines. Intact FUSE889 is greater about 10,000-fold attenuated relative to recombinant human IL18 and that the mature IL18 variant released from FUSE889 by Granzyme B (open square) is approximately 100-fold less active than recombinant human IL18.

[0214] FIG 14F shows the results with FUSE890 (closed reverse triangle), in which the cysteine residue in its pro-peptide variant is replaced with phenylalanine and all of the cysteines in its mature IL18 variant are replaced by alanines. Intact FUSE890 is about than 10,000-fold attenuated relative to recombinant human IL18 and that the mature IL18 variant released from FUSE890 by Granzyme B (open reverse triangle) is approximately 100-fold less active than recombinant human IL18.

[0215] FIG 14G shows the results with FUSE891 (closed triangle), in which the cysteine residue in its pro-peptide variant is replaced with isoleucine and all the cysteines in its mature IL18 variant are replaced by valines. Intact FUSE891 is about 3,000-fold attenuated relative to recombinant human IL18 and that the mature IL18 variant released from FUSE891 (open triangle) by Granzyme B is approximately 100-fold less active than recombinant human IL18.

[0216] FIG 14H shows the results with FUSE892 (closed reverse triangle), in which the cysteine residue in its pro-peptide variant is replaced with histidine and all the cysteines in its mature IL18 variant are replaced by valines. Intact FUSE892 is greater about 3,000-fold attenuated relative to recombinant human IL18 and that the mature IL18 variant released from FUSE892 (open reverse triangle) by Granzyme B is approximately 100-fold less active than recombinant human IL18.

[0217] Summary tables of potency (EC50-SEAP) are show to the right of each non-linear x-y plot.

Example 8

[0218] As shown in figure 15A-15B, we examined the impact of targeting pro-IL18 to within close proximity of its receptor complex (i.e., “cis activity”). Pro-IL-18 variants tested were (a) that in which all the cysteine residues were substituted with serines (pro-IL18AS, FUSE782 and FUSE827) and (b) that in which all the cysteines were substituted with valines (pro-IL18AV, FUSE783 and FUSE785). Pro-IL18AS or pro-IL18AV were fused to the N-terminal knob or hole of a PD1 specific knobs into holes antibody (FUSE782 and FUSE783). The fab for these fusion proteins was derived from nivolumab. To test whether targeting the pro-IL18 variants to PD1 decorated on the same cell that expressed the IL-18R complex (cis effect) enhanced biological activity compared to cells that were not decorated with PD-1 (trans effect), (1) we used HEK Blue IL18 as our IL18R complex positive reporter system, and (2) either used the cell without modification or decorated the cell line with the ectodomain of PD-1 using a bispecific antibody that contains a CD46 specific fab (clone YS5) on the N-terminal hole and the PD-1 ectodomain on the N-terminal knob (FUSE986). CD46 was chosen because of its reported expression the parental HEK 293 cell line (jtc.bmj.com/content/6/1/55), which we confirmed on HEK Blue IL18 (not shown). We also generated pro-IL18AS (FUSE827) and pro-IL18AV (FUSE775) that were functional non targeted in this and could only function in trans. FUSE827 contained no targeting domain (i.e., Fc only) and FUSE775 replaced the PD-1 specific fab with an EGFR specific VHH, 9G8, the ligand for which (EGFR) was not expressed on HEK Blue IL18 (data not shown). FIG. 15A and FIG. 15B are nonlinear x-y plots of IL18 biological activity versus the concentration of each test article using HEK Blue IL18 (FIG. 15A) and PD-1 decorated HEK Blue IL18 (FIG. 15B). As previously observed for pro-IL18AS and pro-IL18AV, serine substitutions results in greater attenuation than valine substitutions. As such, when HEK Blue IL18 (FIG. 15A; trans activity only), was treated with (a) the valine mutants FUSE783 (open reverse triangle) or FUSE775 (closed triangle), we observed about a 1000-fold attenuation relative to recombinant human IL18 and (b) the serine mutants FUSE782 (open triangle) and FUSE827 (closed reverse triangle), we observed about greater than a 100,000-fold attenuation relative to recombinant human IL18.

[0219] With regards to cis activity (FIG. 15B using PD-1 decorated HEK Blue IL18), we observed increased biological activity from the PD-1 targeted versions of pro-IL18AS (FUSE782; about 100-fold relative to non targeted FUSE827) and pro-IL18AV (FUSE783; approximately 30-fold relative to non targeted FUSE775).

[0220] FUSE691 (nivolumab) was used as the negative control antibody in both FIG. 15A and FIG. 15B. No biological activity was observed from this test article. No appreciable difference was observed in the biological activities of recombinant human IL18 or the non targeted test articles (FUSE775 and FUSE827), allowing for comparison across FIG. 15A and FIG. 15B. In this context, the PD-1 targeted versions of pro-IL18AS (FUSE782) and pro-IL18AV (FUSE783) were about 100 and 30-fold more active when exposed to PD-1 decorated HEK Blue IL-18 than non-decorated HEK Blue IL18.

[0221] Summary tables of the potency of each pro-IL18 variant are shown below each graph.

[0222] Various embodiments of the invention are described above in the Detailed Description. While these descriptions directly describe the above embodiments, it is understood that those skilled in the art may conceive modifications and/or variations to the specific embodiments shown and described herein. Any such modifications or variations that fall within the purview of this description are intended to be included therein as well. Unless specifically noted, it is the intention of the inventors that the words and phrases in the specification and claims be given the ordinary and accustomed meanings to those of ordinary skill in the applicable art(s).

[0223] The foregoing description of various embodiments of the invention known to the applicant at this time of filing the application has been presented and is intended for the purposes of illustration and description. The present description is not intended to be exhaustive nor limit the invention to the precise form disclosed and many modifications and variations are possible in the light of the above teachings. The embodiments described serve to explain the principles of the invention and its practical application and to enable others skilled in the art to utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. Therefore, it is intended that the invention not be limited to the particular embodiments disclosed for carrying out the invention.

[0224] While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that, based upon the teachings herein, changes and modifications may be made without departing from this invention and its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as are within the true spirit and scope of this invention. As used herein the term “comprising” or “comprises” is used in reference to compositions, methods, and respective component(s) thereof, that are useful to an embodiment, yet open to the inclusion of unspecified elements, whether useful or not. It will be understood by those within the art that, in general, terms used herein are generally intended as “open” terms (e.g., the term “including” should be interpreted as “including but not limited to,” the term “having” should be interpreted as “having at least,” the term “includes” should be interpreted as “includes but is not limited to,” etc.). Although the open-ended term “comprising,” as a synonym of terms such as including, containing, or having, is used to describe and claim the invention, the present invention, or embodiments thereof, may alternatively be described using other terms such as “consisting of” or “consisting essentially of.”

[0225] Unless stated otherwise, the terms “a” and “an” and “the” and similar references used in the context of describing a particular embodiment of the application (especially in the context of claims) may be construed to cover both the singular and the plural. The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein may be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (for example, “such as”) provided with respect to certain embodiments herein is intended merely to better illuminate

the application and does not pose a limitation on the scope of the application otherwise claimed. The abbreviation, “e.g.” is derived from the Latin *exempli gratia*, and is used herein to indicate a non-limiting example. Thus, the abbreviation “e.g.” is synonymous with the term “for example.” No language in the specification should be construed as indicating any non-claimed element essential to the practice of the application. “Optional” or “optionally” means that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not. Groupings of alternative elements or embodiments of the present disclosure disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. One or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is herein deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

WHAT IS CLAIMED IS:

1. A fusion protein, comprising:
 - a first polypeptide or protein capable of translocating into an endoplasmic reticulum (ER) or a fragment thereof; and
 - an interleukin 18 (IL-18), a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant, wherein the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant is on the C-terminus end of the fusion protein relative to the first polypeptide or protein capable of translocating into the ER.
2. The fusion protein of claim 1, wherein the IL-18 variant has an amino acid sequence comprising amino acid positions 37-193 of SEQ ID NO:250 with one to five amino acid substitutions at positions E42, M87, K89, M96, and M149 of SEQ ID NO:250.
3. The fusion protein of claim 1, wherein the IL-18 variant has an amino acid sequence comprising positions 37-193 of SEQ ID NO:251 with one or more amino acid substitutions at positions C74, C104, C112, and C164 and one to five amino acid substitutions at positions E42, M87, K89, M96, and M149, of SEQ ID NO:251
4. The fusion protein of claim 3, wherein the amino acid substitutions at one or more of C74, C104, C112, and C164 are each independently to valine, alanine or serine.
5. The fusion protein of claim 1, wherein the IL-18 variant has an amino acid sequence comprising positions 37-193 of SEQ ID NO:251 with one to five amino acid substitutions at positions E42, M87, K89, M96, and M149 of SEQ ID NO:251
6. The fusion protein of any one of claims 2-5, wherein the one to five amino acid substitutions are one or more of:
 - E42K, E42R, E42A, E42H, or E42Q;
 - M87K, or M87H;
 - K89G, K89A, or K89E;
 - M96L, or M96I; or
 - M149V or M149I.
7. The fusion protein of any one of claims 2-5, wherein the one to five amino acid substitutions are
 - E42K, E42R, E42A, E42H, or E42Q;
 - M87K, or M87H;
 - K89G, K89A, or K89E;
 - M96L, or M96I; and
 - M149V or M149I.

8. The fusion protein of any one of claims 1-7, wherein the IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant further comprises its propeptide (PP) or a PP variant.
9. The fusion protein of claim 8, wherein the IL-18 propeptide variant comprises a polypeptide having AAEPVEDNX₁INFVAMKFIDNTLYFIAEDDEN (SEQ ID NO:238), wherein X₁ is any amino acid except cysteine.
10. The fusion protein of claim 9, wherein X₁ is alanine, valine, isoleucine, leucin, methionine, phenylalanine, tyrosine or tryptophan (SEQ ID NO:239).
11. The fusion protein of any one of claims 8-10, wherein the fusion protein does not comprise a polypeptide consisting of the sequence X₁-X₂-X₃-X₄ between the propeptide or propeptide variant, and the mature IL-18 or mature IL-18 variant, wherein
 - X₁ is L or absent,
 - X₂ is E or absent,
 - X₃ is S or absent, and
 - X₄ is D or absent, and when X₁, X₂, X₃, and X₄ are present, the polypeptide consisting of the sequence X₁-X₂-X₃-X₄ is LESD (SEQ ID NO:253).
12. The fusion protein of any one of claims 9-11, wherein the PP or the PP variant is on the N-terminus end relative to the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant.
13. The fusion protein of any one of claims 9-11, wherein the PP or the PP variant serves as a masking domain.
14. The fusion protein of any one of claims 1-13, further comprising one or more protease cleavage sites.
15. The fusion protein of claim 14, wherein the one or more protease cleavage sites is
 - between the IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant and the first protein capable of translocating into an endoplasmic reticulum (ER) or fragment thereof, or
 - within the PP, between PP or the PP variant and the IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant, or
 - within the PP, between the PP or the PP variant and the first protein capable of translocating into an endoplasmic reticulum (ER) or fragment thereof, or
 - within the IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant, or
 - within the PP, or
 - a combination thereof.
16. The fusion protein of any one of claims 1-15, further comprising a second protein capable of translocating into the ER or a fragment thereof, wherein the second protein capable of translocating into the ER is on the C-terminus end relative to the interleukin 18 (IL-18), the fragment of the IL-18, the IL-18 variant, or the fragment of the IL-18 variant.

17. The fusion protein of claim 16, further comprising a protease cleavage site between the IL-18, a fragment of IL-18, an IL-18 variant, or a fragment of the IL-18 variant and the second protein capable of translocating into an endoplasmic reticulum (ER) or fragment thereof.
18. The fusion protein of any one of claims 1-17, wherein the interleukin 18 (IL-18), the fragment of the IL-18, the IL-18 variant, or the fragment of the IL-18 variant is fused to the C-terminus of the first protein capable of translocating into the ER.
19. The fusion protein of any one of claims 16-18, wherein the second protein capable of translocating into the ER or a fragment thereof is fused to the C-terminus of the interleukin 18 (IL-18), the fragment of the IL-18, the IL-18 variant, or the fragment of the IL-18 variant.
20. The fusion protein of any one of claims 1-19, wherein the IL-18 variant has diminished binding to IL-18 binding protein (IL-18BP), as compared to a wild type (wt) IL-18.
21. The fusion protein of any one of claims 1-19, wherein the IL-18 variant having a binding affinity to the human IL-18 receptor (IL-18R) within 30-fold of the wild-type IL-18.
22. The fusion protein of any one of claims 1-19, wherein the ratio of binding affinity of the fusion protein comprising the IL-18 variant to IL-18BP : binding affinity of the fusion protein comprising the IL-18 variant to IL-18R is no higher than 3:1.
23. The fusion protein of any one of claims 1-22, wherein the first protein capable of translocating into the ER or a fragment thereof is a globular protein, immunoglobulin protein, or a fragment thereof, or is a short polypeptide or protein engineered with a signal peptide for translocating into the ER, optionally the short polypeptide or protein being about 2kDa or no greater than 250 kDa.
24. The fusion protein of any one of claims 1-23, wherein the first protein capable of translocating into the ER or a fragment thereof is selected from the group consisting of a fragment crystallizable (Fc) region, human serum albumin (HSA), beta2microglobulin, transferrin, fragment antigen-binding region (Fab region), VHH antibody, single-chain variable fragment (scFv), anticalin, designed ankyrin repeat protein (DARPin), a binding domain thereof, and a fragment thereof.
25. The fusion protein of any one of claims 1-23, wherein the first protein capable of translocating into the ER or a fragment thereof of the fusion protein is a type I transmembrane protein or a fragment thereof or a type II transmembrane protein or a fragment thereof.
26. The fusion protein of any one of claims 16-25, wherein the second protein capable of translocating into the ER or a fragment thereof is a globular protein, immunoglobulin protein, or a fragment thereof, or is a short polypeptide or protein engineered with a signal peptide for translocating into the ER, optionally the short polypeptide or protein being about 2kDa or no greater than 250 kDa.
27. The fusion protein of any one of claims 16-26, wherein the second protein capable of translocating into the ER or a fragment thereof is selected from the group consisting of a fragment crystallizable (Fc) region, human serum albumin (HSA), beta2microglobulin, transferrin, fragment antigen-binding region (Fab

- region), VHH antibody, single-chain variable fragment (scFv), anticalin, designed ankyrin repeat protein (DARPin), a binding domain thereof, and a fragment thereof.
28. The fusion protein of any one of claims 16-26, wherein the second protein capable of translocating into the ER or a fragment thereof of the fusion protein is a type I transmembrane protein or a fragment thereof, or a type II transmembrane protein or a fragment thereof.
 29. The fusion protein of any one of claims 24 and 27, wherein the Fc region is an Fc region from IgA, IgM, IgG, or IgE.
 30. The fusion protein of any one of claims 24 and 27, wherein the Fc region is an Fc region from IgG4, KiH, or IgG1.
 31. The fusion protein of any one of claim 24 and 27, wherein the Fc region is an Fc region from Knob-in-hole, HA-TF, Xmab, ZW1, 7.8.60, Electrostatic Steering, DD-KK, EW-RVT, A107, or Duobody.
 32. The fusion protein of any one of claims 1-31 wherein one or more cysteines in the fusion protein is modified.
 33. The fusion protein of any one of claims 1-31, wherein one or more cysteines in the fusion protein are replaced with a natural or non-natural amino acid.
 34. The fusion protein of any one of claims 1-31, wherein one or more cysteines in the IL-18, the fragment of IL-18, the IL-18 variant, or the fragment of the IL-18 variant of the fusion protein are modified or are replaced with a natural or non-natural amino acid.
 35. The fusion protein of any one of claims 8-34, wherein one or more cysteines in the PP or PP variant of the fusion protein are modified or are replaced with a natural or non-natural amino acid.
 36. The fusion protein of any one of claims 33-35, wherein the natural amino acid is each independently selected from serine and valine.
 37. The fusion protein of any one of claims 33-35, wherein the natural amino acid is each independently selected from threonine, asparagine, and glutamine.
 38. The fusion protein of any one of claims 17-37, wherein the protease is selected from the group consisting of EK, TEV, Adam17, cathepsin, MMP2, MMP9, MMP14, Granzyme A, Granzyme B, Granzyme M, Granzyme K, and combinations thereof.
 39. The fusion protein of any one of claims 1-38, having one or more sequences as set forth in any one in Tables 1 and 4.
 40. The fusion protein of claim 1, having polypeptide 1 and polypeptide 2, and optionally polypeptide 3 selected from Table 1.
 41. The fusion protein of claim 1, having polypeptide 1 and polypeptide 2, and optionally polypeptide 3 selected from Table 1, wherein polypeptide 1 and polypeptide 2, and optionally polypeptide 3 are selected from the same row of Table 1.

42. The fusion protein of claim 1, having polypeptide 1 selected from Table 1, wherein polypeptide 1 comprises HSA.
43. The fusion protein of any one of claims 1-42, wherein the IL-18 variant has an amino acid sequence selected from Mature IL-18 column in Table 1.
44. The fusion protein of any one of claims 8-42, wherein the IL-18 variant has an amino acid sequence selected from Mature IL-18 column in Table 1, and the propeptide has an amino acid sequence selected from Propeptide column in Table 1, optionally the same from the same row.
45. An IL-18 propeptide variant comprising a polypeptide having AAEPVEDNX₁INFVAMKFIDNTLYFIAEDDEN, wherein X₁ is any amino acid except cysteine (SEQ ID NO:238).
46. A polynucleotide encoding a fusion protein of any one of claims 1-44 or IL-18 propeptide variant of claim 45.
47. The polynucleotide of claim 46, wherein the first protein capable of translocating into the ER is encoded by a polynucleotide having one or more sequences as set forth in Table 2.
48. The polynucleotide of claim 46, having one or more sequences from the same row as set forth in Table 2.
49. An expression vector comprising the polynucleotide of any one of claims 46-48.
50. A cell transfected with the expression vector of claim 49.
51. A method of producing a fusion protein, comprising:
 - culturing a cell transfected with an expression vector of claim 49, in cell culture medium to allow the fusion protein to be secreted into the cell culture medium.
52. The method of claim 51, wherein the fusion protein is produced at greater than 135 mg/L under transient transfection in CHO cells or HEK-293 cells.
53. A method of producing interleukin 18 (IL-18), a fragment thereof, an IL-18 variant, or a fragment of the IL-18 variant, comprising:
 - culturing a cell transfected with an expression vector of claim 49, in cell culture medium to allow a fusion protein to be produced and secreted into the extracellular space; and
 - contacting a protease to the fusion protein to cleave the fusion protein to produce the IL-18, the fragment thereof, the IL-18 variant, or the fragment of the IL-18 variant.
54. The method of claim 53, further comprising isolating the fusion protein from the culture medium.
55. The method of claim 54, further comprising purifying the fusion protein.
56. The method of claim 53, wherein the protease is selected from the group consisting of EK, TEV, Adam 17, cathepsin, MMP2, MMP9, MMP14, Granzyme A, Granzyme B, Granzyme M, and combinations thereof.
57. The method of any one of claims 53-56, wherein the IL-18, the fragment thereof, the IL-18 variant, or the fragment of the IL-18 variant is produced at greater than 135mg/L.