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(54) **PRODUCTION CELL LINE ENHANCERS**

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(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to discovery of the ectopic expression of EDEM2 in a production cell to improve the yield of a useful multi-subunit protein. Thus, the present invention provides for production cell lines, such as the canonical mammalian biopharmaceutical production cell—the CHO cell, containing recombinant polynucleotides encoding EDEM2. Also disclosed is a production cell containing both an EDEM2-encoding polynucleotide as well an XBP1-encoding polynucleotide. Improved titers of antibodies produced by these cell lines are disclosed, as well as the improved cell densities attained by these cells in culture.

38 Claims, 3 Drawing Sheets

Specification includes a Sequence Listing.

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Fig. 1A

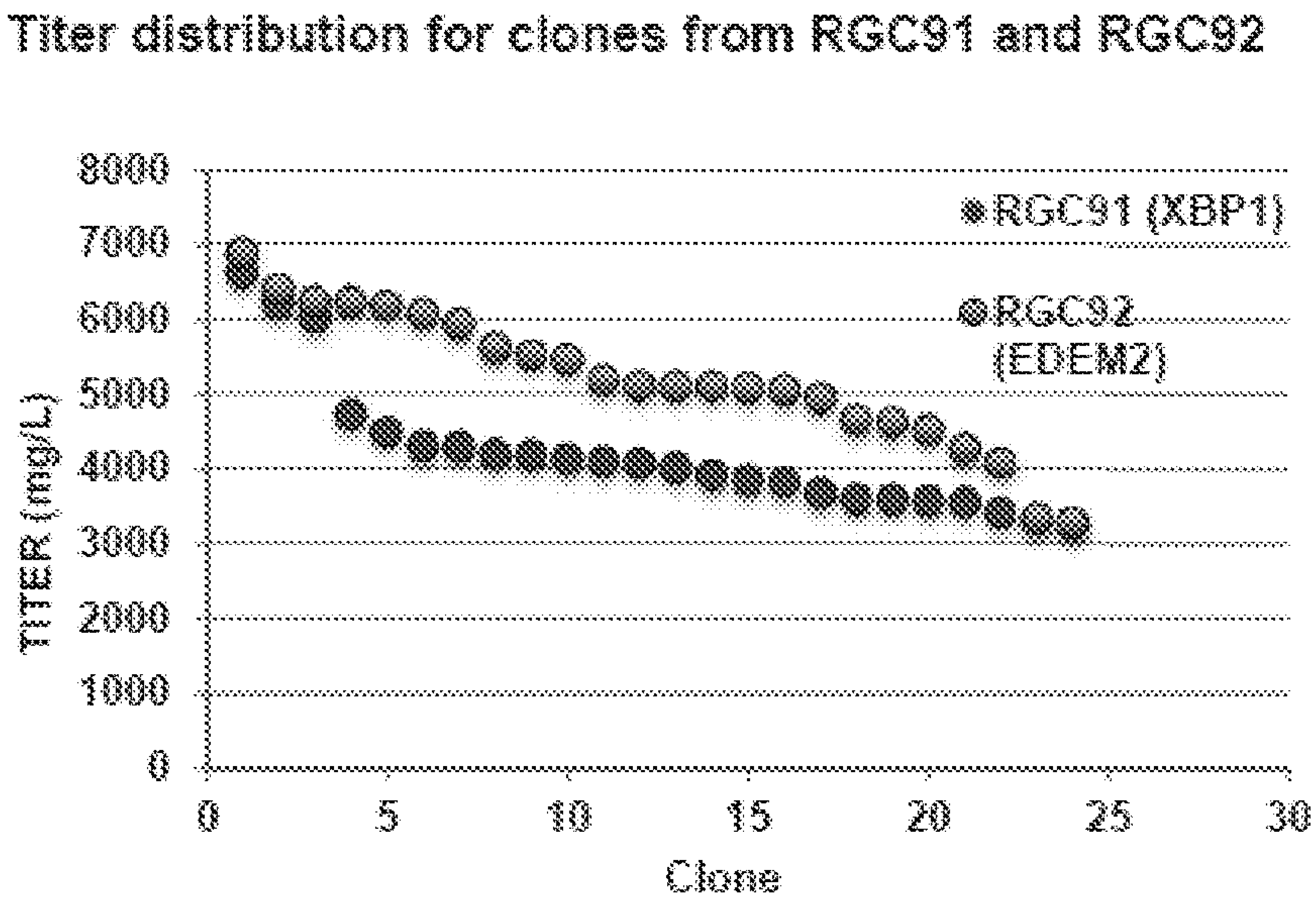

Titer distribution for clones from RGC91 and RGC92
RGC91 (XBP1)
RGC92 (EDEM2)
TITER (mg/L)
8000
7000
6000
5000
4000
3000
2000
1000
0
0
5
10
15
20
25
30
Clone

Fig. 1B

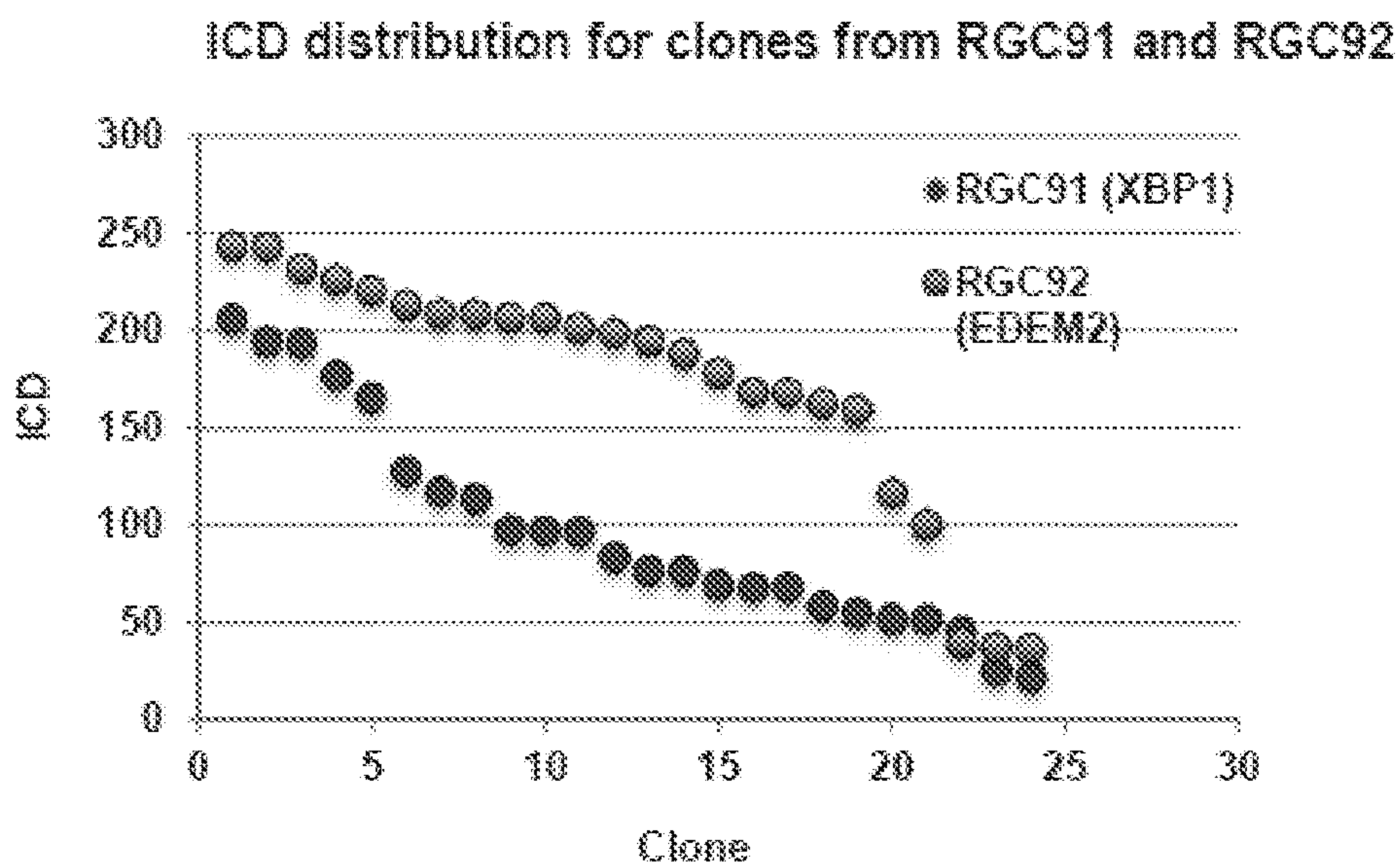

ICD distribution for clones from RGC91 and RGC92
RGC91 (XBP1)
RGC92 (EDEM2)
ICD
300
250
200
150
100
50
0
0
5
10
15
20
25
30
Clone

Fig. 2A Clone stability of XBP1-expressing cells

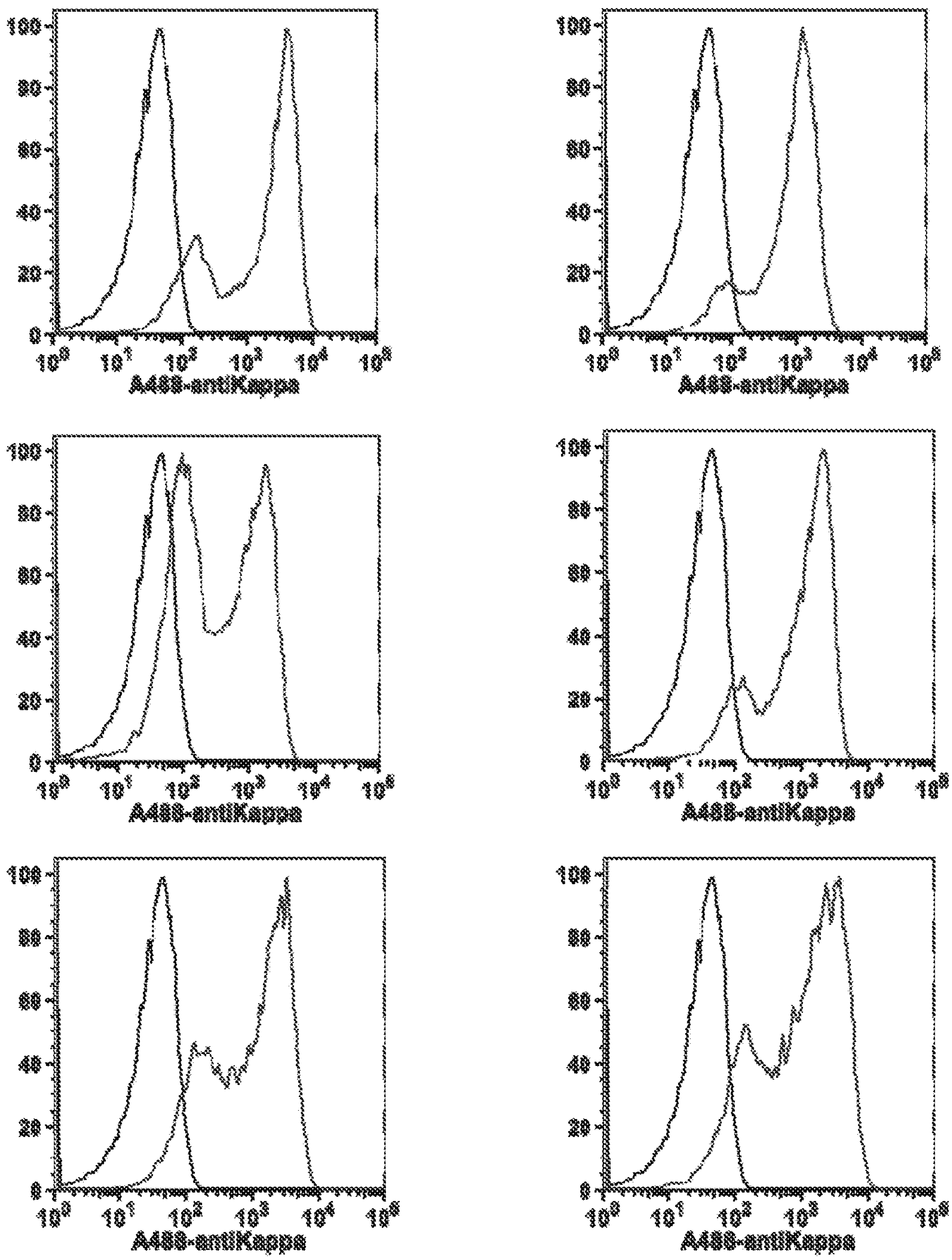
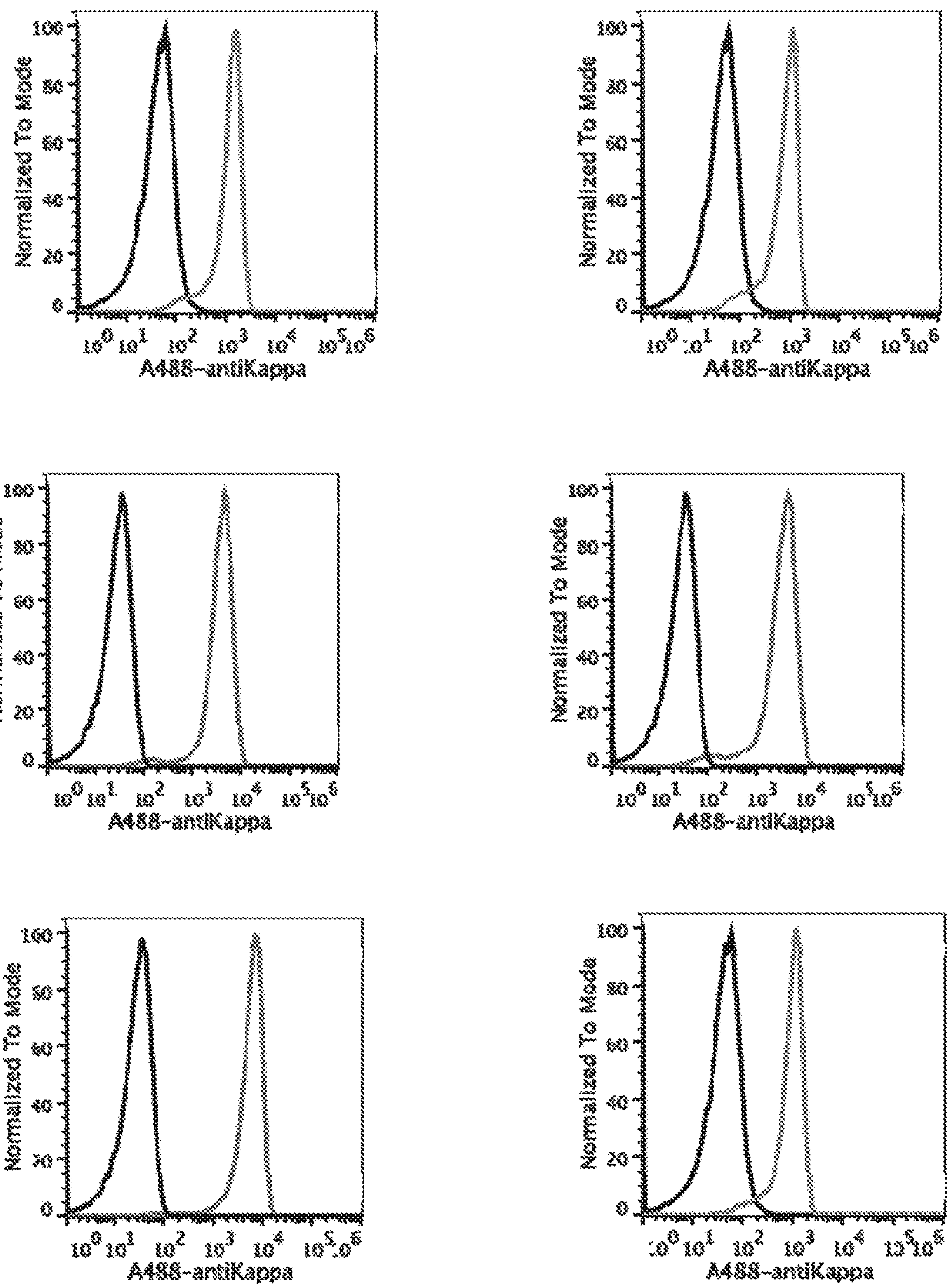


Fig. 2B Clone stability of EDEM2-expressing cells



PRODUCTION CELL LINE ENHANCERS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is *a reissue application of U.S. Pat. No. 9,688,751 B2, which issued on Jun. 27, 2017 having U.S. Ser. No. 15/201,104, which is a* divisional of U.S. patent application Ser. No. 14/555,220 filed 26 Nov. 2014, *now U.S. Pat. No. 9,382,315,* which is divisional of U.S. patent application Ser. No. 13/904,587 filed 29 May 2013, now U.S. Pat. No. 9,079,954, and which is a continuation-in-part of PCT International Application No. PCT/US2013/043116, filed 29 May 2013, which claims the benefit of U.S. patent application Ser. No. 13/904,587, filed 29 May 2013, and claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application No. 61/652,549 filed 29 May 2012, all of which are herein specifically incorporated by reference in their entirety.

SEQUENCE LISTING

[This application incorporates by reference the sequence listing submitted in computer readable form as file 8150US02_ST25.txt created on Nov. 26, 2014 (206,400 bytes).] *The Sequence Listing in the ASCII text file, named as 35463ZA_REI_8150U507_REI_SequenceListing.txt of 202 KB, created on Apr. 16, 2019, and submitted to the United States Patent and Trademark Office via EFS-Web, is incorporated herein by reference.*

FIELD OF THE INVENTION

The invention relates to a cell or cells expressing a recombinant stress-response lectin for the improved production of a multi-subunit protein. Specifically, the invention provides a mammalian cell and cell-line derived therefrom containing a gene encoding EDEM2, and which yields antibody at a high titer.

BACKGROUND OF THE INVENTION

The manufacture of therapeutically active proteins requires proper folding and processing prior to secretion. Proper folding is particularly relevant for proteins, such as antibodies, which consist of multiple subunits that must be properly assembled before secretion. Eukaryotic cells have adapted a system that ensures the proper folding of proteins and the removal of misfolded proteins from the secretory pathway. This system is called the unfolded protein response (UPR) pathway, and it is triggered by the accumulation of misfolded proteins in the endoplasmic reticulum (ER).

An early event of the UPR is the activation of the transcription factor Xbp1, which in turn activates the transcription of endoplasmic reticulum degradation-enhancing alpha-mannosidase-like protein 2 (EDEM2), a member of the endoplasmic reticulum associated degradation (ERAD) pathway. EDEM2 facilitates the removal of misfolded proteins. The ERAD pathway comprises five steps: (1) chaperone-mediated recognition of malformed proteins, (2) targeting of malformed proteins to the retrotranslocation machinery or E3-ligases, which involves EDEM2, (3) initiation of retrotranslocation; (4) ubiquitylation and further retrotranslocation; and (5) proteosome targeting and degradation.

Antibodies are multi-subunit proteins comprising two heavy chains and two light chains, which must be properly folded and associated to form a functional heterotetramer. Any improvement in the efficient and accurate processing of the heavy and light chains to improve the yield or titer of functional antibody heterotetramers is desired.

SUMMARY OF THE INVENTION

Applicants made the surprising discovery that the ectopic expression of EDEM2 in a protein-manufacturing cell line increases the average output of protein per cell, increases the titer of protein secreted into the media, and increases the integrated cell density of production cell lines.

Thus, in one aspect, the invention provides a cell containing (a) a recombinant polynucleotide that encodes a stress-induced mannose-binding lectin and (b) a polynucleotide that encodes a multi-subunit protein. In some embodiments, the stress-induced mannose-binding lectin is an EDEM2 protein, non-limiting examples of which are provided in Table 1, and the multi-subunit protein is an antibody. In other embodiments, the cell also contains a polynucleotide that encodes the active spliced form of XBP1, non-limiting examples of which are provided in Table 2. In one embodiment, the cell is a mammalian cell, such as a CHO cell used in the manufacture of biopharmaceuticals.

In another aspect, the invention provides a cell line derived from the cell described in the previous aspect. By "derived from", what is meant is a population of cells clonally descended from an individual cell and having some select qualities, such as the ability to produce active protein at a given titer, or the ability to proliferate to a particular density. In some embodiments, the cell line, which is derived from a cell harboring the recombinant polynucleotide encoding a stress-induced mannose-binding lectin and a polynucleotide encoding a multi-subunit protein, is capable of producing the multi-subunit protein at a titer of at least 3 grams per liter of media (g/L), at least 5 g/L, or at least 8 g/L. In some embodiments, the cell line can attain an integrated cell density (ICD) that is at least 30% greater, at least 50% greater, at least 60% greater, or at least 90% greater than the integrated cell density attainable by a cell line derived from what is essentially the same cell but without the recombinant polynucleotide encoding the stress-induced mannose-binding lectin.

In another aspect, the invention provides an isolated or recombinant polynucleotide comprising a nucleic acid sequence encoding an EDEM2 protein, which is operably linked (cis) to a constitutive and ubiquitously expressed mammalian promoter, such as the ubiquitin C promoter. In some embodiments, the EDEM2 protein has the amino acid of SEQ ID NO: 8, or an amino acid sequence that is at least 92% identical to any one of SEQ ID NO: 1-7. In some embodiments, the polynucleotide comprises a nucleic acid sequence of SEQ ID NO: 16. In one particular embodiment, the polynucleotide consists of a nucleic acid sequence of SEQ ID NO: 14; and in another particular embodiment, SEQ ID NO: 15.

In another aspect, the invention provides an isolated or recombinant polynucleotide comprising a nucleic acid sequence encoding an XBP1 protein, which is operably linked to (in cis) a constitutive and ubiquitously expressed mammalian promoter, such as the ubiquitin C promoter. In some embodiments, the XBP1 protein has the amino acid of SEQ ID NO: 13, or an amino acid sequence that is at least 86% identical to any one of SEQ ID NO: 9-12. In some embodiments, the polynucleotide comprises a nucleic acid sequence of SEQ ID NO: 18. In one particular embodiment, the polynucleotide consists of a nucleic acid sequence of SEQ ID NO: 17.

In another aspect, the invention provides a cell that contains an EDEM2-encoding polynucleotide, as described in the prior aspect, and a polynucleotide that encodes a multi-subunit protein, such as an antibody. In some embodiments, the cell also contains an XBP1-encoding polynucleotide, as described in the preceding aspect. In one embodiment, the multi-subunit protein is an antibody, and the heavy chain of the antibody comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and the light chain of the antibody comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46. In this and several embodiments, each polypeptide subunit of the multi-subunit protein is encoded by a separate polynucleotide. Thus, for example, a polynucleotide encoding an antibody may include a polynucleotide encoding a heavy chain and a polynucleotide encoding a light chain, hence two subunits. In some embodiments, the cell is a Chinese hamster ovary (CHO) cell.

In one embodiment, the encoded multi-subunit protein is an anti-GDF8 antibody having a heavy chain variable region amino acid sequence of SEQ ID NO: 20 and a light chain variable region amino acid sequence of SEQ ID NO: 22. In one embodiment, the anti-GDF8 antibody comprises a heavy chain having an amino acid sequence of SEQ ID NO: 19 and a light chain having an amino acid sequence of SEQ ID NO: 21. In one embodiment, the polynucleotide that encodes the heavy chain of the anti-GDF8 antibody comprises a nucleic acid sequence of SEQ ID NO: 23; and the polynucleotide that encodes the light chain of the anti-GDF8 antibody comprises a nucleic acid sequence of SEQ ID NO: 25. In one embodiment, the polynucleotide that encodes the heavy chain of the anti-GDF8 antibody consists of a nucleic acid sequence of SEQ ID NO: 24; and the polynucleotide that encodes the light chain of the anti-GDF8 antibody consists of a nucleic acid sequence of SEQ ID NO: 25.

In another embodiment, the encoded multi-subunit protein is an anti-ANG2 antibody having a heavy chain variable region amino acid sequence of SEQ ID NO: 28 and a light chain variable region amino acid sequence of SEQ ID NO: 30. In one embodiment, the anti-ANG2 antibody comprises a heavy chain having an amino acid sequence of SEQ ID NO: 27 and a light chain having an amino acid sequence of SEQ ID NO: 29. In one embodiment, the polynucleotide that encodes the heavy chain of the anti-ANG2 antibody comprises a nucleic acid sequence of SEQ ID NO: 31; and the polynucleotide that encodes the light chain of the anti-ANG2 antibody comprises a nucleic acid sequence of SEQ ID NO: 33. In one embodiment, the polynucleotide that encodes the heavy chain of the anti-ANG2 antibody consists of a nucleic acid sequence of SEQ ID NO: 32; and the polynucleotide that encodes the light chain of the anti-ANG2 antibody consists of a nucleic acid sequence of SEQ ID NO: 34.

In another embodiment, the encoded multi-subunit protein is an anti-ANGPTL4 antibody having a heavy chain variable region amino acid sequence of SEQ ID NO: 36 and a light chain variable region amino acid sequence of SEQ ID NO: 38. In one embodiment, the anti-ANGPTL4 antibody comprises a heavy chain having an amino acid sequence of SEQ ID NO: 35 and a light chain having an amino acid sequence of SEQ ID NO: 37. In one embodiment, the polynucleotide that encodes the heavy chain of the anti-ANGPTL4 antibody comprises a nucleic acid sequence of SEQ ID NO: 39; and the polynucleotide that encodes the light chain of the anti-ANGPTL4 antibody comprises a nucleic acid sequence of SEQ ID NO: 41. In one embodiment, the polynucleotide that encodes the heavy chain of the anti-ANGPTL4 antibody consists of a nucleic acid sequence of SEQ ID NO: 40; and the polynucleotide that encodes the light chain of the anti-ANGPTL4 antibody consists of a nucleic acid sequence of SEQ ID NO: 42.

In another aspect, the invention provides a method of manufacturing a multi-subunit protein, by culturing a cell of the previous aspect in a medium, wherein the multi-subunit protein is synthesized in the cell and subsequently secreted into the medium. In some embodiments, the multi-subunit protein is an antibody, such as for example anti-GDF8, anti-ANG2, anti-ANGPTL4, or an antibody having a heavy chain sequence of SEQ ID NO: 43 and 44, and a light chain sequence of SEQ ID NO: 45 and 46. In some embodiments, the multi-subunit protein attains a titer of at least 3 g/L, at least 5 g/L, at least 6 g/L, or at least 8 g/L. In some embodiments, the cell proliferates in the medium and establishes an integrated cell density of about $\geq 5\times10^7$ cell-day/mL, about $\geq 1\times10^8$ cell-day/mL, or about $\geq 1.5\times10^8$ cell-day/mL.

In another aspect, the invention provides a multi-subunit protein, which is manufactured according to the method described in the preceding aspect. In one embodiment, the manufactured protein is an antibody. In some embodiments, the antibody consists of a heavy chain, which comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and a light chain, which comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46. In one specific embodiment, the manufactured multi-subunit protein is an anti-GDF8 antibody having a heavy chain variable region amino acid sequence of SEQ ID NO: 20 and a light chain variable region amino acid sequence of SEQ ID NO: 22. In another specific embodiment, the manufactured multi-subunit protein is an anti-ANG2 antibody having a heavy chain variable region amino acid sequence of SEQ ID NO: 28 and a light chain variable region amino acid sequence of SEQ ID NO: 30. In yet another specific embodiment, the manufactured multi-subunit protein is an anti-ANGPTL4 antibody having a heavy chain variable region amino acid sequence of SEQ ID NO: 36 and a light chain variable region amino acid sequence of SEQ ID NO: 38.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**A shows consistently higher protein titer (in mg/L) for EDEM2-expressing clonal cell-lines (gray circles) compared to XBP1-expressing clonal cell-lines (black circles).

FIG. **1**B depicts the integrated cell density (cell-days/mL) for EDEM2-expressing clones (gray circles) compared to XBP1-expressing clones (black circles). Each clone (#1-24) expresses the same gene of interest (antibody), under the same regulatory conditions, and expressing either XBP1 (RGC91) or EDEM2 (RGC92) at a transcriptionally active locus.

FIG. **2**A shows the FACS scans (flow cytometry-based autologous secretion trap (FASTR)) of several clones expressing XBP1. Inconsistency in the peaks is indicative of unstable growth (i.e. a variable or heterogeneous mixture) of the cells in the clones tested.

FIG. **2**B shows the FACS scans of several clones expressing EDEM2, having little to no variation in the peaks representative of clonal stability in the clones tested. FIG. **2**B depicts the clonal stability of several clonal cell-lines expressing EDEM2 and an antibody of interest.

DESCRIPTION OF THE INVENTION

Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Unless defined otherwise, all 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. As used herein, the term "about", when used in reference to a particular recited numerical value or range of values, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (e.g., 99.1, 99.2, 99.3, 99.4, etc.).

Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

As used herein, the term "recombinant polynucleotide", which is used interchangeably with "isolated polynucleotide", means a nucleic acid polymer such as a ribonucleic acid or a deoxyribonucleic acid, either single stranded or double stranded, originating by genetic engineering manipulations. A recombinant polynucleotide may be a circular plasmid or a linear construct existing in vitro or within a cell as an episome. A recombinant polynucleotide may be a construct that is integrated within a larger polynucleotide molecule or supermolecular structure, such as a linear or circular chromosome. The larger polynucleotide molecule or supermolecular structure may be within a cell or within the nucleus of a cell. Thus, a recombinant polynucleotide may be integrated within a chromosome of a cell.

As used herein, the term "stress-induced mannose-binding lectin" refers to a mannose-binding protein, which means a protein that binds or is capable of binding mannose, derivatives of mannose, such as mannose-6-phosphate, or a glycoprotein that expresses mannose or a mannose derivative in its glycocalyx; and whose activity is upregulated during stress. Cellular stress includes inter alia starvation, DNA damage, hypoxia, poisoning, shear stress and other mechanical stresses, tumor stress, and the accumulation of misfolded proteins in the endoplasmic reticulum. Exemplary stress-induced mannose-binding lectins include the EDEM proteins EDEM1, EDEM2 and EDEM3, Yos 9, OS9, and XTP3-B (see Vembar and Brodsky, Nat. Rev. Mol. Cell. Biol. 9(12): 944-957, 2008, and references cited therein).

As used herein, the term "EDEM2" means any ortholog, homolog, or conservatively substituted variant of endoplasmic reticulum degradation-enhancing alpha-mannosidase-like protein. EDEM2 proteins are generally known in the art to be involved endoplasmic reticulum-associated degradation (ERAD), being up-regulated by Xbp-1 and facilitating the extraction of misfolded glycoproteins from the calnexin cycle for removal. (See Mast et al., Glycobiology 15(4): 421-436, 2004; Olivari and Molinari, FEBS Lett. 581: 3658-3664, 2007; Olivari et al., J. Biol. Chem. 280(4): 2424-2428, 2005; and Vembar and Brodsky 2008, which are herein incorporated by reference.) Exemplary EDEM2 sequences are depicted in Table 1, which is cross-referenced to the Sequence Listing.

TABLE 1

Animal	SEQ ID NO:	% id human	% id mouse	% id hamster
Mouse	1	93	100	96
Rat	2	94	98	96
Hamster	3	93	96	100
Human	4	100	93	93
Chimpanzee	5	99	94	93
Orangutan	6	97	92	92
Zebra fish	7	69	70	69
Consensus	8	100	100	100

As used herein, the term "Xbp1", also known as XBP1 or X-box binding protein 1, means any ortholog, homolog, or conservatively substituted variant of Xbp1. Xbp1 is a transcription factor and functional element of the UPR. ER stress activates both (1) the transcription factor ATF6, which in turn upregulates the transcription of Xbp1 mRNA, and (2) the ER membrane protein IRE1, which mediates the splicing of the precursor Xbp1 mRNA to produce active Xbp1. As mentioned above, activated Xbp1 in turn upregulates the activity of EDEM2. (See Yoshida et al., Cell Structure and Function 31(2): 117-125, 2006; and Olivari, 2005.) Exemplary Xbp1 amino acid sequences are depicted in Table 2, which is cross-referenced to the Sequence Listing.

TABLE 2

Alumat	SEQ ID NO	% id human	% id mouse	% id hamster
Mouse	9	86	100	92
Hamster	10	86	92	100
Human	11	100	86	86
Zebra fish	12	47	47	48
Consensus	13	100	100	100

As used herein, the term "antibody" is generally intended to refer to immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (e.g., IgM); however, immunoglobulin molecules consisting of only heavy chains (i.e., lacking light chains) are also encompassed within the definition of the term "antibody". Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region comprises three domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region comprises one domain (CL1). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementary determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. An "isolated antibody" or "purified antibody" may be substantially free of other cellular material or chemicals.

The term "specifically binds", or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by a dissociation constant of at least about 1×10^{-6} M or greater. Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. An isolated antibody that specifically binds human GDF8 (for example) may, however, have cross-reactivity to other antigens, such as GDF8 molecules from other species (orthologs).

Various antibodies are used as examples of multi-subunit proteins secreted by cells harboring the polynucleotide encoding a stress-induced mannose-binding lectin. Those examples include anti-GDF8, anti-ANG2, and anti-ANGPTL4 antibodies. These and similar antibodies are described in US Pat. Apps. No. 20110293630, 20110027286, and 20110159015 respectively, which are incorporated herein by reference.

As used herein, the term "cell" refers to a prokaryotic or eukaryotic cell capable of replicating DNA, transcribing RNA, translating polypeptides, and secreting proteins. Cells include animal cells used in the commercial production of biological products, such as insect cells (e.g., Schneider cells, Sf9 cells, Sf21 cells, Tn-368 cells, BTI-TN-5B1-4 cells; see Jarvis, Methods Enzymol. 463: 191-222, 2009; and Potter et al., Int. Rev. Immunol. 10(2-3): 103-112, 1993) and mammalian cells (e.g., CHO or CHO-K1 cells, COS or COS-7 cells, HEK293 cells, PC12 cells, HeLa cells, Hybridoma cells; Trill et al., Curr. Opin. Biotechnol. 6(5): 553-560, 1995; Kipriyanov and Little, Mo. Biotechnol. 12(2): 173-201, 1999). In one embodiment, the cell is a CHO-K1 cell containing the described UPR pathway polynucleotides. For a description of CHO-K1 cells, see also Kao et al., Proc. Nat'l. Acad. Sci. USA 60: 1275-1281, 1968.

As used herein, the term "promoter" means a genetic sequence generally in cis and located upstream of a protein coding sequence, and which facilitates the transcription of the protein coding sequence. Promoters can be regulated (developmental, tissue specific, or inducible (chemical, temperature)) or constitutively active. In certain embodiments, the polynucleotides that encode proteins are operably linked to a constitutive promoter. By "operably linked", what is meant is that the protein-encoding polynucleotide is located three-prime (downstream) and cis of the promoter, and under control of the promoter. In certain embodiments, the promoter is a constitutive mammalian promoter, such as the ubiquitin C promoter (see Schorpp et al., Nucl. Acids Res. 24(9): 1787-1788, 1996); Byun et al., Biochem. Biophys. Res. Comm. 332(2): 518-523, 2005) or the CMV-IE promoter (see Addison et al., J. Gen. Virol. 78(7): 1653-1661, 1997; Hunninghake et al., J. Virol. 63(7): 3026-3033, 1989), or the hCMV-IE promoter (human cytomegalovirus immediate early gene promoter) (see Stinski & Roehr, J. Virol. 55(2): 431-441, 1985; Hunninghake et al., J. Virol. 63(7): 3026-3033, 1989).

As used herein, the phrase "integrated cell density", or "ICD" means the density of cells in a culture medium taken as an integral over a period of time, expressed as cell-days per mL. In some embodiments, the ICD is measured around the twelfth day of cells in culture.

As used herein, the term "culture" means both (1) the composition comprising cells, medium, and secreted multi-subunit protein, and (2) the act of incubating the cells in medium, regardless of whether the cells are actively dividing or not. Cells can be cultured in a vessel as small as a 25 mL flask or smaller, and as large as a commercial bioreactor of 10,000 liters or larger. "Medium" refers to the culture medium, which comprises inter alia nutrients, lipids, amino acids, nucleic acids, buffers and trace elements to allow the growth, proliferation, or maintenance of cells, and the production of the multi-subunit protein by the cells. Cell culture media include serum-free and hydrolysate-free defined media as well as media supplemented with sera (e.g., fetal bovine serum (FBS)) or protein hydrolysates. Non-limiting examples of media, which can be commercially acquired, include RPMI medium 1640, Dulbecco's Modified Eagle Medium (DMEM), DMEM/F12 mixture, F10 nutrient mixture, Ham's F12 nutrient mixture, and minimum essential media (MEM).

As used herein, the phrase "conservatively substituted variant", as applied to polypeptides, means a polypeptide having an amino acid sequence with one of more conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. See, e.g., Pearson (1994) Methods Mol. Biol. 24: 307-331, which is herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al. (1992) Science 256: 1443-45, herein incorporated by reference. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

Embodiments—The Cell

In one aspect, the invention provides a cell useful in the production of a protein having therapeutic or research utility. In some embodiments, the protein consists of multiple subunits, which must be properly folded and assembled to produce sufficient quantities of active protein. Antibodies are an example of multi-subunit proteins having therapeutic or research utility. In some embodiments, the cell harbors a recombinant genetic construct (i.e., a polynucleotide) that encodes one or more of the individual subunits of the multi-subunit protein. In other embodiments, the genetic construct encoding the individual polypeptide subunits is naturally occurring, such as for example the nucleic acid sequences encoding the subunits of an antibody in a B cell.

To facilitate the proper assembly and secretion of the multi-subunit protein, the cell contains a recombinant polynucleotide that encodes a stress-induced mannose-binding lectin, which in some embodiments is a component of the ERAD. In some embodiments, the stress-induced mannose-binding lectin is an endoplasmic reticulum degradation-enhancing alpha-mannosidase-like protein 2 (EDEM2). It is envisioned that any encoded EDEM2 or conservatively-substituted variant can be successfully employed in the instant invention. Table 1 lists some examples of vertebrate EDEM2 proteins. A multiple pairwise comparison of those protein sequences, which was performed using the Clustal W program of Thompson et al., Nucl. Acids Rev. 22(22): 4673-80, 1994 (see also Yuan et al., Bioinformatics 15(10): 862-3, 1999), revealed that each of the disclosed EDEM2 polynucleotide sequences is at least 69% identical to each other EDEM2 sequence. A Clustal W comparison of the disclosed mammalian EDEM2 sequences revealed that each sequence is at least 92% identical to the other. Thus, in some embodiments, the cell contains a polynucleotide that encodes an EDEM2 polypeptide having a sequence that is at least 92% to any one of a mammalian EDEM2. A consensus EDEM2 amino acid sequence was built by aligning a mouse, rat, hamster, chimpanzee, and human EDEM2 polypeptide amino acid sequences. That consensus sequence is depicted as SEQ ID NO: 8. Thus, in some embodiments, the cell contains a polynucleotide that encodes an EDEM2 polypeptide having an amino acid sequence of SEQ ID NO: 8.

In various embodiments, the cell contains a recombinant polynucleotide that encodes an EDEM2 polypeptide having an amino acid sequence that is at least 92% identical to the mouse EDEM2 (mEDEM2) amino acid sequence; and in a particular embodiment, the polypeptide is mEDEM2 or a conservatively substituted variant thereof.

In some embodiments, the multi-subunit protein is an antibody, and the cell contains a polynucleotide encoding any one or more of a polypeptide comprising an amino acid sequence of SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46. SEQ ID NO: 43 and 44 each represent consensus sequences of the roughly N-terminal and C-terminal portions, respectively, of particular antibody heavy chains. Thus, the polynucleotide encoding a protein subunit in one embodiment encodes a polypeptide comprising both SEQ ID NO: 43 and SEQ ID NO: 44. SEQ ID NO: 45 and 46 each represent consensus sequences of the roughly N-terminal and C-terminal portions, respectively, of particular antibody light chains. Thus, the polynucleotide encoding a protein subunit in one embodiment encodes a polypeptide comprising both SEQ ID NO: 45 and SEQ ID NO: 46. In some embodiments, in addition to the recombinant polynucleotide encoding the EDEM2 protein, the cell contains at least two polynucleotides, each of which encodes a particular subunit of the multi-subunit protein. For example, and as exemplified below, the cell contains a polynucleotide encoding an antibody heavy chain comprising an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and another polynucleotide encoding an antibody light chain comprising an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46.

In some embodiments, the cell, in addition to containing the stress-response polynucleotide and one or more polynucleotides encoding a polypeptide subunit, as described above, also contains a polynucleotide that encodes an unfolded protein response transcription factor that operates upstream of EDEM2. The upstream transcription factor is in some cases the spliced form of an XBP1. It is envisioned that any encoded XBP1 can be successfully employed in the instant invention. Table 2 lists some examples of sequences of vertebrate XBP1 spliced-form polypeptides. A multiple pairwise comparison of those polypeptide sequences, which was performed using Clustal W (Thompson 1994; Yuan 1999), revealed that each of the disclosed spliced XBP1 polynucleotide sequences is at least 48% identical to each other XBP1 sequence. A Clustal W comparison of the disclosed mammalian XBP1 sequences revealed that each sequence is at least 86% identical to the other. Thus, in some embodiments, the cell contains a polynucleotide that encodes a spliced-form of an XBP1 polypeptide having a sequence that is at least 86% to any one of a mammalian spliced XBP1. A consensus XBP1 amino acid sequence was built by aligning a mouse, hamster, and human XBP1 amino acid sequences. That consensus sequence is depicted as SEQ ID NO: 13. Thus, in some embodiments, the cell contains a polynucleotide that encodes an XBP1 polypeptide having an amino acid sequence of SEQ ID NO: 13.

In various embodiments, the cell contains a polynucleotide that encodes an XBP1 polypeptide having an amino acid sequence that is at least 86% identical to the mouse XBP1 (mXBP1) amino acid sequence (SEQ ID NO: 9); and in a particular embodiment, the polypeptide is mXBP1, or a conservatively substituted variant thereof.

The invention envisions that any cell may be used to harbor the lectin-encoding polypeptide for the production of a properly folded and active multi-subunit protein. Such cells include the well-known protein production cells such as the bacterium Escherichia coli and similar prokaryotic cells, the yeasts Pichia pastoris and other Pichia and non-pichia yeasts, plant cell explants, such as those of Nicotiana, insect cells, such as Schneider 2 cells, Sf9 and Sf21, and the Trichoplusia ni-derived High Five cells, and the mammalian cells typically used in bioproduction, such as CHO, CHO-K1, COS, HeLa, HEK293, Jurkat, and PC12 cells. In some embodiments, the cell is a CHO-K1 or a modified CHO-K1 cell such as that which is taught in U.S. Pat. Nos. 7,435,553, 7,514,545, and 7,771,997, as well as U.S. Published Patent Application No. US 2010-0304436 A1, each of which is incorporated herein by reference in its entirety.

In some particular embodiments, the invention provides ex vivo a CHO-K1 cell that contains (1) a mEDEM2-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 16, (2) an XBP1-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 18, (3) an antibody heavy chain-encoding polynucleotide comprising a nucleotide sequence that encodes a polypeptide comprising the amino acid sequences of SEQ ID NO: 43 and 44, and (4) an antibody light chain-encoding polynucleotide comprising a nucleotide sequence that encodes a polypeptide comprising the amino acid sequences of SEQ ID NO: 45 and 46.

In one particular embodiment, the invention provides ex vivo a CHO-K1 cell that contains (1) a mEDEM2-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 16, (2) an XBP1-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO:18, (3) an antibody heavy chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 23, and (4) an antibody light chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 25.

In another particular embodiment, the invention provides ex vivo a CHO-K1 cell that contains (1) a mEDEM2-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 16, (2) an XBP1-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 18, (3) an antibody heavy chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 31, and (4) an antibody light chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 33.

In yet another particular embodiment, the invention provides ex vivo a CHO-K1 cell that contains (1) a mEDEM2-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 16, (2) an XBP1-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 18, (3) an antibody heavy chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 39, and (4) an antibody light chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 41.

The Cell Line

In another aspect, the invention provides a cell line, which comprises a plurality of cells descended by clonal expansion from a cell described above. At least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or about 100% of the constituent cells of the cell line contain a recombinant polynucleotide that encodes a stress-induced mannose-binding lectin, which in some embodiments is a component of the ERAD. In some embodiments, the stress-induced mannose-binding lectin is an endoplasmic reticulum degradation-enhancing alpha-mannosidase-like protein 2 (EDEM2). It is envisioned that any encoded EDEM2 or conservatively-substituted variant thereof can be successfully employed in the instant invention. Table 1, as discussed in the previous section, lists some examples of vertebrate EDEM2 proteins. In some embodiments, the constituent cell contains a polynucleotide that encodes an EDEM2 polypeptide having a sequence that is at least 92% identical to any mammalian EDEM2. In some embodiments, the constituent cell contains a polynucleotide that encodes an EDEM2 polypeptide having the mammalian consensus amino acid sequence of SEQ ID NO: 8. In some embodiments, the constituent cell contains a recombinant polynucleotide of SEQ ID NO: 1 or a conservatively substituted variant thereof.

In some embodiments, the multi-subunit protein that is produced by the cell line is an antibody, and the constituent cell of the cell line contains a polynucleotide encoding any one or more of a polypeptide comprising an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44 (which represent consensus sequences of the N-terminal and C-terminal portions, respectively, of particular antibody heavy chains), and SEQ ID NO: 45 and SEQ ID NO: 46 (which represent consensus sequences of the N-terminal and C-terminal portions, respectively, of particular antibody light chains). In some embodiments, in addition to the recombinant polynucleotide encoding the EDEM2 protein, the constituent cell of the cell line contains at least two polynucleotides, each of which encodes a particular subunit of the multi-subunit protein. For example, the constituent cell contains a polynucleotide encoding an antibody heavy chain comprising an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and another polynucleotide encoding an antibody light chain comprising an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46.

In some embodiments, the constituent cell, in addition to containing the stress-response polynucleotide and one or more polynucleotides encoding a polypeptide subunit, as described above, also contains a polynucleotide that encodes an unfolded protein response transcription factor, which operates upstream of EDEM2, such as a spliced form of an XBP1. It is envisioned that any encoded XBP1 can be successfully employed in the instant invention. Table 2, as discussed in the preceding section, lists some examples of sequences of vertebrate XBP1 spliced-form polypeptides. Clustal W analysis of those sequences revealed that each of the disclosed spliced XBP1 polynucleotide sequences is at least 48% identical to each other XBP1 sequence; and a comparison of the mammalian XBP1 sequences revealed that each sequence is at least 86% identical to the other. Thus, in some embodiments, the constituent cell of the cell line contains a polynucleotide that encodes a spliced-form of an XBP1 polypeptide having a sequence that is at least 86% to any one of a mammalian spliced XBP1. In some embodiments, the constituent cell contains a polynucleotide that

encodes an XBP1 polypeptide having a consensus amino acid sequence of SEQ ID NO: 13.

In various embodiments, the cell contains a polynucleotide that encodes an XBP1 polypeptide having an amino acid sequence that is at least 86% identical to the mouse XBP1 (mXBP1) amino acid sequence (SEQ ID NO: 9); and in a particular embodiment, the polypeptide is mXBP1 of SEQ ID NO: 9, or a conservatively substituted variant thereof.

The invention envisions that the cell line comprises constituent cells whose parent is selected from a list of well-known protein production cells such as, e.g., the bacterium Escherichia coli and similar prokaryotic cells, the yeasts Pichia pastoris and other Pichia and non-pichia yeasts, plant cell explants, such as those of Nicotiana, insect cells, such as Schneider 2 cells, Sf9 and Sf21, and the Trichoplusia ni-derived High Five cells, and the mammalian cells typically used in bioproduction, such as CHO, CHO-K1, COS, HeLa, HEK293, Jurkat, and PC12 cells. In some embodiments, the cell is a CHO-K1 or a modified CHO-K1 cell, such as that which is taught in U.S. Pat. Nos. 7,435,553, 7,514,545, and 7,771,997, as well as U.S. Published Patent Application No. US 2010-0304436 A1.

In some embodiments, the cell line, which is cultured in media, is capable of producing the multi-subunit protein and secreting the properly assembled multi-subunit protein into the media to a titer that is at least 3 g/L, at least 5 g/L, or at least 8 g/L.

Furthermore, the constituent cells of the cell line are capable proliferating in culture to such an extent as to attain an integrated cell density that is about 30% greater than the integrated cell density of a cell line that does not contain the recombinant polynucleotide encoding the stress-induced mannose-binding lectin. In some cases, the cell line is able to attain an integrated cell density that is at least about 50% greater, at least 60% greater, or at least 90% greater than the integrated cell density of a cell line that does not contain the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin. In some embodiments, the integrated cell density of the cell line is assessed after about 12 days in culture.

In some particular embodiments, the invention provides a cell-line comprising clonally-derived constituent cells, wherein the constituent cell is a CHO-K1 cell that contains (1) a mEDEM2-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 16, (2) an XBP1-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 18, (3) an antibody heavy chain-encoding polynucleotide comprising a nucleotide sequence that encodes a polypeptide comprising the amino acid sequences of SEQ ID NO: 43 and 44, and (4) an antibody light chain-encoding polynucleotide comprising a nucleotide sequence that encodes a polypeptide comprising the amino acid sequences of SEQ ID NO: 45 and 46.

In one particular embodiment, the invention provides a cell-line comprising clonally-derived constituent cells, wherein the constituent cell is a CHO-K1 cell that contains (1) a mEDEM2-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 16, (2) an XBP1-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 18, (3) an antibody heavy chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 23, and (4) an antibody light chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 25.

In another particular embodiment, the invention provides a cell-line comprising clonally-derived constituent cells, wherein the constituent cell is a CHO-K1 cell that contains

(1) a mEDEM2-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 16, (2) an XBP1-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 18, (3) an antibody heavy chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 31, and (4) an antibody light chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 33.

In yet another particular embodiment, the invention provides a cell-line comprising clonally-derived constituent cells, wherein the constituent cell is a CHO-K1 cell that contains (1) a mEDEM2-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 16, (2) an XBP1-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 18, (3) an antibody heavy chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 39, and (4) an antibody light chain-encoding polynucleotide comprising a nucleotide sequence of SEQ ID NO: 41.

The EDEM2 Polynucleotide

In another aspect, the invention provides a polynucleotide that encodes an EDEM2 protein. The EDEM2-encoding polynucleotide is recombinant and can be manufactured, stored, used or expressed in vitro, as in a test tube, or an in vitro translation system, or in vivo, such as in a cell, which can be ex vivo, as in a cell culture, or in vivo, as in an organism. In some embodiments, the EDEM2-encoding polynucleotide is within a gene, meaning that it is under the control of and down stream of a promoter, and up stream of a polyadenylation site. The EDEM2-encoding polynucleotide or gene can be within a plasmid or other circular or linear vector. The EDEM2-encoding polynucleotide or gene can be within a circular or linear DNA construct, which can be within a cell as an episome or integrated into the cellular genome.

As described above, the EDEM2-encoding polynucleotide encodes any ortholog, homolog or conservatively substituted EDEM2 polypeptide of Table 1, or an EDEM2 polypeptide having an amino acid sequence that is at least 92% identical to any one of SEQ ID NO: 1-5 and 8, including the mammalian consensus sequence of SEQ ID NO: 8.

In some cases, the recombinant or isolated EDEM2-encoding polynucleotide is operably linked to a mammalian promoter. The promoter can be any promoter, but in some cases it is a mammalian promoter, such as for example a ubiquitin C promoter.

In a particular embodiment, the EDEM2-encoding polynucleotide essentially consists of, from 5' to 3', a promoter, such as a ubiquitin C promoter, followed by an optional intron, such as a beta globin intron, followed by an EDEM2 coding sequence, followed by a polyadenylation sequence, such as an SV40 pA sequence. A specific example, which is also a particular embodiment, of such an EDEM2-encoding polynucleotide is described by SEQ ID NO: 16. Conserved variants of that sequence are also envisioned to be embodiments of the invention.

In some cases, the recombinant EDEM2-encoding polynucleotide is part of a plasmid, which can be linear, circular, episomal, integrated, a static DNA construct, or a vector for delivering the EDEM2 gene or expressing the EDEM2 protein. In one particular embodiment, the plasmid contains (1) an EDEM2 gene, which is under the control of a ubiquitin C promoter and terminates with an SV40 polyadenylation signal, and (2) a selectable marker, such as a polynucleotide encoding a polypeptide that confers resistance to zeocin or a polynucleotide encoding a polypeptide that confers resistance to neomycin, under the control of a promoter, such as an SV40 promoter, and terminated with a polyadenylation sequence, such as a PGK pA sequence. In one particular embodiment, the plasmid comprises, in a circular format running in a 5' to 3' direction, a ubiquitin C promoter, a beta globin intron, an EDEM2 coding sequence, an SV40 pA sequence, an SV40 promoter, a neomycin-resistance coding sequence, and a PGK pA sequence. A specific example of this embodiment is exemplified by a plasmid having the sequence of SEQ ID NO: 14. In another particular embodiment, the plasmid comprises, in a circular format running in a 5' to 3' direction, a ubiquitin C promoter, a beta globin intron, an EDEM2 coding sequence, an SV40 pA sequence, an SV40 promoter, a zeocin-resistance coding sequence, and a PGK pA sequence. A specific example of this embodiment is exemplified by a plasmid having the sequence of SEQ ID NO: 15.

The XBP1 Polynucleotide

In another aspect, the invention provides a polynucleotide that encodes an XBP1 protein. The XBP1-encoding polynucleotide is recombinant and can be manufactured, stored, used or expressed in vitro, as in a test tube, or an in vitro translation system, or in vivo, such as in a cell, which can be ex vivo, as in a cell culture, or in vivo, as in an organism. In some embodiments, the XBP1-encoding polynucleotide is within a gene, meaning that it is under the control of and down stream of a promoter, and up stream of a polyadenylation site. The XBP1-encoding polynucleotide can be within a plasmid or other circular or linear vector. The XBP1-encoding polynucleotide or gene can be within a circular or linear DNA construct, which can be within a cell as an episome, or integrated into the cellular genome.

As described above, the XBP1-encoding polynucleotide encodes any ortholog, homolog or conservatively substituted XBP1 polypeptide of Table 2, or an XBP1 polypeptide having an amino acid sequence that is at least 86% identical to any one of SEQ ID NO: 9, 10, and 11, including the mammalian consensus sequence of SEQ ID NO: 13.

In some cases, the recombinant or isolated XBP1-encoding polynucleotide is operably linked to a mammalian promoter. The promoter can be any promoter, but in some cases it is a mammalian promoter, such as for example a ubiquitin C promoter.

In a particular embodiment, the XBP1-encoding polynucleotide essentially consists of, from 5' to 3', a promoter, such as a ubiquitin C promoter, followed by an optional intron, such as a beta globin intron, followed by an XBP1 coding sequence, followed by a polyadenylation sequence, such as an SV40 pA sequence. SEQ ID NO: 18 describes an example of an XBP1-encoding polynucleotide. Conserved variants of that exemplary sequence are also envisioned to be embodiments of the invention.

In some cases, the recombinant XBP1-encoding polynucleotide is part of a plasmid, which can be linear, circular, episomal, integrated, a static DNA construct, or a vector for delivering the XBP1 gene or expressing the spliced and active XBP1 protein. In one particular embodiment, the plasmid contains (1) an XBP1 gene, which is under the control of a ubiquitin C promoter and terminates with an SV40 polyadenylation signal, and (2) a selectable marker, such as a polynucleotide encoding a polypeptide that confers resistance to zeocin or a polynucleotide encoding a polypeptide that confers resistance to neomycin, under the control of a promoter, such as an SV40 promoter, and terminated with a polyadenylation sequence, such as a PGK pA sequence. In one particular embodiment, the plasmid comprises, in a circular format running in a 5' to 3' direction, a ubiquitin C promoter, a beta globin intron, an XBP1 coding sequence, an SV40 pA sequence, an SV40 promoter, a zeocin-resistance coding sequence, and a PGK pA sequence. A specific example of this embodiment is exemplified by a circular plasmid having the sequence of SEQ ID NO: 17.

The Antibody Heavy and Light Chain-Encoding Polynucleotides

In another aspect, the invention provides a polynucleotide that encodes an antibody heavy chain polypeptide (HC). The HC-encoding polynucleotide is recombinant and can be manufactured, stored, used or expressed in vitro, as in a test tube, or an in vitro translation system, or in vivo, such as in a cell, which can be ex vivo, as in a cell culture, or in vivo, as in an organism. In some embodiments, the HC-encoding polynucleotide is within a gene, meaning that it is under the control of and down stream from a promoter, and up stream of a polyadenylation site. The HC-encoding polynucleotide may be within a plasmid or other circular or linear vector. The HC-encoding polynucleotide or gene may be within a circular or linear DNA construct, which may be within a cell as an episome or integrated into the cellular genome.

In some cases, the recombinant or isolated HC-encoding polynucleotide is operably linked to a mammalian promoter. The promoter can be any promoter, but in some cases it is a mammalian promoter, such as for example a ubiquitin C promoter or an hCMV-IE promoter.

In a particular embodiment, the HC-encoding polynucleotide is an HC gene, which essentially comprises, from 5' to 3', a promoter, for example an hCMV-IE promoter, followed by an optional intron, such as a beta globin intron, followed by a heavy chain coding sequence, such as for example a sequence encoding an amino acid sequence of SEQ ID NO: 43 and 44, SEQ ID NO: 19, SEQ ID NO: 27, or SEQ ID NO: 35, followed by a polyadenylation sequence, for example an SV40 pA sequence. A specific example of an HC gene is described by SEQ ID NO: 23, SEQ ID NO: 31, or SEQ ID NO: 39. Conserved variants of any one of these sequences are also envisioned to be embodiments of the invention.

In some cases, the recombinant HC-encoding polynucleotide is part of a plasmid, which can be linear, circular, episomal, integrated, a static DNA construct, or a vector for delivering the heavy chain gene or expressing the heavy chain sububunit. In one particular embodiment, the plasmid contains (1) an HC gene, which is under the control of an hCMV-IE promoter and terminates with an SV40 polyadenylation signal, and (2) a selectable marker, such as a polynucleotide encoding a polypeptide that confers resistance to hygromycin, under the control of a promoter, such as an SV40 promoter, and terminated with a polyadenylation sequence, such as a PGK pA sequence. In one particular embodiment, the plasmid comprises, in a circular format running in a 5' to 3' direction, an hCMV-IE promoter, a beta globin intron, an antibody heavy chain coding sequence (which encodes a HC having an amino acid of SEQ ID NO: 43 and 44, SEQ ID NO: 19, SEQ ID NO: 27, or SEQ ID NO: 35), an SV40 pA sequence, an SV40 promoter, a hygromycin-resistance coding sequence, and a PGK pA sequence. A specific example and particular embodiment of such a plasmid containing an HC gene is described by SEQ ID NO: 24, SEQ ID NO: 32, or SEQ ID NO: 40. Conserved variants of any one of these sequences are also envisioned to be embodiments of the invention.

In another aspect, the invention provides a polynucleotide that encodes an antibody light chain polypeptide (LC). The LC-encoding polynucleotide is recombinant and can be manufactured, stored, used or expressed in vitro, as in a test tube, or an in vitro translation system, or in vivo, such as in a cell, which can be ex vivo, as in a cell culture, or in vivo, as in an organism. In some embodiments, the LC-encoding polynucleotide is within a gene, meaning that it is under the control of and down stream from a promoter, and up stream of a polyadenylation site. The LC-encoding polynucleotide or gene may be within a plasmid or other circular or linear vector. The LC-encoding polynucleotide or gene may be within a circular or linear DNA construct, which may be within a cell as an episome or integrated into the cellular genome.

In some cases, the recombinant or isolated LC-encoding polynucleotide is operably linked to a mammalian promoter. The promoter can be any promoter, but in some cases it is a mammalian promoter, such as, e.g., a ubiquitin C promoter or an hCMV-IE promoter.

In a particular embodiment, the LC-encoding polynucleotide is an LC gene, which essentially comprises, from 5' to 3', a promoter, for example an hCMV-IE promoter, followed by an optional intron, such as a beta globin intron, followed by a light chain coding sequence, such as for example a sequence encoding an amino acid sequence of SEQ ID NO: 45 and 46, SEQ ID NO: 21, SEQ ID NO: 29, or SEQ ID NO: 37, followed by a polyadenylation sequence, such as an SV40 pA sequence. A specific example and particular embodiment of such an LC gene is described by SEQ ID NO: 25, SEQ ID NO: 33, or SEQ ID NO: 41. Conserved variants of any one of these sequences are also envisioned to be embodiments of the invention.

In some cases, the recombinant LC-encoding polynucleotide is part of a plasmid, which may be linear, circular, episomal, integrated, a static DNA construct, or a vector for delivering the light chain gene or expressing the light chain sububunit. In one particular embodiment, the plasmid contains (1) an LC gene, which is under the control of an hCMV-IE promoter and terminates with an SV40 polyadenylation signal, and (2) a selectable marker, such as a polynucleotide encoding a polypeptide that confers resistance to hygromycin, under the control of a promoter, such as an SV40 promoter, and terminated with a polyadenylation sequence, such as a PGK pA sequence. In one particular embodiment, the plasmid comprises, in a circular format running in a 5' to 3' direction, an hCMV-IE promoter, a beta globin intron, an antibody light chain coding sequence (which encodes a LC having an amino acid of SEQ ID NO: 45 and 46, SEQ ID NO: 21, SEQ ID NO: 29, or SEQ ID NO: 37), an SV40 pA sequence, an SV40 promoter, a hygromycin-resistance coding sequence, and a PGK pA sequence. A specific example and particular embodiment of such a plasmid containing an LC gene is described by SEQ ID NO: 26, SEQ ID NO: 34, or SEQ ID NO: 42. Conserved variants of any one of these sequences are also envisioned to be embodiments of the invention.

Methods of Manufacturing Multi-subunit Proteins

In another aspect, the invention provides a method for manufacturing a multi-subunit protein by culturing a cell, or a constituent cell of a cell line, which is capable of producing and secreting relatively large amounts of a properly assembled multi-subunit protein, in a medium, wherein the multi-subunit component is secreted into the medium at a relatively high titer. The cell utilized in this manufacturing process is a cell described in the foregoing aspects, which contains an ERAD lectin-encoding polynucleotide described herein.

Methods of culturing cells, and in particular mammalian cells, for the purpose of producing useful recombinant proteins is well-known in the art (e.g., see De Jesus & Wurm, Eur. J. Pharm. Biopharm. 78:184-188, 2011, and references cited therein). Briefly, cells containing the described polynucleotides are cultured in media, which may contain sera or hydrolysates, or may be chemically defined and optimized for protein production. The cultures may be fed-batch cultures or continuous cultures, as in a chemostat. The cells may be cultured in lab bench size flasks (~25 mL), production scale-up bioreactors (1-5 L), or industrial scale bioreactors (5,000-25,000 L). Production runs may last for several weeks to a month, during which time the multi-subunit protein is secreted into the media.

The subject cell has an enhanced ability to produce and secrete properly assembled multi-subunit proteins. In some embodiments, the multi-subunit protein, for example an antibody, is secreted into the media at a rate of at least 94 ρg/cell/day, at least 37 ρg/cell/day, or at least 39 ρg/cell/day. In some embodiments, the multi-subunit protein attains a titer of at least at least 3 g/L, at least 5 g/L, at least 6 g/L, or at least 8 g/L after about twelve days of culture.

Furthermore, the subject cell has an enhanced ability to proliferate and attain a relatively high cell density, further optimizing productivity. In some embodiments, the cell or cell-line seed train attains an integrated cell density in culture of at least 5×10^7 cell-day/mL, at least 1×10^8 cell-day/mL or at least 1.5×10^8 cell-day/mL.

Optionally, the secreted multi-subunit protein is subsequently purified from the medium into which it was secreted. Protein purification methods are well-known in the art (see e.g., Kelley, mAbs 1(5):443-452). In some embodiments, the protein is harvested by centrifugation to remove the cells from the liquid media supernatant, followed by various chromatography steps and a filtration step to remove inter alia viruses and other contaminants or adulterants. In some embodiments, the chromatography steps include an ion exchange step, such as cation-exchange or anion-exchange. Various affinity chromatographic media may also be employed, such as protein A chromatography for the purification of antibodies.

Optionally, the manufacturing method may include the antecedent steps of creating the cell. Thus, in some embodiments, the method of manufacturing the multi-subunit protein comprises the step of transfecting the cell with the vector that encodes the stress-induced mannose-binding lectin, as described above, followed by selecting stable integrants thereof. Non-limiting examples of vectors include those genetic constructs that contain a polynucleotide that encodes an EDEM2 having an amino acid sequence of any one of SEQ ID NO: 1-8, an amino acid sequence that is at least 92% identical to any one of SEQ ID NO: 1-8, or any one of a conservatively substituted variant of SEQ ID NO: 1-8. Useful vectors also include, for example, a plasmid harboring the gene of SEQ ID NO: 16, the plasmid of SEQ ID NO: 15, and the plasmid of SEQ ID NO: 14. One should keep in mind that the plasmid sequences (e.g., SEQ ID NO: 14, 15, 17, 24, 26, 32, 34, 40, and 42) are circular sequences described in a linear manner in the sequence listing. Thus, in those cases, the 3-prime-most nucleotide of the written sequence may be considered to be immediately 5-prime of the 5-prime-most nucleotide of the sequence as written. In the example of the plasmid of SEQ ID NO: 14, transformants are selected through resistance to neomycin; for SEQ ID NO: 15, by selection through ZEOCIN resistance.

Detailed methods for the construction of polynucleotides and vectors comprising same, are described in U.S. Pat. Nos. 7,435,553 and 7,771,997, which are incorporated herein by reference, and in, e.g., Zwarthoff et al., J. Gen. Virol. 66(4):685-91, 1985; Mory et al., DNA. 5(3):181-93, 1986; and Pichler et al., Biotechnol. Bioeng. 108(2):386-94, 2011.

The starting cell, into which the vector that encodes the stress-induced mannose-binding lectin is placed, may already contain the constructs or genetic elements encoding or regulating the expression of the subunits of the multi-subunit protein, or XBP1 for those embodiments utilizing XBP1. Alternatively, the vector that encodes the stress-induced mannose-binding lectin may be put inside the cell first, and followed by the other constructs.

Multi-Subunit Proteins Manufactured by the Process

In another aspect, the invention provides a multi-subunit protein that is made according to the process disclosed herein. Given the inclusion of one or more elements that facilitate the proper folding, assembly, and post-translational modification of a multi-subunit protein, such as an antibody, one of ordinary skill in the art would reasonably expect such a protein to have distinct structural and functional qualities. For example, an antibody manufactured by the disclosed process is reasonably believed to have a particular glycosylation pattern and a quantitatively greater proportion of non-aggregated heterotetramers.

EXAMPLES

The following examples are presented so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by mole, molecular weight is average molecular weight, percent concentration (%) means the mass of the solute in grams divided by the volume of the solution in milliliters times 100% (e.g., 10% substance X means 0.1 gram of substance X per milliliter of solution), temperature is in degrees Centigrade, and pressure is at or near atmospheric pressure.

Example 1

Cell Lines

CHO-K1 derived host cell line was transfected with two plasmids encoding heavy and light chain of a human antibody. Both plasmids contain the hph gene conferring resistance to hygromycin B (Asselbergs and Pronk, 1992, Mol. Biol. Rep., 17(1):61-70). Cells were transfected using LIPOFECTAMIN reagent (Invitrogen cat.#18324020). Briefly, one day before transfection 3.5 million cells were plated on a 10 cm plate in complete F12 (Invitrogen cat.#11765) containing 10% fetal bovine serum (FBS) (Invitrogen cat.#10100). On the day of transfection the cells were washed once and medium was replaced with OPTIMEM from (Invitrogen cat.#31985). DNA/Lipofectamin complexes were prepared in OPTIMEM medium and then added to the cells. The medium was changed again to the complete F12 with 10% FBS 6 hours later. The stable integration of the plasmids was selected using hygromycin B selection agent at 400 μg/ml. Clonal antibody expressing cell lines were isolated using the FASTR technology (described in the U.S. Pat. No. 6,919,183, which is herein incorporated by reference).

The antibody expressing lines were then re-transfected with the EDEM2 encoding plasmid. EDEM2 plasmids contained either neomycin phosphotransferase (plasmid construct designated "p3") or sh ble (plasmid "p7") genes to confer resistance to either G418 or zeocin respectively. The same transfection method was used. Depending on the selectable marker, cells were selected with either G418 or zeocin at 400 μg/ml or 250 μg/ml, respectively. The clonal cell lines were then isolated using FASTR technology.

TABLE 3

Cell Lines			
Name	Enhancers	Constructs	Protein
C1	EDEM2 + XBP1	HC/LC = p1/p2	αAng2
C2	XBP1	EDEM2 = p3	
		XBP1 = p4	
C3	EDEM2 + XBP1	HC/LC = p5/p6	αGDF8
C4	XBP1	EDEM2 = p7	
C5	EDEM2	XBP1 = p4	
C6	EDEM2 + XBP1	HC/LC = p8/p9	αAngPtl4
C7	XBP1	EDE3M2 = p3	
		XBP1 = p4	

Example 2

The antibody production was evaluated in a scaled-down 12-day fed batch process using shaker flasks. In this method the cells were seeded in a shaker flask at the density of 0.8 million cells per mL in the production medium (defined media with high amino acid). The culture was maintained for about 12 days, and was supplemented with three feeds as well as glucose. The viable cell density, and antibody titer were monitored throughout the batch.

To determine the effect of mEDEM2 on enhanced protein production, the production of proteins by CHO cell lines containing mEDEM2 and mXBP1 were compared to production by control cells that contained mXBP1, but not mEDEM2. Protein titers were higher in those cell lines expressing mEDEM2 versus those cell lines that did not express mEDEM2.

TABLE 4

TITERS			
Cell Line	Enhancers	Production rate (ρg/cell/day)	Titre g/L (% increase)
C1	EDEM2 + XBP1	39	8.1 (93)
C2	XBP1	39	4.2
C3	EDEM2 + XBP1	37	5.9 (55)
C8	XBP1	32	3.8
C6	EDEM2 + XBP1	94	5.3 (152)
C7	XBP1	52	2.1
C5	EDEM2	29	3.1 (343)
C9	—	9	0.7

Example 3

Integrated Cell Days

Integrated Cell Density ("ICD") is a phrase used to describe the growth of the culture throughout the fed batch process. In the course of the 12-day production assay, we monitored viable cell density on days 0, 3, 5, 7, 10, and 12. This data was then plotted against time. ICD is the integral of viable cell density, calculated as the area under the cell density curve. EDEM2 transfected lines have higher ICD in a 12-day fed batch process (see Table 5).

TABLE 5

INTEGRATED CELL DENSITIES		
Cell Line	Enhancers	ICD 10^6 cell-day/mL (% increase)
C1	EDEM2 + XBP1	205 (93)
C2	XBP1	106
C3	EDEM2 + XBP1	157 (34)
C4	XBP1	117
C6	EDEM2 + XBP1	56 (51)
C7	XBP1	37
C5	EDEM2	116 (59)
C9	—	73

Example 4

Anti-GDF8 Antibody Production

The effect of ectopic expression of EDEM2, XBP1, or both on the production of an anti-GDF8 antibody having a heavy chain sequence of SEQ ID NO: 19 and a light chain sequence of SEQ ID NO: 21 was examined. Individual cell-lines were examined for titer and integrated cell density and placed into "bins", or ranges of values. Ectopic expression of EDEM2 significantly increased the number of cell lines that express antibody in the 5-6 g/L titer range. The combination of XBP1 and EDEM2 showed more than an additive effect toward the increase in high titer cell lines. The expression of EDEM2 in the antibody secreting cells also significantly increased the number of cell lines that attain a high ICD (see Table 6).

TABLE 6

con-	Titre Bins (g/l)				ICD Bins (10^6 cell-day/mL)		
struct	<1	1-3	3-5	5-6	30-50	50-100	100-200
E + X	0%	33.3%	44.4%	22.2%	11.1%	50%	38.9%
X	0%	37.5%	54%	8.3%	14.3%	85.7%	0%
E	0%	33%	60%	7%	0%	27%	73%
—	82%	18%	0%	0%	13%	67%	21%

Example 5

Productivity and Stability of EDEM2-Expressing Cells

The effect of ectopic expression of XBP1 or EDEM2 on the production of a monospecific antibody of interest (identified as clonal cell lines RGC91 or RGC92, respectively) was examined. Individual cell lines were examined for protein titer and integrated cell density, as well as stability.

Modified CHO K1 host cells stably expressing XBP1 (RGC91) or EDEM2 (RGC92) at a transcriptionally active locus (U.S. Pat. No. 8,389,239B2, issued Mar. 5, 2013) were transfected with a recombinant plasmid vector comprising the antibody gene of interest and a hygromycin resistance gene (hyg).

400 μg/mL hygromycin was used for selection of transfected cells. Positive integrants expressing the antibody of interest (randomly integrated in the CHO genome), and also stably expressing either XBP1 or EDEM2, were confirmed and isolated by fluorescence-activated cell sorting (FACS) analysis. The isolated clones were expanded in suspension cultures in serum-free production medium. Clones were

isolated from selected pools and were subjected to a 12 day fed batch productivity assay, and the protein titer of the antibody of interest was determined. Integrated cell density is calculated by measuring viable cell count on a given day in the production assay (counts are taken every 3 days and plotted on a curve against cell count).

As shown in FIG. 1A, the average protein titers for clones isolated from RGC91 and RGC92 was 4.2 and 5.2, respectively (for 24 representative antibody-expressing clones). Ectopic expression of EDEM2 increased the number of clones that attain antibody titer above 5 g/L (FIG. 1A) compared to XBP1-expressing clones. Clonal cell lines expressing EDEM2 isolated from the RGC92 host also maintained higher (25%-100% higher) integrated cell densities when compared to clones isolated from XBP1-expressing RGC91 host (see FIG. 1B). EDEM2 clones established an ICD greater than 100 (FIG. 1B) in most clones tested. Clones isolated from EDEM2 expressing RGC92 host also resulted in significantly higher stability (FIG. 2B), as observed in flow cytometry-based autologous secretion trap (FASTR) scans (for reference, U.S. Pat. No. 6,919,183B2, issued Jul. 19, 2005) showing a homogenous producing population, in the representative sample of 24 clonal cell lines tested. Many of the clones isolated from XBP1 expressing RGC91 host appear to have a non-producing heterogeneous cell population (FIG. 2A). Without being bound to any one theory, EDEM2 facilitated the removal of misfolded proteins in the high expressing clones, thereby reducing stress in the cell during protein production and resulting in a more stable cell population.

SEQUENCE LISTING

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<160> NUMBER OF SEQ ID NOS: 46

<210> SEQ ID NO 1
<211> LENGTH: 577
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 1

Met Pro Phe Arg Leu Leu Ile Pro Leu Gly Leu Val Cys Val Leu Leu
1               5                   10                  15

Pro Leu His His Gly Ala Pro Gly Pro Asp Gly Thr Ala Pro Asp Pro
            20                  25                  30

Ala His Tyr Arg Glu Arg Val Lys Ala Met Phe Tyr His Ala Tyr Asp
        35                  40                  45

Ser Tyr Leu Glu Asn Ala Phe Pro Tyr Asp Glu Leu Arg Pro Leu Thr
    50                  55                  60

Cys Asp Gly His Asp Thr Trp Gly Ser Phe Ser Leu Thr Leu Ile Asp
65                  70                  75                  80

Ala Leu Asp Thr Leu Leu Ile Leu Gly Asn Thr Ser Glu Phe Gln Arg
                85                  90                  95

Val Val Glu Val Leu Gln Asp Asn Val Asp Phe Asp Ile Asp Val Asn
            100                 105                 110

Ala Ser Val Phe Glu Thr Asn Ile Arg Val Val Gly Gly Leu Leu Ser
        115                 120                 125

Ala His Leu Leu Ser Lys Lys Ala Gly Val Glu Val Glu Ala Gly Trp
    130                 135                 140

Pro Cys Ser Gly Pro Leu Leu Arg Met Ala Glu Glu Ala Ala Arg Lys
145                 150                 155                 160

Leu Leu Pro Ala Phe Gln Thr Pro Thr Gly Met Pro Tyr Gly Thr Val
                165                 170                 175

Asn Leu Leu His Gly Val Asn Pro Gly Glu Thr Pro Val Thr Cys Thr
            180                 185                 190

Ala Gly Ile Gly Thr Phe Ile Val Glu Phe Ala Thr Leu Ser Ser Leu
        195                 200                 205

Thr Gly Asp Pro Val Phe Glu Asp Val Ala Arg Val Ala Leu Met Arg
    210                 215                 220

Leu Trp Glu Ser Arg Ser Asp Ile Gly Leu Val Gly Asn His Ile Asp
225                 230                 235                 240

Val Leu Thr Gly Lys Trp Val Ala Gln Asp Ala Gly Ile Gly Ala Gly
                245                 250                 255

Val Asp Ser Tyr Phe Glu Tyr Leu Val Lys Gly Ala Ile Leu Leu Gln
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            260                 265                 270

Asp Lys Lys Leu Met Ala Met Phe Leu Glu Tyr Asn Lys Ala Ile Arg
        275                 280                 285

Asn Tyr Thr His Phe Asp Asp Trp Tyr Leu Trp Val Gln Met Tyr Lys
    290                 295                 300

Gly Thr Val Ser Met Pro Val Phe Gln Ser Leu Glu Ala Tyr Trp Pro
305                 310                 315                 320

Gly Leu Gln Ser Leu Ile Gly Asp Ile Asp Asn Ala Met Arg Thr Phe
                325                 330                 335

Leu Asn Tyr Tyr Thr Val Trp Lys Gln Phe Gly Gly Leu Pro Glu Phe
            340                 345                 350

Tyr Asn Ile Pro Gln Gly Tyr Thr Val Glu Lys Arg Glu Gly Tyr Pro
        355                 360                 365

Leu Arg Pro Glu Leu Ile Glu Ser Ala Met Tyr Leu Tyr Arg Ala Thr
    370                 375                 380

Gly Asp Pro Thr Leu Leu Glu Leu Gly Arg Asp Ala Val Glu Ser Ile
385                 390                 395                 400

Glu Lys Ile Ser Lys Val Glu Cys Gly Phe Ala Thr Ile Lys Asp Leu
                405                 410                 415

Arg Asp His Lys Leu Asp Asn Arg Met Glu Ser Phe Phe Leu Ala Glu
            420                 425                 430

Thr Val Lys Tyr Leu Tyr Leu Leu Phe His Pro Asn Asn Phe Ile His
        435                 440                 445

Asn Asn Gly Ser Thr Phe Asp Ser Val Met Thr Pro His Gly Glu Cys
    450                 455                 460

Ile Leu Gly Ala Gly Gly Tyr Ile Phe Asn Thr Glu Ala His Pro Ile
465                 470                 475                 480

Asp Pro Ala Ala Leu His Cys Cys Arg Arg Leu Lys Glu Glu Gln Trp
                485                 490                 495

Glu Val Glu Asp Leu Ile Lys Glu Phe Tyr Ser Leu Lys Gln Ser Arg
            500                 505                 510

Pro Lys Arg Ala Gln Arg Lys Thr Val Arg Ser Gly Pro Trp Glu Pro
        515                 520                 525

Gln Ser Gly Pro Ala Thr Leu Ser Ser Pro Ala Asn Gln Pro Arg Glu
    530                 535                 540

Lys Gln Pro Ala Gln Gln Arg Thr Pro Leu Leu Ser Cys Pro Ser Gln
545                 550                 555                 560

Pro Phe Thr Ser Lys Leu Ala Leu Leu Gly Gln Val Phe Leu Asp Ser
                565                 570                 575

Ser


<210> SEQ ID NO 2
<211> LENGTH: 576
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 2

Met Pro Phe Arg Leu Leu Ile Pro Leu Gly Leu Val Cys Val Leu Leu
1               5                   10                  15

Pro Leu His His Gly Ala Pro Gly Pro Glu Gly Thr Ala Pro Asp Pro
            20                  25                  30

Ala His Tyr Arg Glu Arg Val Lys Ala Met Phe Tyr His Ala Tyr Asp
        35                  40                  45

Ser Tyr Leu Glu Asn Ala Phe Pro Tyr Asp Glu Leu Arg Pro Leu Thr
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    50                  55                  60

Cys Asp Gly His Asp Thr Trp Gly Ser Phe Ser Leu Thr Leu Ile Asp
65                  70                  75                  80

Ala Leu Asp Thr Leu Leu Ile Leu Gly Asn Thr Ser Glu Phe Gln Arg
                85                  90                  95

Val Val Glu Val Leu Gln Asp Asn Val Asp Phe Asp Ile Asp Val Asn
            100                 105                 110

Ala Ser Val Phe Glu Thr Asn Ile Arg Val Val Gly Gly Leu Leu Ser
        115                 120                 125

Ala His Leu Leu Ser Lys Lys Ala Gly Val Glu Val Glu Ala Gly Trp
    130                 135                 140

Pro Cys Ser Gly Pro Leu Leu Arg Met Ala Glu Glu Ala Ala Arg Lys
145                 150                 155                 160

Leu Leu Pro Ala Phe Gln Thr Pro Thr Gly Met Pro Tyr Gly Thr Val
                165                 170                 175

Asn Leu Leu His Gly Val Asn Pro Gly Glu Thr Pro Val Thr Cys Thr
            180                 185                 190

Ala Gly Ile Gly Thr Phe Ile Val Glu Phe Ala Thr Leu Ser Ser Leu
        195                 200                 205

Thr Gly Asp Pro Val Phe Glu Asp Val Ala Arg Val Ala Leu Met Arg
    210                 215                 220

Leu Trp Glu Ser Arg Ser Asp Ile Gly Leu Val Gly Asn His Ile Asp
225                 230                 235                 240

Val Leu Thr Gly Lys Trp Val Ala Gln Asp Ala Gly Ile Gly Ala Gly
                245                 250                 255

Val Asp Ser Tyr Phe Glu Tyr Leu Val Lys Gly Ala Ile Leu Leu Gln
            260                 265                 270

Asp Lys Lys Leu Met Ala Met Phe Leu Glu Tyr Asn Lys Ala Ile Arg
        275                 280                 285

Asn Tyr Thr His Phe Asp Asp Trp Tyr Leu Trp Val Gln Met Tyr Lys
    290                 295                 300

Gly Thr Val Ser Met Pro Val Phe Gln Ser Leu Glu Ala Tyr Trp Pro
305                 310                 315                 320

Gly Leu Gln Ser Leu Ile Gly Asp Ile Asp Asn Ala Met Arg Thr Phe
                325                 330                 335

Leu Asn Tyr Tyr Thr Val Trp Lys Gln Phe Gly Gly Leu Pro Glu Phe
            340                 345                 350

Tyr Asn Ile Pro Gln Gly Tyr Thr Val Glu Lys Arg Glu Gly Tyr Pro
        355                 360                 365

Leu Arg Pro Glu Leu Ile Glu Ser Ala Met Tyr Leu Tyr Arg Ala Thr
    370                 375                 380

Gly Asp Pro Thr Leu Leu Glu Leu Gly Arg Asp Ala Val Glu Ser Ile
385                 390                 395                 400

Glu Lys Ile Ser Lys Val Glu Cys Gly Phe Ala Thr Ile Lys Asp Leu
                405                 410                 415

Arg Asp His Lys Leu Asp Asn Arg Met Glu Ser Phe Phe Leu Ala Glu
            420                 425                 430

Thr Val Lys Tyr Leu Tyr Leu Leu Phe His Pro Asn Asn Phe Ile His
        435                 440                 445

Asn Asn Gly Ser Thr Phe Asp Ser Val Met Thr Pro His Gly Glu Cys
    450                 455                 460

Ile Leu Gly Ala Gly Gly Tyr Ile Phe Asn Thr Glu Ala His Pro Ile
465                 470                 475                 480
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Asp Pro Ala Ala Leu His Cys Cys Arg Arg Leu Lys Glu Glu Gln Trp
                485                 490                 495

Glu Val Glu Asp Leu Ile Lys Glu Phe Tyr Ser Leu Arg Gln Ser Arg
            500                 505                 510

Ser Arg Ala Gln Arg Lys Thr Val Ser Ser Gly Pro Trp Glu Pro Pro
        515                 520                 525

Ala Gly Pro Gly Thr Leu Ser Ser Pro Glu Asn Gln Pro Arg Glu Lys
    530                 535                 540

Gln Pro Ala Arg Gln Arg Ala Pro Leu Leu Ser Cys Pro Ser Gln Pro
545                 550                 555                 560

Phe Thr Ser Lys Leu Ala Leu Leu Gly Gln Val Phe Leu Asp Ser Ser
                565                 570                 575


<210> SEQ ID NO 3
<211> LENGTH: 578
<212> TYPE: PRT
<213> ORGANISM: Cricetulus griseus

<400> SEQUENCE: 3

Met Pro Phe Arg Leu Leu Ile Pro Leu Gly Leu Val Cys Val Phe Leu
1               5                   10                  15

Pro Leu His His Gly Ala Pro Gly Pro Asp Gly Thr Ala Pro Asp Pro
            20                  25                  30

Ala His Tyr Arg Glu Arg Val Lys Ala Met Phe Tyr His Ala Tyr Asp
        35                  40                  45

Ser Tyr Leu Glu Asn Ala Phe Pro Tyr Asp Glu Leu Arg Pro Leu Thr
    50                  55                  60

Cys Asp Gly His Asp Thr Trp Gly Ser Phe Ser Leu Thr Leu Ile Asp
65                  70                  75                  80

Ala Leu Asp Thr Leu Leu Ile Leu Gly Asn Thr Ser Glu Phe Gln Arg
                85                  90                  95

Val Val Glu Val Leu Gln Asp Asn Val Asp Phe Asp Ile Asp Val Asn
            100                 105                 110

Ala Ser Val Phe Glu Thr Asn Ile Arg Val Val Gly Gly Leu Leu Ser
        115                 120                 125

Ala His Leu Leu Ser Lys Lys Ala Gly Val Glu Val Glu Ala Gly Trp
    130                 135                 140

Pro Cys Ser Gly Pro Leu Leu Arg Met Ala Glu Glu Ala Ala Arg Lys
145                 150                 155                 160

Leu Leu Pro Ala Phe Gln Thr Pro Thr Gly Met Pro Tyr Gly Thr Val
                165                 170                 175

Asn Leu Leu His Gly Val Asn Pro Gly Glu Thr Pro Val Thr Cys Thr
            180                 185                 190

Ala Gly Ile Gly Thr Phe Ile Val Glu Phe Ala Thr Leu Ser Ser Leu
        195                 200                 205

Thr Gly Asp Pro Val Phe Glu Asp Val Ala Arg Leu Ala Leu Met Arg
    210                 215                 220

Leu Trp Glu Ser Arg Ser Asp Ile Gly Leu Val Gly Asn His Ile Asp
225                 230                 235                 240

Val Leu Thr Gly Lys Trp Val Ala Gln Asp Ala Gly Ile Gly Ala Gly
                245                 250                 255

Val Asp Ser Tyr Phe Glu Tyr Leu Val Lys Gly Ala Ile Leu Leu Gln
            260                 265                 270

Asp Lys Lys Leu Met Ala Met Phe Leu Glu Tyr Asn Arg Ala Ile Arg
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        275                 280                 285

Asn Tyr Thr His Phe Asp Asp Trp Tyr Leu Trp Val Gln Met Tyr Lys
    290                 295                 300

Gly Thr Val Ser Met Pro Val Phe Gln Ser Leu Glu Ala Tyr Trp Pro
305                 310                 315                 320

Gly Leu Gln Ser Leu Ile Gly Asp Ile Asp Asn Ala Met Arg Thr Phe
                325                 330                 335

Leu Asn Tyr Tyr Thr Val Trp Lys Gln Phe Gly Gly Leu Pro Glu Phe
            340                 345                 350

Tyr Asn Ile Ala Gln Gly Tyr Thr Val Glu Lys Arg Glu Gly Tyr Pro
        355                 360                 365

Leu Arg Pro Glu Leu Ile Glu Ser Ala Met Tyr Leu Tyr Arg Ala Thr
    370                 375                 380

Gly Asp Pro Thr Leu Leu Glu Leu Gly Arg Asp Ala Val Glu Ser Ile
385                 390                 395                 400

Glu Lys Ile Ser Lys Val Glu Cys Gly Phe Ala Thr Ile Lys Asp Leu
                405                 410                 415

Arg Asp His Lys Leu Asp Asn Arg Met Glu Ser Phe Phe Leu Ala Glu
            420                 425                 430

Thr Val Lys Tyr Leu Tyr Leu Leu Phe His Pro Asn Asn Phe Ile His
        435                 440                 445

Asn Asn Gly Ser Thr Phe Asp Ser Val Met Thr Pro His Gly Glu Cys
    450                 455                 460

Ile Leu Gly Ala Gly Gly Tyr Ile Phe Asn Thr Glu Ala His Pro Ile
465                 470                 475                 480

Asp Pro Ala Ala Leu His Cys Cys Arg Arg Leu Lys Glu Glu Gln Trp
                485                 490                 495

Glu Val Glu Asp Leu Met Arg Glu Leu His Ser Leu Lys Gln Ser Arg
            500                 505                 510

Ser Arg Ala Gln Arg Lys Thr Thr Ser Ser Gly Pro Trp Glu Pro Pro
        515                 520                 525

Ala Gly Pro Gly Ser Pro Ser Ala Pro Gly Lys Gln Asp Gln Pro Arg
    530                 535                 540

Glu Lys Gln Pro Ala Lys Gln Arg Thr Pro Leu Leu Ser Cys Pro Ser
545                 550                 555                 560

Gln Pro Phe Thr Ser Lys Leu Ala Leu Leu Gly Gln Val Phe Leu Asp
                565                 570                 575

Ser Ser


<210> SEQ ID NO 4
<211> LENGTH: 578
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Met Pro Phe Arg Leu Leu Ile Pro Leu Gly Leu Leu Cys Ala Leu Leu
1               5                   10                  15

Pro Gln His His Gly Ala Pro Gly Pro Asp Gly Ser Ala Pro Asp Pro
            20                  25                  30

Ala His Tyr Arg Glu Arg Val Lys Ala Met Phe Tyr His Ala Tyr Asp
        35                  40                  45

Ser Tyr Leu Glu Asn Ala Phe Pro Phe Asp Glu Leu Arg Pro Leu Thr
    50                  55                  60

Cys Asp Gly His Asp Thr Trp Gly Ser Phe Ser Leu Thr Leu Ile Asp
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65                  70                  75                  80

Ala Leu Asp Thr Leu Leu Ile Leu Gly Asn Val Ser Glu Phe Gln Arg
                85                  90                  95

Val Val Glu Val Leu Gln Asp Ser Val Asp Phe Asp Ile Asp Val Asn
            100                 105                 110

Ala Ser Val Phe Glu Thr Asn Ile Arg Val Val Gly Gly Leu Leu Ser
        115                 120                 125

Ala His Leu Leu Ser Lys Lys Ala Gly Val Glu Val Glu Ala Gly Trp
    130                 135                 140

Pro Cys Ser Gly Pro Leu Leu Arg Met Ala Glu Glu Ala Ala Arg Lys
145                 150                 155                 160

Leu Leu Pro Ala Phe Gln Thr Pro Thr Gly Met Pro Tyr Gly Thr Val
                165                 170                 175

Asn Leu Leu His Gly Val Asn Pro Gly Glu Thr Pro Val Thr Cys Thr
            180                 185                 190

Ala Gly Ile Gly Thr Phe Ile Val Glu Phe Ala Thr Leu Ser Ser Leu
        195                 200                 205

Thr Gly Asp Pro Val Phe Glu Asp Val Ala Arg Val Ala Leu Met Arg
    210                 215                 220

Leu Trp Glu Ser Arg Ser Asp Ile Gly Leu Val Gly Asn His Ile Asp
225                 230                 235                 240

Val Leu Thr Gly Lys Trp Val Ala Gln Asp Ala Gly Ile Gly Ala Gly
                245                 250                 255

Val Asp Ser Tyr Phe Glu Tyr Leu Val Lys Gly Ala Ile Leu Leu Gln
            260                 265                 270

Asp Lys Lys Leu Met Ala Met Phe Leu Glu Tyr Asn Lys Ala Ile Arg
        275                 280                 285

Asn Tyr Thr Arg Phe Asp Asp Trp Tyr Leu Trp Val Gln Met Tyr Lys
    290                 295                 300

Gly Thr Val Ser Met Pro Val Phe Gln Ser Leu Glu Ala Tyr Trp Pro
305                 310                 315                 320

Gly Leu Gln Ser Leu Ile Gly Asp Ile Asp Asn Ala Met Arg Thr Phe
                325                 330                 335

Leu Asn Tyr Tyr Thr Val Trp Lys Gln Phe Gly Gly Leu Pro Glu Phe
            340                 345                 350

Tyr Asn Ile Pro Gln Gly Tyr Thr Val Glu Lys Arg Glu Gly Tyr Pro
        355                 360                 365

Leu Arg Pro Glu Leu Ile Glu Ser Ala Met Tyr Leu Tyr Arg Ala Thr
    370                 375                 380

Gly Asp Pro Thr Leu Leu Glu Leu Gly Arg Asp Ala Val Glu Ser Ile
385                 390                 395                 400

Glu Lys Ile Ser Lys Val Glu Cys Gly Phe Ala Thr Ile Lys Asp Leu
                405                 410                 415

Arg Asp His Lys Leu Asp Asn Arg Met Glu Ser Phe Phe Leu Ala Glu
            420                 425                 430

Thr Val Lys Tyr Leu Tyr Leu Leu Phe Asp Pro Thr Asn Phe Ile His
        435                 440                 445

Asn Asn Gly Ser Thr Phe Asp Thr Val Ile Thr Pro Tyr Gly Glu Cys
    450                 455                 460

Ile Leu Gly Ala Gly Gly Tyr Ile Phe Asn Thr Glu Ala His Pro Ile
465                 470                 475                 480

Asp Pro Ala Ala Leu His Cys Cys Gln Arg Leu Lys Glu Glu Gln Trp
                485                 490                 495
```

Glu Val Glu Asp Leu Met Arg Glu Phe Tyr Ser Leu Lys Arg Ser Arg
500 505 510

Ser Lys Phe Gln Lys Asn Thr Val Ser Ser Gly Pro Trp Glu Pro Pro
515 520 525

Ala Arg Pro Gly Thr Leu Phe Ser Pro Glu Asn His Asp Gln Ala Arg
530 535 540

Glu Arg Lys Pro Ala Lys Gln Lys Val Pro Leu Leu Ser Cys Pro Ser
545 550 555 560

Gln Pro Phe Thr Ser Lys Leu Ala Leu Leu Gly Gln Val Phe Leu Asp
565 570 575

Ser Ser

<210> SEQ ID NO 5
<211> LENGTH: 578
<212> TYPE: PRT
<213> ORGANISM: Pan troglodytes

<400> SEQUENCE: 5

Met Pro Phe Arg Leu Leu Ile Pro Leu Gly Leu Leu Cys Ala Leu Leu
1 5 10 15

Pro Leu His His Gly Ala Pro Gly Pro Asp Gly Ser Ala Pro Asp Pro
20 25 30

Ala His Tyr Arg Glu Arg Val Lys Ala Met Phe Tyr His Ala Tyr Asp
35 40 45

Ser Tyr Leu Glu Asn Ala Phe Pro Phe Asp Glu Leu Arg Pro Leu Thr
50 55 60

Cys Asp Gly His Asp Thr Trp Gly Ser Phe Ser Leu Thr Leu Ile Asp
65 70 75 80

Ala Leu Asp Thr Leu Leu Ile Leu Gly Asn Val Ser Glu Phe Gln Arg
85 90 95

Val Val Glu Val Leu Gln Asp Ser Val Asp Phe Asp Ile Asp Val Asn
100 105 110

Ala Ser Val Phe Glu Thr Asn Ile Arg Val Val Gly Gly Leu Leu Ser
115 120 125

Ala His Leu Leu Ser Lys Lys Ala Gly Val Glu Val Glu Ala Gly Trp
130 135 140

Pro Cys Ser Gly Pro Leu Leu Arg Met Ala Glu Glu Ala Ala Arg Lys
145 150 155 160

Leu Leu Pro Ala Phe Gln Thr Pro Thr Gly Met Pro Tyr Gly Thr Val
165 170 175

Asn Leu Leu His Gly Val Asn Pro Gly Glu Thr Pro Val Thr Cys Thr
180 185 190

Ala Gly Ile Gly Thr Phe Ile Val Glu Phe Ala Thr Leu Ser Ser Leu
195 200 205

Thr Gly Asp Pro Val Phe Glu Asp Val Ala Arg Val Ala Leu Met Arg
210 215 220

Leu Trp Glu Ser Arg Ser Asp Ile Gly Leu Val Gly Asn His Ile Asp
225 230 235 240

Val Leu Thr Gly Lys Trp Val Ala Gln Asp Ala Gly Ile Gly Ala Gly
245 250 255

Val Asp Ser Tyr Phe Glu Tyr Leu Val Lys Gly Ala Ile Leu Leu Gln
260 265 270

Asp Lys Lys Leu Met Ala Met Phe Leu Glu Tyr Asn Lys Ala Ile Arg
275 280 285

```
Asn Tyr Thr Arg Phe Asp Asp Trp Tyr Leu Trp Val Gln Met Tyr Lys
    290                 295                 300

Gly Thr Val Ser Met Pro Val Phe Gln Ser Leu Glu Ala Tyr Trp Pro
305                 310                 315                 320

Gly Leu Gln Ser Leu Ile Gly Asp Ile Asp Asn Ala Met Arg Thr Phe
                325                 330                 335

Leu Asn Tyr Tyr Thr Val Trp Lys Gln Phe Gly Gly Leu Pro Glu Phe
            340                 345                 350

Tyr Asn Ile Pro Gln Gly Tyr Thr Val Glu Lys Arg Glu Gly Tyr Pro
        355                 360                 365

Leu Arg Pro Glu Leu Ile Glu Ser Ala Met Tyr Leu Tyr Arg Ala Thr
    370                 375                 380

Gly Asp Pro Thr Leu Leu Glu Leu Gly Arg Asp Ala Val Glu Ser Ile
385                 390                 395                 400

Glu Lys Ile Ser Lys Val Glu Cys Gly Phe Ala Thr Ile Lys Asp Leu
                405                 410                 415

Arg Asp His Lys Leu Asp Asn Arg Met Glu Ser Phe Phe Leu Ala Glu
            420                 425                 430

Thr Val Lys Tyr Leu Tyr Leu Leu Phe Asp Pro Thr Asn Phe Ile His
        435                 440                 445

Asn Asn Gly Ser Thr Phe Asp Ala Val Ile Thr Pro Tyr Gly Glu Cys
    450                 455                 460

Ile Leu Gly Ala Gly Gly Tyr Ile Phe Asn Thr Glu Ala His Pro Ile
465                 470                 475                 480

Asp Pro Ala Ala Leu His Cys Cys Gln Arg Leu Lys Glu Glu Gln Trp
                485                 490                 495

Glu Val Glu Asp Leu Met Arg Glu Phe Tyr Ser Leu Lys Arg Ser Arg
            500                 505                 510

Ser Lys Phe Gln Lys Lys Thr Val Ser Ser Gly Pro Trp Glu Pro Pro
        515                 520                 525

Ala Arg Pro Gly Thr Leu Phe Ser Pro Glu Asn His Asp Gln Ala Arg
    530                 535                 540

Glu Arg Lys Pro Ala Lys Gln Lys Val Pro Leu Leu Ser Cys Pro Ser
545                 550                 555                 560

Gln Pro Phe Thr Ser Lys Leu Ala Leu Leu Gly Gln Val Phe Leu Asp
                565                 570                 575

Ser Ser
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<210> SEQ ID NO 6
<211> LENGTH: 513
<212> TYPE: PRT
<213> ORGANISM: Pongo pygmaeus

<400> SEQUENCE: 6

```
Met Asn Thr Leu Ser Cys Ser Leu Phe Ser Leu Thr Leu Ile Asp Ala
1               5                   10                  15

Leu Asp Thr Leu Leu Ile Leu Gly Asn Val Ser Glu Phe Gln Arg Val
            20                  25                  30

Val Glu Val Leu Gln Asp Asn Val Asp Phe Asp Ile Asp Val Asn Ala
        35                  40                  45

Ser Val Phe Glu Thr Asn Ile Arg Val Val Gly Gly Leu Leu Ser Ala
    50                  55                  60

His Leu Leu Ser Lys Lys Ala Gly Val Glu Val Glu Ala Gly Trp Pro
65                  70                  75                  80
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Cys Ser Gly Pro Leu Leu Arg Met Ala Glu Glu Ala Ala Arg Lys Leu
                85                  90                  95

Leu Pro Ala Phe Gln Thr Pro Thr Gly Met Pro Tyr Gly Thr Val Asn
            100                 105                 110

Leu Leu His Gly Val Asn Pro Gly Glu Thr Pro Val Thr Cys Thr Ala
        115                 120                 125

Gly Ile Gly Thr Phe Ile Val Glu Phe Ala Thr Leu Ser Ser Leu Thr
    130                 135                 140

Gly Asp Pro Val Phe Glu Asp Val Ala Arg Val Ala Leu Met Arg Leu
145                 150                 155                 160

Trp Glu Ser Arg Ser Asp Ile Gly Leu Val Gly Asn His Ile Asp Val
                165                 170                 175

Leu Thr Gly Lys Trp Val Ala Gln Asp Ala Gly Ile Gly Ala Gly Val
            180                 185                 190

Asp Ser Tyr Phe Glu Tyr Leu Val Lys Gly Ala Ile Leu Leu Gln Asp
        195                 200                 205

Lys Lys Leu Met Ala Met Phe Leu Glu Tyr Asn Lys Ala Ile Arg Asn
    210                 215                 220

Tyr Thr Arg Phe Asp Asp Trp Tyr Leu Trp Val Gln Met Tyr Lys Gly
225                 230                 235                 240

Thr Val Ser Met Pro Val Phe Gln Ser Leu Glu Ala Tyr Trp Pro Gly
                245                 250                 255

Leu Gln Ser Leu Ile Gly Asp Ile Asp Asn Ala Met Arg Thr Phe Leu
            260                 265                 270

Asn Tyr Tyr Thr Val Trp Lys Gln Phe Gly Gly Leu Pro Glu Phe Tyr
        275                 280                 285

Asn Ile Pro Gln Gly Tyr Thr Val Glu Lys Arg Glu Gly Tyr Pro Leu
    290                 295                 300

Arg Pro Glu Leu Ile Glu Ser Ala Met Tyr Leu Tyr Arg Ala Thr Gly
305                 310                 315                 320

Asp Pro Thr Leu Leu Glu Leu Gly Arg Asp Ala Val Glu Ser Ile Glu
                325                 330                 335

Lys Ile Ser Lys Val Glu Cys Gly Phe Ala Thr Ile Lys Asp Leu Arg
            340                 345                 350

Asp His Lys Leu Asp Asn Arg Met Glu Ser Phe Phe Leu Ala Glu Thr
        355                 360                 365

Val Lys Tyr Leu Tyr Leu Leu Phe Asp Pro Thr Asn Phe Ile His Asn
    370                 375                 380

Asn Gly Ser Thr Phe Asp Ala Val Ile Thr Pro Tyr Gly Glu Cys Ile
385                 390                 395                 400

Leu Gly Ala Gly Gly Tyr Ile Phe Asn Thr Glu Ala His Pro Ile Asp
                405                 410                 415

Pro Ala Ala Leu His Cys Cys Gln Arg Leu Lys Glu Glu Gln Trp Glu
            420                 425                 430

Val Glu Asp Leu Met Arg Glu Phe Tyr Ser Leu Lys Arg Asn Arg Ser
        435                 440                 445

Lys Phe Gln Lys Lys Thr Val Ser Ser Gly Pro Trp Glu Pro Pro Ala
    450                 455                 460

Arg Pro Gly Thr Leu Phe Ser Pro Glu Asn His Asp Gln Ala Arg Gly
465                 470                 475                 480

Arg Lys Pro Ala Lys Gln Lys Val Pro Leu Leu Ser Cys Pro Ser Gln
                485                 490                 495
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Pro Phe Thr Ser Lys Leu Ala Leu Leu Gly Gln Val Phe Leu Asp Ser
500 505 510

Ser

<210> SEQ ID NO 7
<211> LENGTH: 572
<212> TYPE: PRT
<213> ORGANISM: Danio rerio

<400> SEQUENCE: 7

Leu Tyr Tyr Leu Pro Leu Phe Thr Ser Arg Tyr Phe Met Leu Thr Phe
1 5 10 15

Leu Phe Ser Ala Ile Phe Cys Ala Ala Tyr Leu Ser Pro Ile Ile Ser
20 25 30

His Val Lys Gly Arg Asp Phe Thr Glu Gln Glu Met Ser His Tyr Arg
35 40 45

Asp Arg Val Lys Ser Met Phe Tyr His Ala Tyr Asn Ser Tyr Leu Asp
50 55 60

Asn Ala Tyr Pro Tyr Asp Glu Leu Arg Pro Leu Thr Cys Asp Gly Gln
65 70 75 80

Asp Thr Trp Gly Ser Phe Ser Leu Thr Leu Ile Asp Ala Leu Asp Thr
85 90 95

Leu Leu Ile Leu Gly Asn His Thr Glu Phe Gln Arg Val Ala Thr Leu
100 105 110

Leu Gln Asp Thr Val Asp Phe Asp Ile Asp Val Asn Ala Ser Val Phe
115 120 125

Glu Thr Asn Ile Arg Val Val Gly Gly Leu Leu Ser Ala His Leu Leu
130 135 140

Ser Lys Arg Ala Gly Met Lys Val Glu Glu Gly Trp Pro Cys Ser Gly
145 150 155 160

Pro Leu Leu Arg Met Ala Glu Asp Ala Ala Arg Lys Leu Leu Pro Ala
165 170 175

Phe Gln Thr Pro Thr Gly Met Pro Tyr Gly Thr Val Asn Leu Leu Arg
180 185 190

Gly Val Asn Pro Gly Glu Thr Pro Val Thr Cys Thr Ala Gly Val Gly
195 200 205

Thr Phe Ile Leu Glu Phe Ser Thr Leu Ser Arg Leu Thr Gly Asp Pro
210 215 220

Val Phe Glu Asn Val Ala Arg Lys Ala Leu Arg Ala Leu Trp Arg Thr
225 230 235 240

Arg Ser Asp Ile Gly Leu Val Gly Asn His Ile Asp Val Ile Thr Ser
245 250 255

Lys Trp Val Ala Gln Asp Ala Gly Ile Gly Ala Gly Val Asp Ser Tyr
260 265 270

Phe Glu Tyr Leu Val Arg Gly Ala Ile Met Leu Gln Asp Glu Glu Leu
275 280 285

Leu Thr Met Phe Tyr Glu Phe Asp Lys Ser Ile Lys Asn Tyr Thr Lys
290 295 300

Phe Asp Asp Trp Tyr Leu Trp Val Gln Met His Lys Gly Thr Val Ser
305 310 315 320

Met Pro Val Phe Gln Ser Leu Glu Ala Phe Trp Pro Gly Met Gln Ser
325 330 335

Leu Ile Gly Asp Ile Ser Ser Ala Thr Lys Ser Phe His Asn Tyr Tyr
340 345 350

```
Ser Val Trp Arg Gln Phe Gly Gly Leu Pro Glu Phe Tyr Ser Ile Pro
        355                 360                 365

Gln Gly Tyr Thr Val Asp Lys Arg Glu Gly Tyr Pro Leu Arg Pro Glu
    370                 375                 380

Leu Ile Glu Ser Ala Met Tyr Leu Tyr Lys Ala Thr Gly Asp Pro Ser
385                 390                 395                 400

Phe Ile Gln Leu Gly Arg Asp Ala Val Glu Ser Ile Asp Arg Ile Ser
                405                 410                 415

Arg Val Asn Cys Gly Phe Ala Thr Val Lys Asp Val Arg Asp His Lys
            420                 425                 430

Leu Asp Asn Arg Met Glu Ser Phe Phe Leu Ala Glu Thr Ile Lys Tyr
        435                 440                 445

Leu Tyr Leu Leu Phe Asp Pro Asp Asn Phe Leu His Asn Thr Gly Thr
    450                 455                 460

Glu Phe Glu Leu Gly Gly Leu Arg Gly Asp Cys Ile Leu Ser Ala Gly
465                 470                 475                 480

Gly Tyr Val Phe Asn Thr Glu Ala His Pro Leu Asp Pro Ala Ala Leu
                485                 490                 495

His Cys Cys Ser Arg Glu Gln Gln Asp Arg Arg Glu Ile Gln Asp Ile
            500                 505                 510

Leu Leu Ser Phe Ser Gln Pro His Thr Glu Glu Pro Ser Arg Asp Gln
        515                 520                 525

Ser Ala Gly Gly Ser Pro Glu Ser Ile Ala Leu Lys Pro Gly Glu Gln
    530                 535                 540

Arg Lys Ala Pro Val Leu Ser Cys Pro Thr Gln Pro Phe Ser Ala Lys
545                 550                 555                 560

Leu Ala Val Met Gly Gln Val Phe Ser Asp Asn Ser
                565                 570
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<210> SEQ ID NO 8
<211> LENGTH: 579
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
<220> FEATURE:
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<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: V or L
<220> FEATURE:
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<223> OTHER INFORMATION: V or A
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<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: L or F
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<222> LOCATION: (26)..(26)
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<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: T or S
<220> FEATURE:
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<222> LOCATION: (57)..(57)
<223> OTHER INFORMATION: Y or F
<220> FEATURE:
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<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: T or V
<220> FEATURE:
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<222> LOCATION: (104)..(104)
<223> OTHER INFORMATION: N or S
<220> FEATURE:
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<222> LOCATION: (220)..(220)
<223> OTHER INFORMATION: V or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (285)..(285)
<223> OTHER INFORMATION: K or R
<220> FEATURE:
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<222> LOCATION: (292)..(292)
<223> OTHER INFORMATION: H or R
<220> FEATURE:
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<222> LOCATION: (356)..(356)
<223> OTHER INFORMATION: P or A
<220> FEATURE:
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<222> LOCATION: (442)..(442)
<223> OTHER INFORMATION: H or D
<220> FEATURE:
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<222> LOCATION: (444)..(444)
<223> OTHER INFORMATION: N or T
<220> FEATURE:
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<222> LOCATION: (456)..(456)
<223> OTHER INFORMATION: S, T, or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (458)..(458)
<223> OTHER INFORMATION: M or I
<220> FEATURE:
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<222> LOCATION: (461)..(461)
<223> OTHER INFORMATION: H or Y
<220> FEATURE:
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<222> LOCATION: (489)..(489)
<223> OTHER INFORMATION: R or Q
<220> FEATURE:
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<222> LOCATION: (502)..(502)
<223> OTHER INFORMATION: I or M
<220> FEATURE:
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<222> LOCATION: (503)..(503)
<223> OTHER INFORMATION: K or R
<220> FEATURE:
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<222> LOCATION: (505)..(505)
<223> OTHER INFORMATION: F or L
<220> FEATURE:
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<222> LOCATION: (506)..(506)
<223> OTHER INFORMATION: Y or H
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (509)..(509)
<223> OTHER INFORMATION: K or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (510)..(510)
<223> OTHER INFORMATION: Q or R
<220> FEATURE:
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<222> LOCATION: (513)..(513)
<223> OTHER INFORMATION: P or S
<220> FEATURE:
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<222> LOCATION: (514)..(516)
<223> OTHER INFORMATION: KRA, RA, or KF (one amino acid may be missing)
<220> FEATURE:
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<220> FEATURE:

<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (519)..(519)
<223> OTHER INFORMATION: K or N
<220> FEATURE:
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<222> LOCATION: (522)..(522)
<223> OTHER INFORMATION: R or S
<220> FEATURE:
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<222> LOCATION: (529)..(529)
<223> OTHER INFORMATION: Q or P
<220> FEATURE:
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<222> LOCATION: (530)..(530)
<223> OTHER INFORMATION: S or A
<220> FEATURE:
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<222> LOCATION: (534)..(534)
<223> OTHER INFORMATION: T or S
<220> FEATURE:
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<222> LOCATION: (535)..(535)
<223> OTHER INFORMATION: L or P
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (536)..(536)
<223> OTHER INFORMATION: S or F
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<222> LOCATION: (537)..(537)
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      missing)
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<222> LOCATION: (544)..(544)
<223> OTHER INFORMATION: P or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (547)..(547)
<223> OTHER INFORMATION: K or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (548)..(548)
<223> OTHER INFORMATION: Q or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (551)..(551)
<223> OTHER INFORMATION: Q, R, or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (553)..(553)
<223> OTHER INFORMATION: R or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (554)..(554)
<223> OTHER INFORMATION: T, A, or V

<400> SEQUENCE: 8

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Met Pro Phe Arg Leu Leu Ile Pro Leu Gly Leu Xaa Cys Xaa Xaa Leu
1               5                   10                  15

Pro Leu His His Gly Ala Pro Gly Pro Xaa Gly Xaa Ala Pro Asp Pro
            20                  25                  30

Ala His Tyr Arg Glu Arg Val Lys Ala Met Phe Tyr His Ala Tyr Asp
        35                  40                  45
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Ser Tyr Leu Glu Asn Ala Phe Pro Xaa Asp Glu Leu Arg Pro Leu Thr
    50                  55                  60

Cys Asp Gly His Asp Thr Trp Gly Ser Phe Ser Leu Thr Leu Ile Asp
65                  70                  75                  80

Ala Leu Asp Thr Leu Leu Ile Leu Gly Asn Xaa Ser Glu Phe Gln Arg
                85                  90                  95

Val Val Glu Val Leu Gln Asp Xaa Val Asp Phe Asp Ile Asp Val Asn
            100                 105                 110

Ala Ser Val Phe Glu Thr Asn Ile Arg Val Val Gly Gly Leu Leu Ser
        115                 120                 125

Ala His Leu Leu Ser Lys Lys Ala Gly Val Glu Val Glu Ala Gly Trp
    130                 135                 140

Pro Cys Ser Gly Pro Leu Leu Arg Met Ala Glu Glu Ala Ala Arg Lys
145                 150                 155                 160

Leu Leu Pro Ala Phe Gln Thr Pro Thr Gly Met Pro Tyr Gly Thr Val
                165                 170                 175

Asn Leu Leu His Gly Val Asn Pro Gly Glu Thr Pro Val Thr Cys Thr
            180                 185                 190

Ala Gly Ile Gly Thr Phe Ile Val Glu Phe Ala Thr Leu Ser Ser Leu
        195                 200                 205

Thr Gly Asp Pro Val Phe Glu Asp Val Ala Arg Xaa Ala Leu Met Arg
    210                 215                 220

Leu Trp Glu Ser Arg Ser Asp Ile Gly Leu Val Gly Asn His Ile Asp
225                 230                 235                 240

Val Leu Thr Gly Lys Trp Val Ala Gln Asp Ala Gly Ile Gly Ala Gly
                245                 250                 255

Val Asp Ser Tyr Phe Glu Tyr Leu Val Lys Gly Ala Ile Leu Leu Gln
            260                 265                 270

Asp Lys Lys Leu Met Ala Met Phe Leu Glu Tyr Asn Xaa Ala Ile Arg
        275                 280                 285

Asn Tyr Thr Xaa Phe Asp Asp Trp Tyr Leu Trp Val Gln Met Tyr Lys
    290                 295                 300

Gly Thr Val Ser Met Pro Val Phe Gln Ser Leu Glu Ala Tyr Trp Pro
305                 310                 315                 320

Gly Leu Gln Ser Leu Ile Gly Asp Ile Asp Asn Ala Met Arg Thr Phe
                325                 330                 335

Leu Asn Tyr Tyr Thr Val Trp Lys Gln Phe Gly Gly Leu Pro Glu Phe
            340                 345                 350

Tyr Asn Ile Xaa Gln Gly Tyr Thr Val Glu Lys Arg Glu Gly Tyr Pro
        355                 360                 365

Leu Arg Pro Glu Leu Ile Glu Ser Ala Met Tyr Leu Tyr Arg Ala Thr
    370                 375                 380

Gly Asp Pro Thr Leu Leu Glu Leu Gly Arg Asp Ala Val Glu Ser Ile
385                 390                 395                 400

Glu Lys Ile Ser Lys Val Glu Cys Gly Phe Ala Thr Ile Lys Asp Leu
                405                 410                 415

Arg Asp His Lys Leu Asp Asn Arg Met Glu Ser Phe Phe Leu Ala Glu
            420                 425                 430

Thr Val Lys Tyr Leu Tyr Leu Leu Phe Xaa Pro Xaa Asn Phe Ile His
        435                 440                 445

Asn Asn Gly Ser Thr Phe Asp Xaa Val Xaa Thr Pro Xaa Gly Glu Cys
    450                 455                 460
```

```
Ile Leu Gly Ala Gly Gly Tyr Ile Phe Asn Thr Glu Ala His Pro Ile
465                 470                 475                 480

Asp Pro Ala Ala Leu His Cys Cys Xaa Arg Leu Lys Glu Glu Gln Trp
                485                 490                 495

Glu Val Glu Asp Leu Xaa Xaa Glu Xaa Xaa Ser Leu Xaa Xaa Ser Arg
            500                 505                 510

Xaa Xaa Xaa Xaa Gln Xaa Xaa Thr Val Xaa Ser Gly Pro Trp Glu Pro
        515                 520                 525

Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa Gln Xaa
    530                 535                 540

Arg Glu Xaa Xaa Pro Ala Xaa Gln Xaa Xaa Pro Leu Leu Ser Cys Pro
545                 550                 555                 560

Ser Gln Pro Phe Thr Ser Lys Leu Ala Leu Leu Gly Gln Val Phe Leu
                565                 570                 575

Asp Ser Ser


<210> SEQ ID NO 9
<211> LENGTH: 371
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 9

Met Val Val Val Ala Ala Ala Pro Ser Ala Ala Thr Ala Ala Pro Lys
1               5                   10                  15

Val Leu Leu Leu Ser Gly Gln Pro Ala Ser Gly Gly Arg Ala Leu Pro
            20                  25                  30

Leu Met Val Pro Gly Pro Arg Ala Ala Gly Ser Glu Ala Ser Gly Thr
        35                  40                  45

Pro Gln Ala Arg Lys Arg Gln Arg Leu Thr His Leu Ser Pro Glu Glu
    50                  55                  60

Lys Ala Leu Arg Arg Lys Leu Lys Asn Arg Val Ala Ala Gln Thr Ala
65                  70                  75                  80

Arg Asp Arg Lys Lys Ala Arg Met Ser Glu Leu Glu Gln Gln Val Val
                85                  90                  95

Asp Leu Glu Glu Glu Asn His Lys Leu Gln Leu Glu Asn Gln Leu Leu
            100                 105                 110

Arg Glu Lys Thr His Gly Leu Val Val Glu Asn Gln Glu Leu Arg Thr
        115                 120                 125

Arg Leu Gly Met Asp Thr Leu Asp Pro Asp Glu Val Pro Glu Val Glu
    130                 135                 140

Ala Lys Gly Ser Gly Val Arg Leu Val Ala Gly Ser Ala Glu Ser Ala
145                 150                 155                 160

Ala Gly Ala Gly Pro Val Val Thr Ser Pro Glu His Leu Pro Met Asp
                165                 170                 175

Ser Asp Thr Val Ala Ser Ser Asp Ser Glu Ser Asp Ile Leu Leu Gly
            180                 185                 190

Ile Leu Asp Lys Leu Asp Pro Val Met Phe Phe Lys Cys Pro Ser Pro
        195                 200                 205

Glu Ser Ala Ser Leu Glu Glu Leu Pro Glu Val Tyr Pro Glu Gly Pro
    210                 215                 220

Ser Ser Leu Pro Ala Ser Leu Ser Leu Ser Val Gly Thr Ser Ser Ala
225                 230                 235                 240

Lys Leu Glu Ala Ile Asn Glu Leu Ile Arg Phe Asp His Val Tyr Thr
                245                 250                 255
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Lys Pro Leu Val Leu Glu Ile Pro Ser Glu Thr Glu Ser Gln Thr Asn
            260                 265                 270

Val Val Val Lys Ile Glu Glu Ala Pro Leu Ser Ser Ser Glu Glu Asp
        275                 280                 285

His Pro Glu Phe Ile Val Ser Val Lys Lys Glu Pro Leu Glu Asp Asp
    290                 295                 300

Phe Ile Pro Glu Leu Gly Ile Ser Asn Leu Leu Ser Ser Ser His Cys
305                 310                 315                 320

Leu Arg Pro Pro Ser Cys Leu Leu Asp Ala His Ser Asp Cys Gly Tyr
                325                 330                 335

Glu Gly Ser Pro Ser Pro Phe Ser Asp Met Ser Ser Pro Leu Gly Thr
            340                 345                 350

Asp His Ser Trp Glu Asp Thr Phe Ala Asn Glu Leu Phe Pro Gln Leu
        355                 360                 365

Ile Ser Val
    370


<210> SEQ ID NO 10
<211> LENGTH: 369
<212> TYPE: PRT
<213> ORGANISM: Cricetulus griseus

<400> SEQUENCE: 10

Met Val Val Val Ala Ala Ser Pro Ser Ala Ala Thr Ala Ala Pro Lys
1               5                   10                  15

Val Leu Leu Leu Ser Gly Gln Pro Ala Ala Asp Gly Arg Ala Leu Pro
            20                  25                  30

Leu Met Val Pro Gly Ser Arg Ala Ala Gly Ser Glu Ala Asn Gly Ala
        35                  40                  45

Pro Gln Ala Arg Lys Arg Gln Arg Leu Thr His Leu Ser Pro Glu Glu
    50                  55                  60

Lys Ala Leu Arg Arg Lys Leu Lys Asn Arg Val Ala Ala Gln Thr Ala
65                  70                  75                  80

Arg Asp Arg Lys Lys Ala Arg Met Ser Glu Leu Glu Gln Gln Val Val
                85                  90                  95

Asp Leu Glu Glu Glu Asn Gln Lys Leu Leu Leu Glu Asn Gln Leu Leu
            100                 105                 110

Arg Glu Lys Thr His Gly Leu Val Ile Glu Asn Gln Glu Leu Arg Thr
        115                 120                 125

Arg Leu Gly Met Asp Val Leu Thr Thr Glu Glu Ala Pro Glu Thr Glu
    130                 135                 140

Ser Lys Gly Asn Gly Val Arg Pro Val Ala Gly Ser Ala Glu Ser Ala
145                 150                 155                 160

Ala Gly Ala Gly Pro Val Val Thr Ser Pro Glu His Leu Pro Met Asp
                165                 170                 175

Ser Asp Thr Val Asp Ser Ser Asp Ser Glu Ser Asp Ile Leu Leu Gly
            180                 185                 190

Ile Leu Asp Lys Leu Asp Pro Val Met Phe Phe Lys Cys Pro Ser Pro
        195                 200                 205

Glu Ser Ala Asn Leu Glu Glu Leu Pro Glu Val Tyr Pro Gly Pro Ser
    210                 215                 220

Ser Leu Pro Ala Ser Leu Ser Leu Ser Val Gly Thr Ser Ser Ala Lys
225                 230                 235                 240

Leu Glu Ala Ile Asn Glu Leu Ile Arg Phe Asp His Val Tyr Thr Lys
                245                 250                 255
```

```
Pro Leu Val Leu Glu Ile Pro Ser Glu Thr Glu Ser Gln Thr Asn Val
            260                 265                 270

Val Val Lys Ile Glu Glu Ala Pro Leu Ser Ser Ser Glu Glu Asp His
        275                 280                 285

Pro Glu Phe Ile Val Ser Val Lys Lys Glu Pro Glu Glu Asp Phe Ile
    290                 295                 300

Pro Glu Pro Gly Ile Ser Asn Leu Leu Ser Ser Ser His Cys Leu Lys
305                 310                 315                 320

Pro Ser Ser Cys Leu Leu Asp Ala Tyr Ser Asp Cys Gly Tyr Glu Gly
                325                 330                 335

Ser Pro Ser Pro Phe Ser Asp Met Ser Ser Pro Leu Gly Ile Asp His
            340                 345                 350

Ser Trp Glu Asp Thr Phe Ala Asn Glu Leu Phe Pro Gln Leu Ile Ser
        355                 360                 365

Val


<210> SEQ ID NO 11
<211> LENGTH: 376
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Met Val Val Val Ala Ala Ala Pro Asn Pro Ala Asp Gly Thr Pro Lys
1               5                   10                  15

Val Leu Leu Leu Ser Gly Gln Pro Ala Ser Ala Ala Gly Ala Pro Ala
            20                  25                  30

Gly Gln Ala Leu Pro Leu Met Val Pro Ala Gln Arg Gly Ala Ser Pro
        35                  40                  45

Glu Ala Ala Ser Gly Gly Leu Pro Gln Ala Arg Lys Arg Gln Arg Leu
    50                  55                  60

Thr His Leu Ser Pro Glu Glu Lys Ala Leu Arg Arg Lys Leu Lys Asn
65                  70                  75                  80

Arg Val Ala Ala Gln Thr Ala Arg Asp Arg Lys Lys Ala Arg Met Ser
                85                  90                  95

Glu Leu Glu Gln Gln Val Val Asp Leu Glu Glu Glu Asn Gln Lys Leu
            100                 105                 110

Leu Leu Glu Asn Gln Leu Leu Arg Glu Lys Thr His Gly Leu Val Val
        115                 120                 125

Glu Asn Gln Glu Leu Arg Gln Arg Leu Gly Met Asp Ala Leu Val Ala
    130                 135                 140

Glu Glu Glu Ala Glu Ala Lys Gly Asn Glu Val Arg Pro Val Ala Gly
145                 150                 155                 160

Ser Ala Glu Ser Ala Ala Gly Ala Gly Pro Val Val Thr Pro Pro Glu
                165                 170                 175

His Leu Pro Met Asp Ser Gly Gly Ile Asp Ser Ser Asp Ser Glu Ser
            180                 185                 190

Asp Ile Leu Leu Gly Ile Leu Asp Asn Leu Asp Pro Val Met Phe Phe
        195                 200                 205

Lys Cys Pro Ser Pro Glu Pro Ala Ser Leu Glu Glu Leu Pro Glu Val
    210                 215                 220

Tyr Pro Glu Gly Pro Ser Ser Leu Pro Ala Ser Leu Ser Leu Ser Val
225                 230                 235                 240

Gly Thr Ser Ser Ala Lys Leu Glu Ala Ile Asn Glu Leu Ile Arg Phe
                245                 250                 255
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Asp His Ile Tyr Thr Lys Pro Leu Val Leu Glu Ile Pro Ser Glu Thr
            260                 265                 270

Glu Ser Gln Ala Asn Val Val Val Lys Ile Glu Glu Ala Pro Leu Ser
        275                 280                 285

Pro Ser Glu Asn Asp His Pro Glu Phe Ile Val Ser Val Lys Glu Glu
    290                 295                 300

Pro Val Glu Asp Asp Leu Val Pro Glu Leu Gly Ile Ser Asn Leu Leu
305                 310                 315                 320

Ser Ser Ser His Cys Pro Lys Pro Ser Ser Cys Leu Leu Asp Ala Tyr
                325                 330                 335

Ser Asp Cys Gly Tyr Gly Gly Ser Leu Ser Pro Phe Ser Asp Met Ser
            340                 345                 350

Ser Leu Leu Gly Val Asn His Ser Trp Glu Asp Thr Phe Ala Asn Glu
        355                 360                 365

Leu Phe Pro Gln Leu Ile Ser Val
    370                 375


<210> SEQ ID NO 12
<211> LENGTH: 383
<212> TYPE: PRT
<213> ORGANISM: Danio rerio

<400> SEQUENCE: 12

Met Val Val Val Thr Ala Gly Thr Gly Gly Ala His Lys Val Leu Leu
1               5                   10                  15

Ile Ser Gly Lys Gln Ser Ala Ser Thr Gly Ala Thr Gln Gly Gly Tyr
            20                  25                  30

Ser Arg Ser Ile Ser Val Met Ile Pro Asn Gln Ala Ser Ser Asp Ser
        35                  40                  45

Asp Ser Thr Thr Ser Gly Pro Pro Leu Arg Lys Arg Gln Arg Leu Thr
    50                  55                  60

His Leu Ser Pro Glu Glu Lys Ala Leu Arg Arg Lys Leu Lys Asn Arg
65                  70                  75                  80

Val Ala Ala Gln Thr Ala Arg Asp Arg Lys Lys Ala Lys Met Gly Glu
                85                  90                  95

Leu Glu Gln Gln Val Leu Glu Leu Glu Leu Glu Asn Gln Lys Leu His
            100                 105                 110

Val Glu Asn Arg Leu Leu Arg Asp Lys Thr Ser Asp Leu Leu Ser Glu
        115                 120                 125

Asn Glu Glu Leu Arg Gln Arg Leu Gly Leu Asp Thr Leu Glu Thr Lys
    130                 135                 140

Glu Gln Val Gln Val Leu Glu Ser Ala Val Ser Asp Leu Gly Leu Val
145                 150                 155                 160

Thr Gly Ser Ser Glu Ser Ala Ala Gly Ala Gly Pro Ala Val Pro Lys
                165                 170                 175

Ser Glu Asp Phe Thr Met Asp Thr His Ser Pro Gly Pro Ala Asp Ser
            180                 185                 190

Glu Ser Asp Leu Leu Leu Gly Ile Leu Asp Ile Leu Asp Pro Glu Leu
        195                 200                 205

Phe Leu Lys Thr Asp Leu Pro Glu Ala Gln Glu Pro Gln Gln Glu Leu
    210                 215                 220

Val Leu Val Gly Gly Ala Gly Glu Gln Val Pro Ser Ser Ala Pro Ala
225                 230                 235                 240

Ala Leu Gly Pro Ala Pro Val Lys Leu Glu Ala Leu Asn Glu Leu Ile
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                245                 250                 255

His Phe Asp His Ile Tyr Thr Lys Pro Ala Glu Val Leu Val Ser Glu
            260                 265                 270

Glu Ser Ile Cys Glu Val Lys Ala Glu Asp Ser Val Ala Phe Ser Glu
        275                 280                 285

Thr Glu Glu Glu Ile Gln Val Glu Asp Gln Thr Val Ser Val Lys Asp
    290                 295                 300

Glu Pro Glu Glu Val Val Ile Pro Ala Glu Asn Gln Asn Pro Asp Ala
305                 310                 315                 320

Ala Asp Asp Phe Leu Ser Asp Thr Ser Phe Gly Gly Tyr Glu Lys Ala
                325                 330                 335

Ser Tyr Leu Thr Asp Ala Tyr Ser Asp Ser Gly Tyr Glu Arg Ser Pro
            340                 345                 350

Ser Pro Phe Ser Asn Ile Ser Ser Pro Leu Cys Ser Glu Gly Ser Trp
        355                 360                 365

Asp Asp Met Phe Ala Ser Glu Leu Phe Pro Gln Leu Ile Ser Val
    370                 375                 380
```

<210> SEQ ID NO 13
<211> LENGTH: 373
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: A or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: S or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: A or P
<220> FEATURE:
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<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: T or D
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: A or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: A or T
<220> FEATURE:
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<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: S or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: G, D, or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: R or Q
<220> FEATURE:
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<222> LOCATION: (37)..(37)
<223> OTHER INFORMATION: G or A
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE

<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: A or G
<220> FEATURE:
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<222> LOCATION: (46)..(48)
<223> OTHER INFORMATION: S, N, or ASG (two amino acids may be missing)
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
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<223> OTHER INFORMATION: T, A, or L
<220> FEATURE:
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<222> LOCATION: (105)..(105)
<223> OTHER INFORMATION: H or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (108)..(108)
<223> OTHER INFORMATION: Q or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (123)..(123)
<223> OTHER INFORMATION: V or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (130)..(130)
<223> OTHER INFORMATION: T or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (136)..(136)
<223> OTHER INFORMATION: T, V, or A
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<223> OTHER INFORMATION: D, T, or V
<220> FEATURE:
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<222> LOCATION: (139)..(139)
<223> OTHER INFORMATION: P, T, or A
<220> FEATURE:
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<222> LOCATION: (140)..(140)
<223> OTHER INFORMATION: D or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (142)..(142)
<223> OTHER INFORMATION: V, A, or none
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (143)..(143)
<223> OTHER INFORMATION: P or none
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (145)..(145)
<223> OTHER INFORMATION: V, T, or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (147)..(147)
<223> OTHER INFORMATION: A or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (150)..(150)
<223> OTHER INFORMATION: S or N
<220> FEATURE:
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<222> LOCATION: (151)..(151)
<223> OTHER INFORMATION: G or E
<220> FEATURE:
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<222> LOCATION: (154)..(154)
<223> OTHER INFORMATION: L or P
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (171)..(171)
<223> OTHER INFORMATION: S or P
<220> FEATURE:
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<222> LOCATION: (180)..(180)
<223> OTHER INFORMATION: D or G
<220> FEATURE:

<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (181)..(181)
<223> OTHER INFORMATION: T or G
<220> FEATURE:
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<222> LOCATION: (182)..(182)
<223> OTHER INFORMATION: V or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (183)..(183)
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<220> FEATURE:
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<220> FEATURE:
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<223> OTHER INFORMATION: S or N
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<223> OTHER INFORMATION: V or I
<220> FEATURE:
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<223> OTHER INFORMATION: T or A
<220> FEATURE:
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<223> OTHER INFORMATION: S or P
<220> FEATURE:
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<222> LOCATION: (289)..(289)
<223> OTHER INFORMATION: E or N
<220> FEATURE:
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<223> OTHER INFORMATION: K or E
<220> FEATURE:
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<222> LOCATION: (303)..(303)
<223> OTHER INFORMATION: L, V, or none
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (305)..(305)
<223> OTHER INFORMATION: D or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (307)..(307)
<223> OTHER INFORMATION: F or L
<220> FEATURE:
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<222> LOCATION: (308)..(308)
<223> OTHER INFORMATION: I or V
<220> FEATURE:
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<222> LOCATION: (311)..(311)
<223> OTHER INFORMATION: L or P
<220> FEATURE:
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<222> LOCATION: (323)..(323)
<223> OTHER INFORMATION: L or P
<220> FEATURE:
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<222> LOCATION: (324)..(324)
<223> OTHER INFORMATION: R or K
<220> FEATURE:
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<222> LOCATION: (326)..(326)
<223> OTHER INFORMATION: P or S

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<220> FEATURE:
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<222> LOCATION: (333)..(333)
<223> OTHER INFORMATION: H or Y
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (339)..(339)
<223> OTHER INFORMATION: E or G
<220> FEATURE:
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<222> LOCATION: (342)..(342)
<223> OTHER INFORMATION: P or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (351)..(351)
<223> OTHER INFORMATION: P or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (354)..(354)
<223> OTHER INFORMATION: T, I, or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (355)..(355)
<223> OTHER INFORMATION: D or N

<400> SEQUENCE: 13

Met Val Val Val Ala Ala Xaa Pro Xaa Xaa Ala Xaa Xaa Xaa Pro Lys
1               5                   10                  15

Val Leu Leu Leu Ser Gly Gln Pro Ala Xaa Xaa Gly Xaa Ala Leu Pro
            20                  25                  30

Leu Met Val Pro Xaa Xaa Arg Xaa Ala Gly Ser Glu Ala Xaa Xaa Xaa
        35                  40                  45

Gly Xaa Pro Gln Ala Arg Lys Arg Gln Arg Leu Thr His Leu Ser Pro
    50                  55                  60

Glu Glu Lys Ala Leu Arg Arg Lys Leu Lys Asn Arg Val Ala Ala Gln
65                  70                  75                  80

Thr Ala Arg Asp Arg Lys Lys Ala Arg Met Ser Glu Leu Glu Gln Gln
                85                  90                  95

Val Val Asp Leu Glu Glu Glu Asn Xaa Lys Leu Xaa Leu Glu Asn Gln
            100                 105                 110

Leu Leu Arg Glu Lys Thr His Gly Leu Val Xaa Glu Asn Gln Glu Leu
        115                 120                 125

Arg Xaa Arg Leu Gly Met Asp Xaa Leu Xaa Xaa Xaa Glu Xaa Xaa Glu
    130                 135                 140

Xaa Glu Xaa Lys Gly Xaa Xaa Val Arg Xaa Val Ala Gly Ser Ala Glu
145                 150                 155                 160

Ser Ala Ala Gly Ala Gly Pro Val Val Thr Xaa Pro Glu His Leu Pro
                165                 170                 175

Met Asp Ser Xaa Xaa Xaa Xaa Ser Ser Asp Ser Glu Ser Asp Ile Leu
            180                 185                 190

Leu Gly Ile Leu Asp Xaa Leu Asp Pro Val Met Phe Phe Lys Cys Pro
        195                 200                 205

Ser Pro Glu Xaa Ala Xaa Leu Glu Glu Leu Pro Glu Val Tyr Pro Xaa
    210                 215                 220

Gly Pro Ser Ser Leu Pro Ala Ser Leu Ser Leu Ser Val Gly Thr Ser
225                 230                 235                 240

Ser Ala Lys Leu Glu Ala Ile Asn Glu Leu Ile Arg Phe Asp His Xaa
                245                 250                 255

Tyr Thr Lys Pro Leu Val Leu Glu Ile Pro Ser Glu Thr Glu Ser Gln
            260                 265                 270

Xaa Asn Val Val Val Lys Ile Glu Glu Ala Pro Leu Ser Xaa Ser Glu
```

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        275                 280                 285

Xaa Asp His Pro Glu Phe Ile Val Ser Val Lys Xaa Glu Pro Xaa Glu
    290                 295                 300

Xaa Asp Xaa Xaa Pro Glu Xaa Gly Ile Ser Asn Leu Leu Ser Ser Ser
305                 310                 315                 320

His Cys Xaa Xaa Pro Xaa Ser Cys Leu Leu Asp Ala Xaa Ser Asp Cys
                325                 330                 335

Gly Tyr Xaa Gly Ser Xaa Ser Pro Phe Ser Asp Met Ser Ser Xaa Leu
            340                 345                 350

Gly Xaa Xaa His Ser Trp Glu Asp Thr Phe Ala Asn Glu Leu Phe Pro
        355                 360                 365

Gln Leu Ile Ser Val
    370


<210> SEQ ID NO 14
<211> LENGTH: 7686
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic plasmid

<400> SEQUENCE: 14

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ctcctgatac cattgggtct tgtttgcgtt ctcctccctc tccatcacgg cgccccaggt    120

ccagacggta ccgcacctga tcctgcccat taccgcgaac gcgttaaagc catgttctac    180

cacgcctatg actcctatct ggaaaatgca ttcccctatg atgagctccg acccettacc    240

tgcgatggtc atgatacttg ggctcttttt tcccttaccc ttattgacgc tctggacaca    300

ctccttatcc tcggaaacac cagcgaattt caaagagtag ttgaagtact tcaggacaat    360

gtcgactttg acatcgatgt gaacgcatca gttttcgaaa caaatataag agtcgttgga    420

ggtctgctct ccgcccacct tctctctaaa aaagccggag tagaagttga agctggctgg    480

ccctgctccg gacccctcct tcgtatggct gaagaagctg cccgcaaact ccttcccgct    540

tttcagaccc caaccggtat gccctatggt actgttaacc tcctgcacgg agtaaatccc    600

ggcgaaaccc ccgtcacatg tacagccgga attggaacct ttattgtgga atttgcaacc    660

cttagcagcc tgaccggaga tcctgtattc gaagacgtgg ctcgggttgc cctgatgcga    720

ctgtgggaat ccaggtctga tatcggtctg gtcggtaacc atatagacgt actcactggt    780

aaatgggttg cacaagacgc tggaattggg gcaggcgtgg attcttattt tgaatatctc    840

gtaaaagggg ccatactctt gcaggacaaa aaacttatgg ctatgttcct ggaatataac    900

aaagctatta ggaactacac acacttcgat gattggtatt tgtgggtcca aatgtataaa    960

ggaaccgttt ctatgcctgt ctttcagtca ctggaggctt attggcctgg tctgcaatcc   1020

ctgatcggag acattgacaa tgcaatgagg acattcctta attattacac tgtttggaag   1080

cagttcggcg gattgcccga attttacaac attcctcaag gctatacagt tgaaaaaaga   1140

gaaggatatc ccctgcgccc cgagcttatt gaaagcgcta tgtatctgta tcgtgcaaca   1200

ggtgatccaa ccctgcttga actgggacga gacgccgtcg aatcaatcga gaaaatttca   1260

aaagtggaat gcggctttgc aacaattaaa gatcttagag accacaaact ggataatcgc   1320

atggagtcat tctttttggc tgagaccgtc aagtatctgt atctgctttt tcatcccaac   1380

aacttcatcc ataataacgg gtccaccttc gattcagtca tgacccctca cggtgaatgc   1440

atactcggag ctggaggcta tatttttaac actgaagctc acccaattga cccagctgcc   1500
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cttcattgtt gtcgacgtct gaaagaagaa caatgggagg ttgaagattt gatcaaagaa   1560
ttttactcac ttaaacaaag tcgacctaaa cgcgcacaga gaaaaactgt aagatctggt   1620
ccttgggaac ctcagtccgg cccagcaact ctttcatccc ccgccaacca accacgagaa   1680
aaacaaccag cccaacagag aaccccccctg ctcagctgcc cctctcagcc cttcacttca   1740
aaactcgccc tgcttggaca ggtgtttctg gactcctctt gatttaaaca cgcggccgct   1800
aatcagccat accacatttg tagaggtttt acttgcttta aaaaacctcc cacacctccc   1860
cctgaacctg aaacataaaa tgaatgcaat tgttgttgtt aacttgttta ttgcagctta   1920
taatggttac aaataaagca atagcatcac aaatttcaca aataaagcat ttttttcact   1980
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gacctgtggt gacatctcct gaacatctgc ctatggattc tgatacagtg gcttcttctg   2460
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gttttacttg ctttaaaaaa cctcccacac ctccccctga acctgaaaca taaaatgaat   3120
gcaattgttg ttgttaactt gtttattgca gcttataatg gttacaaata aagcaatagc   3180
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atcacaaatt tcacaaataa agcatttttt tcactgcatt ctagttgtgg tttgtccaaa   3240

ctcatcaatg tatcttatca tgtc                                          3264


<210> SEQ ID NO 19
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Glu Val Gln Val Leu Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ala Tyr
            20                  25                  30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Ala Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Gly Ala Trp Lys Met Ser Gly Leu Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Thr Val Ile Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
    210                 215                 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
            260                 265                 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350
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Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440                 445


<210> SEQ ID NO 20
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser
1               5                   10                  15

Cys Ala Ala Ser Gly Phe Thr Phe Ser Ala Tyr Ala Met Thr Trp Val
            20                  25                  30

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly
        35                  40                  45

Ser Gly Gly Ser Ala Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr
    50                  55                  60

Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser
65                  70                  75                  80

Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Asp Gly Ala
                85                  90                  95

Trp Lys Met Ser Gly Leu Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110


<210> SEQ ID NO 21
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asp Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ile Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Thr Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Arg Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asp Ser Ala Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125
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Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 22
<211> LENGTH: 100
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
1               5                   10                  15

Thr Cys Arg Ala Ser Gln Asp Ile Ser Asp Tyr Leu Ala Trp Tyr Gln
            20                  25                  30

Gln Lys Pro Gly Lys Ile Pro Arg Leu Leu Ile Tyr Thr Thr Ser Thr
        35                  40                  45

Leu Gln Ser Gly Val Pro Ser Arg Phe Arg Gly Ser Gly Ser Gly Thr
    50                  55                  60

Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr
65                  70                  75                  80

Tyr Tyr Cys Gln Lys Tyr Asp Ser Ala Pro Leu Thr Phe Gly Gly Gly
                85                  90                  95

Thr Lys Val Glu
            100


<210> SEQ ID NO 23
<211> LENGTH: 2971
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

<400> SEQUENCE: 23

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cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc cccgcccatt     120

gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc attgacgtca     180

atgggtggag tatttacggt aaactgccca cttggcagta catcaagtgt atcatatgcc     240

aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt atgcccagta     300

catgacctta tgggactttc ctacttggca gtacatctac gtattagtca tcgctattac     360

catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg actcacgggg     420

atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc aaaatcaacg     480

ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg gtaggcgtgt     540

acggtgggag gtctatataa gcagagctca tgatagaagc actctactat tcgtcgaccg     600

atcctgagaa cttcagggtg agtttgggga cccttgattg ttctttcttt ttcgctattg     660
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taaaattcat gttatatgga gggggcaaag ttttcagggt gttgtttaga atgggaagat    720
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gacaaccatt gtctcctctt attttctttt cattttctgt aactttttcg ttaaacttta    840
gcttgcattt gtaacgaatt tttaaattca cttttgttta tttgtcagat tgtaagtact    900
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cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc   1980
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gttgagtcca aatatggtcc cccatgccca ccctgcccag cacctgagtt cctgggggga   2100
ccatcagtct tcctgttccc cccaaaaccc aaggacactc tcatgatctc ccggacccct   2160
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aatgaatgca attgttgttg ttaacttgtt tattgcagct tataatggtt acaaataaag   2880
caatagcatc acaaatttca caaataaagc atttttttca ctgcattcta gttgtggttt   2940
gtccaaactc atcaatgtat cttatcatgt c                                   2971
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<210> SEQ ID NO 24
<211> LENGTH: 7013
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic plasmid

<400> SEQUENCE: 24

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caacgacccc cgcccattga cgtcaataat gacgtatgtt cccatagtaa cgccaatagg 180

gactttccat tgacgtcaat gggtggagta tttacggtaa actgcccact tggcagtaca 240

tcaagtgtat catatgccaa gtacgccccc tattgacgtc aatgacggta aatggcccgc 300

ctggcattat gcccagtaca tgaccttatg ggactttcct acttggcagt acatctacgt 360

attagtcatc gctattacca tggtgatgcg gttttggcag tacatcaatg ggcgtggata 420

gcggtttgac tcacggggat ttccaagtct ccaccccatt gacgtcaatg ggagtttgtt 480

ttggcaccaa aatcaacggg actttccaaa atgtcgtaac aactccgccc cattgacgca 540

aatgggcggt aggcgtgtac ggtgggaggt ctatataagc agagctcatg atagaagcac 600

tctactattc gtcgaccgat cctgagaact tcagggtgag tttggggacc cttgattgtt 660

ctttcttttt cgctattgta aaattcatgt tatatggagg gggcaaagtt ttcagggtgt 720

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taaaatactc tgagtccaaa ccgggcccct ctgctaacca tgttcatgcc ttcttctctt 1200

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ccctccagca gcttgggcac gaagacctac acctgcaacg tagatcacaa gcccagcaac 2040

accaaggtgg acaagagagt tgagtccaaa tatggtcccc catgcccacc ctgcccagca 2100

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cagggtcgat gcgacgcaat cgtccgatcc ggagccggga ctgtcgggcg tacacaaatc   6120
gcccgcagaa gcgcggccgt ctggaccgat ggctgtgtag aagtactcgc cgatagtgga   6180
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aaattgatga tctattaaac aataaagatg tccactaaaa tggaagtttt tcctgtcata   6300
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atggttcacg tagtgggcca tcgccctgat agacggtttt tcgccctttg acgttggagt   6840
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ccacgttctt taatagtgga ctcttgttcc aaactggaac aacactcaac cctatctcgg 6900

tctattcttt tgatttataa gggattttgc cgatttcggc ctattggtta aaaaatgagc 6960

tgatttaaca aaaatttaac gcgaattaat tctgtggaat gtgtgtcagt tag 7013

<210> SEQ ID NO 25
<211> LENGTH: 2272
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

<400> SEQUENCE: 25

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cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc cccgcccatt 120

gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc attgacgtca 180

atgggtggag tatttacggt aaactgccca cttggcagta catcaagtgt atcatatgcc 240

aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt atgcccagta 300

catgacctta tgggactttc ctacttggca gtacatctac gtattagtca tcgctattac 360

catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg actcacgggg 420

atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc aaaatcaacg 480

ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg gtaggcgtgt 540

acggtgggag gtctatataa gcagagctca tgatagaagc actctactat tcgtcgaccg 600

atcctgagaa cttcagggtg agtttgggga cccttgattg ttctttcttt ttcgctattg 660

taaaattcat gttatatgga gggggcaaag ttttcagggt gttgtttaga atgggaagat 720

gtcccttgta tcaccatgga ccctcatgat aattttgttt ctttcacttt ctactctgtt 780

gacaaccatt gtctcctctt attttctttt cattttctgt aactttttcg ttaaacttta 840

gcttgcattt gtaacgaatt tttaaattca cttttgttta tttgtcagat tgtaagtact 900

ttctctaatc acttttttttt caaggcaatc agggtatatt atattgtact tcagcacagt 960

tttagagaac aattgttata attaaatgat aaggtagaat atttctgcat ataaattctg 1020

gctggcgtgg aaatattctt attggtagaa acaactacac cctggtcatc atcctgcctt 1080

tctctttatg gttacaatga tatacactgt ttgagatgag gataaaatac tctgagtcca 1140

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acgtgctggt tgttgtgctg tctcatcatt ttggcaaaga attaagctta tactcgagct 1260

ctagattggg aacccgggtc tctcgaattc gagatctcca ccatgcacag acctagacgt 1320

cgtggaactc gtccacctcc actggcactg ctcgctgctc tcctcctggc tgcacgtggt 1380

gctgatgcag acatccagat gacccagtct ccagcctccc tgtctgcatc tgttggagac 1440

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cagaaaccag ggaaaattcc taggctcctg atctatacta catccacttt gcaatcaggg 1560

gtcccatctc ggttccgtgg cagtgggtct gggacagatt tcactctcac catcagcagc 1620

ctgcagcctg aagatgttgc aacttattac tgtcagaagt atgacagtgc cccgctcact 1680

ttcggcggag ggaccaaggt ggagatcaaa cgaactgtgg ctgcaccatc tgtcttcatc 1740

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catcagggcc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtg ttaggcggcc 2040

gctaatcagc cataccacat ttgtagaggt tttacttgct ttaaaaaacc tcccacacct 2100

ccccctgaac ctgaaacata aaatgaatgc aattgttgtt gttaacttgt ttattgcagc 2160

ttataatggt tacaaataaa gcaatagcat cacaaatttc acaaataaag cattttttc 2220

actgcattct agttgtggtt tgtccaaact catcaatgta tcttatcatg tc 2272

<210> SEQ ID NO 26
<211> LENGTH: 6335
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic plasmid

<400> SEQUENCE: 26

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acgtggtgct gatgcagaca tccagatgac ccagtctcca gcctccctgt ctgcatctgt 180

tggagacaga gtcaccatca cttgtcgggc gagtcaggac attagcgatt atttagcctg 240

gtatcagcag aaaccaggga aaattcctag gctcctgatc tatactacat ccactttgca 300

atcaggggtc ccatctcggt tccgtggcag tgggtctggg acagatttca ctctcaccat 360

cagcagcctg cagcctgaag atgttgcaac ttattactgt cagaagtatg acagtgcccc 420

gctcactttc ggcggaggga ccaaggtgga gatcaaacga actgtggctg caccatctgt 480

cttcatcttc ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct 540

gctgaataac ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca 600

atcgggtaac tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct 660

cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga 720

agtcacccat cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgtta 780

ggcggccgct aatcagccat accacatttg tagaggtttt acttgcttta aaaaacctcc 840

cacacctccc cctgaacctg aaacataaaa tgaatgcaat tgttgttgtt aacttgttta 900

ttgcagctta taatggttac aaataaagca atagcatcac aaatttcaca aataaagcat 960

ttttttcact gcattctagt tgtggtttgt ccaaactcat caatgtatct tatcatgtct 1020

accggtaggg cccctctctt catgtgagca aaaggccagc aaaaggccag gaaccgtaaa 1080

aaggccgcgt tgctggcgtt tttccatagg ctccgccccc ctgacgagca tcacaaaaat 1140

cgacgctcaa gtcagaggtg gcgaaacccg acaggactat aaagatacca ggcgtttccc 1200

cctggaagct ccctcgtgcg ctctcctgtt ccgaccctgc cgcttaccgg atacctgtcc 1260

gcctttctcc cttcgggaag cgtggcgctt tctcaatgct cacgctgtag gtatctcagt 1320

tcggtgtagg tcgttcgctc caagctgggc tgtgtgcacg aaccccccgt tcagcccgac 1380

cgctgcgcct tatccggtaa ctatcgtctt gagtccaacc cggtaagaca cgacttatcg 1440

ccactggcag cagccactgg taacaggatt agcagagcga ggtatgtagg cggtgctaca 1500

gagttcttga agtggtggcc taactacggc tacactagaa ggacagtatt tggtatctgc 1560

gctctgctga agccagttac cttcggaaaa agagttggta gctcttgatc cggcaaacaa 1620

accaccgctg gtagcggtgg tttttttgtt tgcaagcagc agattacgcg cagaaaaaaa 1680

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<210> SEQ ID NO 27

<211> LENGTH: 452
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Asp Ile His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Gly Pro Ala Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Gly Leu Ile Thr Phe Gly Gly Leu Ile Ala Pro Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
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385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Gly Lys
450

<210> SEQ ID NO 28
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser
1 5 10 15

Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Asp Ile His Trp Val
20 25 30

Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Gly Pro
35 40 45

Ala Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys Gly Arg Phe Thr Ile
50 55 60

Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu
65 70 75 80

Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Leu Ile Thr
85 90 95

Phe Gly Gly Leu Ile Ala Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

<210> SEQ ID NO 29
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asp Asn Ser Gln
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 30
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu
1 5 10 15

Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Thr Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asp Asn Ser Gln Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 31
<211> LENGTH: 2986
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

<400> SEQUENCE: 31

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gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc attgacgtca 180

atgggtggag tatttacggt aaactgccca cttggcagta catcaagtgt atcatatgcc 240

aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt atgcccagta 300

catgacctta tgggactttc ctacttggca gtacatctac gtattagtca tcgctattac 360

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic plasmid

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aaggccgcgt tgctggcgtt tttccatagg ctccgccccc ctgacgagca tcacaaaaat   1140

cgacgctcaa gtcagaggtg gcgaaacccg acaggactat aaagatacca ggcgtttccc   1200

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gcctttctcc cttcgggaag cgtggcgctt tctcaatgct cacgctgtag gtatctcagt   1320

tcggtgtagg tcgttcgctc caagctgggc tgtgtgcacg aaccccccgt tcagcccgac   1380

cgctgcgcct tatccggtaa ctatcgtctt gagtccaacc cggtaagaca cgacttatcg   1440

ccactggcag cagccactgg taacaggatt agcagagcga ggtatgtagg cggtgctaca   1500

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gctctgctga agccagttac cttcggaaaa agagttggta gctcttgatc cggcaaacaa   1620

accaccgctg gtagcggtgg tttttttgtt tgcaagcagc agattacgcg cagaaaaaaa   1680

ggatctcaag aagatccttt gatcttttct acggggtctg acgctcagtg gaacgaaaac   1740
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tggtctgaca gttaccaatg cttaatcagt gaggcaccta tctcagcgat ctgtctattt   1920
cgttcatcca tagttgcctg actccccgtc gtgtagataa ctacgatacg ggagggctta   1980
ccatctggcc ccagtgctgc aatgataccg cgagacccac gctcaccggc tccagattta   2040
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gcctccatcc agtctattaa ttgttgccgg gaagctagag taagtagttc gccagttaat   2160
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cattgacgtc aatgggagtt tgttttggca ccaaaatcaa cgggactttc caaaatgtcg   5580
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gatatacact gtttgagatg aggataaaat actctgagtc caaaccgggc ccctctgcta   6240
accatgttca tgccttcttc tctttcctac agctcctggg caacgtgctg gttgttgtgc   6300
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<210> SEQ ID NO 35
<211> LENGTH: 449
<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

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Gln Val Gln Leu Gln Gln Ser Gly Ala Gly Leu Leu Lys Pro Ser Glu
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Tyr Gly Gly Ser Phe Ser Ile His
            20                  25                  30

His Trp Thr Trp Ile Arg His Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn His Arg Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Ile Ser Ile Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ser Ala Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Gly Leu Arg Phe Leu Asp Trp Leu Ser Ser Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400
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Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440                 445

Lys


<210> SEQ ID NO 36
<211> LENGTH: 103
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Gln Ser Gly Ala Gly Leu Leu Lys Pro Ser Glu Thr Leu Ser Leu Thr
1               5                   10                  15

Cys Thr Val Tyr Gly Gly Ser Phe Ser Ile His His Trp Thr Trp Ile
            20                  25                  30

Arg His Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Glu Ile Asn His
        35                  40                  45

Arg Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile
    50                  55                  60

Ser Ile Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ala Val
65                  70                  75                  80

Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Leu Arg Phe
                85                  90                  95

Leu Asp Trp Leu Ser Ser Tyr
            100


<210> SEQ ID NO 37
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asp Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Asn Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ala Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Asn Tyr Asn Thr Ala Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
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                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 38
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1               5                   10                  15

Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asp Tyr Leu
            20                  25                  30

Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Asn Leu Leu Ile Tyr
        35                  40                  45

Ala Ala Ser Ala Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65                  70                  75                  80

Asp Val Ala Thr Tyr Tyr Cys Gln Asn Tyr Asn Thr Ala Pro Leu Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100                 105


<210> SEQ ID NO 39
<211> LENGTH: 2977
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic construct

<400> SEQUENCE: 39

tagttattaa tagtaatcaa ttacggggtc attagttcat agcccatata tggagttccg     60

cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc cccgcccatt    120

gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc attgacgtca    180

atgggtggag tatttacggt aaactgccca cttggcagta catcaagtgt atcatatgcc    240

aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt atgcccagta    300

catgacctta tgggactttc ctacttggca gtacatctac gtattagtca tcgctattac    360

catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg actcacgggg    420

atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc aaaatcaacg    480

ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg gtaggcgtgt    540

acggtgggag gtctatataa gcagagctca tgatagaagc actctactat tcgtcgaccg    600

atcctgagaa cttcagggtg agtttgggga cccttgattg ttctttcttt ttcgctattg    660

taaaattcat gttatatgga gggggcaaag ttttcagggt gttgtttaga atgggaagat    720

gtcccttgta tcaccatgga ccctcatgat aattttgttt ctttcacttt ctactctgtt    780

gacaaccatt gtctcctctt attttctttt cattttctgt aacttttttcg ttaaacttta    840

gcttgcattt gtaacgaatt tttaaattca cttttgttta tttgtcagat tgtaagtact    900
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ttctctaatc actttttttt caaggcaatc agggtatatt atattgtact tcagcacagt    960
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gctggcgtgg aaatattctt attggtagaa acaactacac cctggtcatc atcctgcctt   1080
tctctttatg gttacaatga tatacactgt ttgagatgag gataaaatac tctgagtcca   1140
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<210> SEQ ID NO 40
<211> LENGTH: 7019
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic plasmid

<400> SEQUENCE: 40

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caacgacccc cgcccattga cgtcaataat gacgtatgtt cccatagtaa cgccaatagg    180
gactttccat tgacgtcaat gggtggagta tttacggtaa actgcccact tggcagtaca    240
tcaagtgtat catatgccaa gtacgccccc tattgacgtc aatgacggta aatggcccgc    300
ctggcattat gcccagtaca tgaccttatg ggactttcct acttggcagt acatctacgt    360
attagtcatc gctattacca tggtgatgcg gttttggcag tacatcaatg ggcgtggata    420
gcggtttgac tcacggggat ttccaagtct ccaccccatt gacgtcaatg ggagtttgtt    480
ttggcaccaa aatcaacggg actttccaaa atgtcgtaac aactccgccc cattgacgca    540
aatgggcggt aggcgtgtac ggtgggaggt ctatataagc agagctcatg atagaagcac    600
tctactattc gtcgaccgat cctgagaact tcagggtgag tttggggacc cttgattgtt    660
ctttcttttt cgctattgta aaattcatgt tatatggagg gggcaaagtt ttcagggtgt    720
tgtttagaat gggaagatgt cccttgtatc accatggacc ctcatgataa ttttgtttct    780
ttcactttct actctgttga caaccattgt ctcctcttat tttcttttca ttttctgtaa    840
ctttttcgtt aaactttagc ttgcatttgt aacgaatttt taaattcact tttgtttatt    900
tgtcagattg taagtacttt ctctaatcac tttttttttca aggcaatcag ggtatattat    960
attgtacttc agcacagttt tagagaacaa ttgttataat taaatgataa ggtagaatat   1020
ttctgcatat aaattctggc tggcgtggaa atattcttat tggtagaaac aactacaccc   1080
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<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic plasmid

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cgtcaatgac ggtaaatggc ccgcctggca ttatgcccag tacatgacct tatgggactt   5400

tcctacttgg cagtacatct acgtattagt catcgctatt accatggtga tgcggttttg   5460

gcagtacatc aatgggcgtg gatagcggtt tgactcacgg ggatttccaa gtctccaccc   5520

cattgacgtc aatgggagtt tgttttggca ccaaaatcaa cgggactttc caaaatgtcg   5580

taacaactcc gccccattga cgcaaatggg cggtaggcgt gtacggtggg aggtctatat   5640

aagcagagct catgatagaa gcactctact attcgtcgac cgatcctgag aacttcaggg   5700

tgagtttggg gacccttgat tgttctttct ttttcgctat tgtaaaattc atgttatatg   5760

gagggggcaa agttttcagg gtgttgttta gaatgggaag atgtcccttg tatcaccatg   5820

gaccctcatg ataattttgt ttctttcact ttctactctg ttgacaacca ttgtctcctc   5880

ttattttctt ttcattttct gtaacttttt cgttaaactt tagcttgcat ttgtaacgaa   5940

tttttaaatt cacttttgtt tatttgtcag attgtaagta ctttctctaa tcactttttt   6000

ttcaaggcaa tcagggtata ttatattgta cttcagcaca gttttagaga acaattgtta   6060

taattaaatg ataaggtaga atatttctgc atataaattc tggctggcgt ggaaatattc   6120

ttattggtag aaacaactac accctggtca tcatcctgcc tttctcttta tggttacaat   6180

gatatacact gtttgagatg aggataaaat actctgagtc caaaccgggc ccctctgcta   6240

accatgttca tgccttcttc tctttcctac agctcctggg caacgtgctg gttgttgtgc   6300

tgtctcatca ttttggcaaa gaattaagct tatac                              6335
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<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence
<220> FEATURE:
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<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 43

Xaa Asp Val Trp Gly Gln Gly Thr Thr Val Xaa Val Ser Ser Ala Ser
1               5                   10                  15

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Xaa Ser Xaa Ser Thr
            20                  25                  30

Ser Xaa Xaa Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
        35                  40                  45

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
    50                  55                  60

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
65                  70                  75                  80

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Xaa Thr Tyr Xaa
                85                  90                  95

Cys Asn Val Xaa His Lys Pro Ser Asn Thr Lys Val Asp Lys Xaa Val
            100                 105                 110

Glu Xaa Lys
        115


<210> SEQ ID NO 44
<211> LENGTH: 225
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<220> FEATURE:
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 44

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Xaa Leu Gly Gly
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Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            20                  25                  30

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Xaa Glu
        35                  40                  45

Asp Pro Glu Val Xaa Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    50                  55                  60

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Xaa Asn Ser Thr Tyr Arg
65                  70                  75                  80

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
                85                  90                  95

Glu Tyr Lys Cys Lys Val Ser Asn Lys Xaa Leu Pro Xaa Xaa Ile Glu
            100                 105                 110

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        115                 120                 125

Thr Leu Pro Pro Ser Xaa Xaa Glu Xaa Thr Lys Asn Gln Val Ser Leu
    130                 135                 140

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
145                 150                 155                 160

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
                165                 170                 175

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Xaa Leu Thr Val Asp
            180                 185                 190

Lys Ser Arg Trp Gln Xaa Gly Asn Val Phe Ser Cys Ser Val Met His
        195                 200                 205

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Xaa
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    210                 215                 220

Gly
225


<210> SEQ ID NO 45
<211> LENGTH: 60
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 45

Ser Asp Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Xaa Xaa Pro Xaa
1               5                   10                  15

Leu Leu Ile Tyr Xaa Xaa Ser Xaa Xaa Xaa Xaa Gly Val Pro Xaa Arg
            20                  25                  30

Phe Xaa Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Xaa
        35                  40                  45

Leu Xaa Pro Glu Asp Xaa Ala Xaa Tyr Tyr Cys Gln
    50                  55                  60


<210> SEQ ID NO 46
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: consensus sequence
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<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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-continued

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<400> SEQUENCE: 46

Thr Phe Gly Xaa Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
1               5                   10                  15

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
            20                  25                  30

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
        35                  40                  45

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
    50                  55                  60

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
65                  70                  75                  80

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
                85                  90                  95

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
            100                 105                 110

Phe Asn Arg Gly Glu Cys
        115
```

What is claimed:

1. An isolated polynucleotide comprising a nucleotide sequence, which encodes an endoplasmic reticulum degradation-enhancing alpha-mannosidase-like protein 2 (EDEM2), a promoter, and a multi-subunit protein, wherein the EDEM2 comprises an amino acid sequence that is at least 92% identical to SEQ ID NO: 1, and wherein the multi-subunit protein comprises at least one *antibody* heavy chain **[**antibody and**]** *or* at least one *antibody* light chain **[**antibody**]**.

2. The isolated polynucleotide of claim **1**, wherein the promoter is selected from the group consisting of ubiquitin C, CMV-IE and SV40.

3. The isolated polynucleotide of claim **2**, wherein the EDEM2 comprises the amino acid sequence of SEQ ID NO: 8.

4. The isolated polynucleotide of claim **2**, wherein the EDEM2 consists essentially of the amino acid sequence of SEQ ID NO: 8.

5. The isolated polynucleotide of claim **2**, wherein the EDEM2 comprises the amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, *and* SEQ ID NO: 6 **[**and SEQ ID NO: 7**]**.

6. The isolated polynucleotide of claim **2**, wherein the EDEM2 consists essentially of the amino acid sequence of SEQ ID NO: 1.

7. The isolated polynucleotide of claim **1**, wherein the **[**nucleotide sequence further**]** *multi-subunit protein* comprises at least one antibody heavy chain **[**or**]** *and* at least one antibody light chain.

8. The isolated polynucleotide of claim **7**, wherein the nucleotide sequence encodes the heavy chain comprising amino acid sequences SEQ ID NO: 43 and SEQ ID NO: 44 and the light chain comprising amino acid sequences SEQ ID NO: 45 and SEQ ID NO: 46.

9. The isolated polynucleotide of claim **7**, where the nucleotide sequence encodes an anti-GDF8 antibody heavy chain, operably linked to a mammalian ubiquitin C promoter or a human CMV-IE promoter.

10. The isolated polynucleotide of claim **9**, wherein the anti-GDF8 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 20.

11. The isolated polynucleotide of claim **9**, wherein the anti-GDF8 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 19.

12. The isolated polynucleotide of claim **9** comprising the nucleotide sequence of SEQ ID NO: 23.

13. The isolated polynucleotide of claim **9** comprising the nucleotide sequence of SEQ ID NO: 24.

14. The isolated polynucleotide of claim **7**, wherein the nucleotide sequence encodes an anti-GDF8 antibody light chain, operably linked to a mammalian ubiquitin C promoter or a human CMV-IE promoter.

15. The isolated polynucleotide of claim **14**, wherein the anti-GDF8 antibody light chain comprises the amino acid sequence of SEQ ID NO: 22.

16. The isolated polynucleotide of claim **14**, wherein the anti-GDF8 antibody light chain comprises the amino acid sequence of SEQ ID NO: 21.

17. The isolated polynucleotide of claim **14** comprising the nucleotide sequence of SEQ ID NO: 25.

18. The isolated polynucleotide claim **14** comprising the nucleotide sequence of SEQ ID NO: 26.

19. The isolated polynucleotide of claim **7**, wherein the nucleotide sequence encodes an anti-ANG2 antibody heavy chain, operably linked to a mammalian ubiquitin C promoter or a human CMV-IE promoter.

20. The isolated polynucleotide of claim **19**, wherein the anti-ANG2 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 28.

21. The isolated polynucleotide of claim **19**, wherein the anti-ANG2 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 27.

22. The isolated polynucleotide of claim **19** comprising the nucleotide sequence of SEQ ID NO: 31.

23. The isolated polynucleotide of claim **19** comprising the nucleotide sequence of SEQ ID NO: 32.

24. The isolated polynucleotide of claim **7**, wherein the nucleotide sequence encodes an anti-ANG2 antibody light chain, operably linked to a promoter.

25. The isolated polynucleotide of claim **24**, wherein the anti-ANG2 antibody light chain comprises the amino acid sequence of SEQ ID NO: 30.

26. The isolated polynucleotide of claim **24**, wherein the anti-ANG2 antibody light chain comprises the amino acid sequence of SEQ ID NO: 29.

27. The isolated polynucleotide of claim **24** comprising the nucleotide sequence of SEQ ID NO: 33.

28. The isolated polynucleotide of claim **24** comprising the nucleotide sequence of SEQ ID NO: 34.

29. The isolated polynucleotide of claim **7**, wherein the nucleotide sequence encodes an anti-AngPtl4 antibody heavy chain, operably linked to a mammalian ubiquitin C promoter or a human CMV-IE promoter.

30. The isolated polynucleotide of claim **29**, wherein the anti-AngPtl4 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 36.

31. The isolated polynucleotide of claim **29**, wherein the anti-AngPtl4 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 35.

32. The isolated polynucleotide of claim **29** comprising the nucleotide sequence of SEQ ID NO: 39.

33. The isolated polynucleotide of claim **29** comprising the nucleotide sequence of SEQ ID NO: 40.

34. The isolated polynucleotide of claim **7**, wherein the nucleotide sequence encodes an anti-AngPtl4 antibody light chain, operably linked to a mammalian ubiquitin C promoter or a human CMV-IE promoter.

35. The isolated polynucleotide of claim **34**, wherein the anti-AngPtl4 antibody light chain comprises the amino acid sequence of SEQ ID NO: 38.

36. The isolated polynucleotide of claim **34**, wherein the anti-AngPtl4 antibody light chain comprises the amino acid sequence of SEQ ID NO: 37.

37. The isolated polynucleotide of claim **34** comprising the nucleotide sequence of SEQ ID NO: 41.

38. The isolated polynucleotide of claim **34** comprising the nucleotide sequence of SEQ ID NO: 42.

* * * * *