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(54) Title: LAMININ 8 AND METHODS FOR ITS USE (57) Abstract The present invention provides substantially purified laminin 8, methods for making recombinant laminin 8, cells that express recombinant laminin 8, and methods for using the recombinant laminin 8 to accelerate the healing of injuries to vascular tissue and tissue of mesenchymal origin, and to promote cell attachment and migration.		

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LAMININ 8 AND METHODS FOR ITS USE

Cross Reference

This application claims priority to U.S. Provisional Patent Application Serial
5 Nos. 60/131,720 filed April 30, 1999; 60/149,738 filed August 19, 1999; 60/155,945
filed September 24, 1999; and 60/182,012 filed February 11, 2000; all of which are
incorporated herein by reference in their entirety.

Field of the Invention

10 This application relates to purified laminin 8 and methods for its use.

Background of the Invention

Basal laminae (basement membranes) are sheet-like, cell-associated
extracellular matrices that play a central role in cell growth, tissue development, and
15 tissue maintenance. They are present in virtually all tissues, and appear in the earliest
stages of embryonic development.

Basal laminae are central to a variety of architectural and cell-interactive
functions: (See for example, Malinda and Kleinman, *Int. J. Biochem. Cell Biol.* 28:957-
959 (1996); Aumailley and Krieg, *J. Invest. Dermatology* 106:209-214 (1996))

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1. They serve as architectural supports for tissues, providing adhesive substrata for cells.
2. They create perm-selective barriers between tissue compartments that impede the migration of cells and passively regulate the exchange of macromolecules.
- 25 These properties are illustrated by the kidney glomerular basement membrane, which functions as an important filtration structure, creating an effective blood-tissue barrier that is not permeable to most proteins and cells.
3. Basal laminae create highly interactive surfaces that can promote cell migration and cell elongation during embryogenesis and wound repair. Following an
30 injury, they provide a surface upon which cells regenerate to restore normal tissue function.
4. Basal laminae present information encoded in their structure to contacting cells that is important for differentiation and tissue maintenance. This information is

communicated to the cells through various receptors that include the integrins, dystroglycan, and cell surface proteoglycans. Signaling is dependent not only on the presence of matrix ligands and corresponding receptors that interact with sufficient affinities, but also on such topographical factors as ligand density in a three-dimensional matrix "landscape", and on the ability of basal lamina components to cluster receptors. Because these matrix proteins can be long-lived, basal laminae create a "surface memory" in the basal lamina for resident and transient cells.

The basal lamina is largely composed of laminin and type IV collagen heterotrimers that in turn become organized into complex polymeric structures. To date, six type IV collagen chains and at least twelve laminin subunits have been identified. These chains possess shared and unique functions and are expressed with specific temporal (developmental) and spatial (tissue-site specific) patterns.

Laminins are a family of heterotrimeric glycoproteins that reside primarily in the basal lamina. They function via binding interactions with neighboring cell receptors, and by forming laminin networks, and they are important signaling molecules that can strongly influence cellular function. Laminins are important in both maintaining cell/tissue phenotype as well as promoting cell growth and differentiation in tissue repair and development.

Laminins are large, multi-domain proteins, with a common structural organization. The laminin molecule integrates various matrix and cell interactive functions into one molecule.

The laminin molecule is comprised of an α -, β -, and γ -chain subunit joined together through a coiled-coil domain. Within this structure are identifiable domains that possess binding activity towards other laminin and basal lamina molecules, and membrane-bound receptors. Domains VI, IVb, and IVa form globular structures, and domains V, IIIb, and IIIa (which contain cysteine-rich EGF-like elements) form rod-like structures. (Kamiguchi et al., Ann. Rev. Neurosci. 21:97-125 (1998)) Domains I and II of the three chains participate in the formation of a triple-stranded coiled-coil structure (the long arm).

Table 1 shows the individual chains that each laminin type is composed of:

TABLE 1. Known laminin family members

<i>Protein</i>	<i>Chains</i>
Laminin-1	$\alpha 1\beta 1\gamma 1$
Laminin-2	$\alpha 2\beta 1\gamma 1$
Laminin-3	$\alpha 1\beta 2\gamma 1$
Laminin-4	$\alpha 2\beta 2\gamma 1$
Laminin-5	$\alpha 3\beta 3\gamma 2$
Laminin-6	$\alpha 3\beta 1\gamma 1$
Laminin-7	$\alpha 3\beta 2\gamma 1$
Laminin-8	$\alpha 4\beta 1\gamma 1$
Laminin-9	$\alpha 4\beta 2\gamma 1$
Laminin-10	$\alpha 5\beta 1\gamma 1$
Laminin-11	$\alpha 5\beta 2\gamma 1$
Laminin-12	$\alpha 2\beta 1\gamma 3$

Four structurally-defined family groups of laminins have been identified. The first group of five identified laminin molecules all share the $\beta 1$ and $\gamma 1$ chains, and vary by their α -chain composition ($\alpha 1$ to $\alpha 5$ chain). The second group of five identified laminin molecules all share the $\beta 2$ and $\gamma 1$ chain, and again vary by their α -chain composition. The third group of identified laminin molecules has one identified member, laminin 5, with a chain composition of $\alpha 3\beta 3\gamma 2$. The fourth group of identified laminin molecules has one identified member, laminin 12, with the newly identified $\gamma 3$ chain ($\alpha 2\beta 1\gamma 3$)

Some progress has been made in elucidating the relationship between domain structure and function. (See, for example, Wewer and Engvall, Neuromusc. Disord. 6:409-418 (1996).) The overall sequence similarity among the homologous domains in different chains varies, but it is highest in domain VI (thought to play a key role in laminin polymerization), followed by domains V (possibly involved in protein-protein interactions) and III (entactin/nidogen binding; possible cell adhesion sites), and is lowest in domains I, II (both thought to be involved in intermolecular assembly, and containing possible cell adhesion sites), and G. Not all domains are present in all 3 types of chains. The globular G domain (thought to be involved in cell receptor binding) is present only in the α chains. Other domains may not be present in all chains within a certain chain type. For example, domain VI is absent from $\alpha 3$, $\alpha 4$, and $\gamma 2$ chains. (Wewer and Engvall, 1996)

As a result of their large size (>600 kD) and unique structure, the laminin molecules can be resolved in the electron microscope. (Wewer and Engvall, 1996) Typically, laminins appear as cross-shaped molecules in an EM. The three short arms of the cross represent the amino terminal portions of each of the three separate laminin chains (one short arm per chain). The long arm of the cross is composed of the C-terminal parts of the three chains, which together form a coiled coil structure. (Wewer and Engvall, 1996) The long arm ends with the globular G domain.

The coiled-coil domain of the long arm is crucial for assembly of the three chains of laminin. (Yurchenco et al., Proc. Natl. Acad. Sci. 94:10189-10194 (1997)). Disulfide bonds bridge and stabilize all three chains in the most proximal region of the long arm and join the β and γ chains in the most distal region of the long arm.

A model of laminin receptor-facilitated self-assembly, based on studies conducted with cultured skeletal myotubes and Schwann cells, predicts that laminins bind to their receptors, which freely diffuse in a fluidic membrane, when ligand-free. Receptor engagement forces the laminins into a high local two-dimensional concentration, facilitating their mass-action driven assembly into ordered surface polymers. In this process, the engaged receptors are also reorganized, accompanied by cytoskeletal rearrangements. (Colognato, J. Cell Biol. 145:619-631 (1999)) This reorganization activates the receptors, causing signal transduction with the alteration of cell expression, shape and/or behavior. The evidence is that laminins must possess both cell-interacting and architecture-forming sites, which are located in different protein domains and on different subunits.

One class of laminin receptors are the integrins, which are cell surface receptors that mediate many cell-matrix and cell-cell interactions. Integrins are heterodimers, consisting of an α and a β subunit. 16 α - and 8 β -subunits are known, and at least 22 combinations of α and β subunits have been identified to date. Some integrins have only one or a few known ligands, whereas others appear to be very promiscuous. Binding to integrins is generally of low affinity, and is dependent on divalent cations. Integrins, activated through binding to their ligands, transduce signals via kinase activation cascades, such as focal adhesion and mitogen-activated kinases. Several different integrins bind different laminin isoforms more or less

specifically. (Aumailley et al., In The Laminins, Timpl and Ekblom, eds., Harwood Academic Publishers, Amsterdam. pp. 127-158 (1996))

Laminin 8, a recently identified laminin, is composed of $\alpha 4$, $\beta 1$, and $\gamma 1$ laminin chains. The laminin $\alpha 4$ chain is widely distributed both in adults and during
5 development. (Iivanainen et al., J. Biol. Chem. 272:27862-27868 (1997)) In adults it is found in the basement membrane surrounding cardiac, skeletal, and smooth muscle fibers, and in lung alveolar septa. Furthermore, it is found in the endothelial basement membrane both in capillaries and larger vessels, and in the perineurial basement membrane of peripheral nerves, as well as in intersinusoidal spaces, large
10 arteries, and smaller arterioles of bone marrow. (Frieser et al., Eur. J. Biochemistry 246:727-735 (1997); Miner et al., J. Cell Biol. 137:685-701 (1997); Geberhiwot et al., Exptl. Cell Res. 253:723-732 (1999); Gu et al., Blood 93:2533-2542 (1999); Iivanainen et al., J. Biol. Chem. 272:27862-27868 (1997))

Laminin 8 is a major laminin isoform in the vascular endothelium (Iivanainen
15 et al., J. Biol. Chem. 272:27862-27868 (1997); Frieser et al., 1997), is expressed and adhered to by platelets (Geberhiwot et al., Exptl. Cell Res. 253:723-732 (1999)), and is the only laminin isoform synthesized in 3T3-L1 adipocytes, with its level of synthesis shown to increase upon adipose conversion of the cells. (Niimi et al., Matrix Biology 16:223-230 (1997)) Laminin 8 was further speculated to be the
20 laminin isoform generally expressed in mesenchymal cell lineages to induce microvessels in connective tissues. (Niimi et al., 1997).

Laminin 8 has also been identified in mouse bone marrow primary cell cultures, arteriolar walls, and intersinusoidal spaces where data indicated that it is the major laminin isoform in the developing bone marrow. (Gu et al., Blood 93:2533-
25 2542 (1999)). The investigators concluded that, due to its localization in adult bone marrow adjacent to hematopoietic cells, laminin isoforms containing the $\alpha 4$ chain are the most likely to have biologically relevant interactions with developing hematopoietic cells. (Gu et al., 1999)

Despite the broad tissue distribution of the laminin $\alpha 4$ chain and laminin 8,
30 there is not a means to prepare substantially purified laminin 8 from cell or tissue sources for research and therapeutic purposes, nor has a means for recombinant expression of laminin 8 been developed. Such research and therapeutic purposes

include, but are not limited to, methods for treating injuries to tissue of mesenchymal origin, such as bone, cartilage, tendon, and ligament, treating injuries to vascular tissue, promoting cell attachment and migration, promoting therapeutic angiogenesis and neural regeneration, ex vivo cell therapy, improving the biocompatibility of medical devices, and preparing improved cell culture devices and media.

Thus, there is a need in the art for adequate amounts of substantially purified laminin-8 for research and therapeutic purposes, and methods for making laminin 8. Such laminin 8 could be prepared either from cell lines in culture, or via recombinant DNA technology.

A preferred method of production is the use of recombinant DNA technology to engineer a human cell line of choice to produce recombinant laminin-8 ("r-laminin 8"). A recombinant-based method of laminin-8 production has several advantages over purification from human tissue or isolation from human cell lines in culture:

1. The recombinant produced protein is free of human pathogens. While this is also true for endogenous cell culture produced protein, protein derived from human tissue carries a risk for contamination by HIV, hepatitis, and other infectious agents.

2. Expression levels of the protein, and hence yields, can be improved through the use of genetically engineered genes/vectors that enhance the production of the encoded protein.

3. It is possible to engineer additional peptide sequences to the protein chain that provides a binding site for a commercially viable affinity purification procedure.

4. The method can provide for the modification of protein structure/function through the addition, substitution, elimination, and/or other modifications of protein domain structures. For example, it may be desirable to introduce an integrin binding site (e.g. RGD), switch integrin recognition sites, or engineer in a stable binding site to a synthetic substrate. Thus, the creation of expression vectors that express laminin chains generates enormous flexibility for future uses and creates a basis for creating second generation "designer" laminins.

Summary of the Invention

The present invention fulfills the need in the art for a source of substantially purified laminin 8 protein, methods for making substantially purified recombinant laminin 8 (hereinafter referred to as r-laminin 8), pharmaceutical compositions comprising laminin 8, and methods of using laminin 8 for treating injuries to tissue of mesenchymal origin, such as bone, cartilage, tendon, and ligament, treating injuries to vascular tissue, promoting cell attachment and migration, ex vivo cell therapy, improving the biocompatibility of medical devices, and preparing improved cell culture devices and media.

In one aspect, the present invention provides recombinant host cells that express laminin 8 chains and secrete r-laminin 8. In another aspect, the present invention provides substantially purified laminin 8, and methods for producing substantially purified r-laminin 8.

In a further aspect, the present invention provides pharmaceutical compositions, comprising laminin 8 together with a pharmaceutically acceptable carrier. Such pharmaceutical compositions can optionally be provided with other extracellular matrix components.

In further aspect, the present invention provides methods and kits for accelerating the healing of injuries to tissue of mesenchymal origin, such as bone, cartilage, tendon, and ligament, treating injuries to vascular tissue, and for improving the biocompatibility of grafts used for treating such injuries. In specific examples, laminin 8 or pharmaceutical compositions thereof are used to:

- a. promote re-endothelialization at the site of vascular injuries;
- b. improve the "take" of grafts;
- c. improve the biocompatibility of medical devices;
- d. treat neural injuries (neural regeneration);
- e. regulate angiogenesis; and
- d. promote cell attachment and migration

by providing an amount effective of r-laminin 8 for the various methods. In preferred embodiments of all of these methods, recombinant laminin 8 is used. The kits comprise an amount of laminin 8 effective for the desired effect, and instructions for the use thereof.

In a further aspect, the present invention provides improved medical devices and grafts, and methods for preparing improved medical devices and grafts, wherein the improvement comprises applying an amount effective of laminin 8 or the pharmaceutical compositions of the invention to the device or graft for the desired application.

In a further aspect, the invention provides improved cell culture devices, and methods for preparing improved cell culture devices, for the growth and maintenance of cells in culture, by providing an amount effective of laminin 8 for the attachment of cells to a cell culture device for the subsequent proliferation/differentiation/stasis of the cells.

In another aspect, the invention provides a cell culture growth supplement, comprising laminin 8. In another aspect, the invention provides an improved cell culture growth media, wherein the improvement comprises the addition of r-laminin 8.

Brief Description of the Figures

Figure 1 is a photograph of a 3-12% gradient SDS-PAGE gel. LN-1 is laminin 1/nidogen (ndg) complex with component chain identities indicated on the left; LN-8 is recombinant laminin 8. Interpretation of r-laminin 8 protein band identities are indicated based on western blotting data: $\alpha 4$ = reactivity with anti-human laminin $\alpha 4$ and also anti-FLAG monoclonal antibody (mAb); $\beta 1$ = reactivity with polyclonal anti-murine laminin $\alpha 1/\beta 1/\gamma 1$; $\gamma 1$ = reactivity with anti-human laminin $\gamma 1$ mAb; * = reactivity with both anti-laminin $\gamma 1$ mAb and anti-murine $\alpha 1/\beta 1/\gamma 1$. Both samples were run on the same gel which was subsequently silver stained.

Figure 2 is a rotary shadowed electron micrograph of r-laminin 8. Top: low magnification field showing several r-laminin 8 molecules. Bottom: Individual molecules. Each molecule has two short arms and one long arm. In some molecules, a very short (5-10 nm) rod-like stub can be seen at the junction of the arms. Arrow: G-domain can be seen as consisting of two moieties in some molecules. (Bar = 50 nm)

Figure 3 is a graph depicting a titration of cell adhesion to r-laminin 8 or laminin 1.

Figure 4 is a graph depicting HT-1080 cell adhesion to r-laminin 8 or laminin 1 coated at 10 µg/ml on 96 well plates in the presence and absence of various function-blocking integrin antibodies and other compounds.

Figure 5 is a graph depicting bovine capillary endothelial (BCE) cell adhesion to laminin 8 or laminin 1 coated at 10 µg/ml on 96 well plates in the presence and absence of various function-blocking integrin antibodies and other compounds.

Figure 6 is a graph depicting immortal mouse brain endothelial (IBE) cell adhesion to laminin 8 or laminin 1 coated at 10 µg/ml on 96 well plates in the presence and absence of various function-blocking integrin antibodies and other compounds.

Figure 7 is a graph depicting integrin α6β4-transfected K562 cell adhesion to r-laminin 8 or laminin 1 coated at 10 µg/ml on 96 well plates in the presence and absence of various function-blocking integrin antibodies and other compounds.

Figure 8 is a graph depicting integrin α6-transfected K562 cell adhesion to r-laminin 8 or laminin 1 coated at 10 µg/ml on 96 well plates in the presence and absence of various function-blocking integrin antibodies and other compounds.

Detailed Description of the Preferred Embodiments

All references, patents and patent applications are hereby incorporated by reference in their entirety.

Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in *Methods in Enzymology* (M.P. Deutscher, ed., (1990) Academic Press, Inc.); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA), *Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed.* (R.I. Freshney. 1987. Liss, Inc. New York, NY), *Gene Transfer and Expression Protocols*, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.), and the Ambion 1998 Catalog (Ambion, Austin, TX).

As used herein "laminin 8" encompasses both r-laminin 8 and heterotrimeric laminin 8 from naturally occurring sources.

As used herein, the term "r-laminin 8" refers to recombinant heterotrimeric laminin 8, expressed by a cell that has been transfected with one or more expression vectors comprising at least one nucleic acid sequence encoding a laminin 8 chain selected from the $\alpha 4$, $\beta 1$ and $\gamma 1$ chains, or a portion of the chains that are capable of forming a heterotrimeric laminin 8 and maintaining laminin 8 activity, or processed forms thereof. Such r-laminin 8 can thus comprise $\alpha 4$, $\beta 1$, and $\gamma 1$ sequences from a single organism, or from different organisms. Various laminin 8 chain DNA sequences are known in the art, and the use of each to prepare the r-laminin 8 of the invention is contemplated. (See, for example, Iivanainen et al., FEBS Letters 365:183-188 (1995); Frieser et al., Eur. J. Biochem. 246:727-735 (1997); Richards et al., Eur. J. Biochem. 238:813-821 (1996); Liu and Mayne, 15:433-437 (1996); Vuolteenaho et al., J. Biol. Chem. 265:15611-15616 (1990); Kallunki et al., J. Biol. Chem. 266:221-228 (1991); Sasaki et al., J. Biol. Chem. 263:16536-16544 (1988); Sasaki and Yamada, J. Biol. Chem. 262:17111-17117 (1987); Sasaki et al., Proc. Natl. Acad. Sci. 84:935-939 (1987); Pikkarainen et al., J. Biol. Chem. 262:10454-10462 (1987); all references incorporated by reference herein in their entirety).

The invention encompasses those laminin molecules wherein one or two of the chains that make up the recombinant heterotrimeric laminin 8 are encoded by endogenous laminin 8 chains. In a preferred embodiment, cells are transfected with one or more expression vectors comprising nucleic acid sequences encoding each of the $\alpha 4$, $\beta 1$ and $\gamma 1$ chains, or a portion of each of the chains that are capable of forming a heterotrimeric laminin 8 and maintaining laminin 8 activity.

In the present invention, laminin 8 is a secreted protein, which is capable of being directed to the ER, secretory vesicles, and the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Such processing event can be variable, and thus may yield different versions of the final "mature protein". The substantially purified laminin 8 of the present invention includes heterotrimers comprising both the full length and any such processed laminin 8 chains.

As used herein, the term “substantially purified” means that the laminin 8 so designated has been separated from its in vivo cellular environment.

As used herein, a laminin 8 polypeptide chain refers to a polypeptide chain according to one or more of the following:

5 (a) comprises a polypeptide structure selected from the group consisting of:

1. R1-R2-R3
2. R1-R2-R3(e)
3. R3
4. R3(e)
- 10 5. R1-R3
6. R1-R3(e)
7. R2-R3
8. R2-R3(e)

wherein R1 is an amino terminal methionine; R2 is a signal sequence
15 that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or an artificial sequence; R3 is a secreted laminin chain selected from the $\alpha 4$, $\beta 1$, and $\gamma 1$ chains; and R3(e) is a secreted laminin chain selected from the $\alpha 4$, $\beta 1$, and $\gamma 1$ chains that further comprises an epitope tag (such as those described below),
20 which can be placed at any position within the laminin chain amino acid sequence; and/or

(b) is encoded by a polynucleotide that is substantially similar to one or more of the disclosed laminin chain polynucleotide sequences or portions thereof (SEQ ID NOS.: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, or 27); and/or

25 (c) is encoded by a polynucleotide that hybridizes under high or low stringency conditions to the coding regions, or portions thereof, of one or more of the recombinant laminin 8 chain DNA sequences disclosed herein (SEQ ID NOS.: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27), or complementary sequences thereof; and/or

(d) has at least 70% identity to one or more of the disclosed laminin 8
30 polypeptide chain amino acid sequences (SEQ ID NOS.: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, or 28), preferably at least 80% identity, and most preferably at least about 90% identity.

The phrase "substantially similar" is used herein in reference to polynucleotide or polypeptide sequences having one or more conservative variations from the laminin 8 sequences disclosed herein, including but not limited to deletions, insertions, inversions, repeats, and substitutions, wherein the resulting laminin chain is functionally equivalent to those disclosed herein.

For example, conservative polynucleotide variants may contain alterations in coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, including but not limited to optimizing codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring conservative variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring conservative variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, conservative polynucleotide variants may be generated to improve or alter the characteristics of the expressed laminin chain polypeptides. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein. (See, for example, Ron et al., J. Biol. Chem. 268: 2984-2988 (1993); Dobeli et al., J. Biotechnology 7:199-216 (1988)) Ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. (See, for example, Gayle et al., J. Biol. Chem 268:22105-22111 (1993)) Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained.

Guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein

the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

The “substantially similar” polypeptides of the present invention also include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more amino acid residues having substituents groups, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating

purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

"Stringency of hybridization" is used herein to refer to conditions under which nucleic acid hybrids are stable. The invention also includes nucleic acids that hybridize under high stringency conditions (as defined herein) to all or a portion of the coding sequences of the laminin chain polynucleotides disclosed herein, or their complements. The hybridizing portion of the hybridizing nucleic acids is typically at least 50 nucleotides in length. As known to those of skill in the art, the stability of hybrids is reflected in the melting temperature (T_M) of the hybrids. T_M decreases approximately 1-1.5°C with every 1% decrease in sequence homology. In general, the stability of a hybrid is a function of sodium ion concentration and temperature. Typically, the hybridization reaction is performed under conditions of lower stringency, followed by washes of varying, but higher, stringency. Reference to hybridization stringency relates to such washing conditions. Thus, as used herein, high stringency refers to an overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

Also contemplated are laminin 8-encoding nucleic acid sequences that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4 ; 0.02M EDTA,

pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

5 Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking
10 reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

As used herein, "percent identity" of two amino acids or of two nucleic acids is determined using the algorithm of Karlin and Altschul (Proc. Natl. Acad. Sci. USA 87:2264-2268, 1990), modified as in Karlin and Altschul (Proc. Natl. Acad. Sci. USA
15 90:5873-5877, 1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al. (J. Mol. Biol. 215:403-410, 1990). BLAST nucleotide searches are performed with the NBLAST program, score = 100, wordlength = 12, to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches are performed with the XBLAST program, score =
20 50, wordlength = 3, to obtain an amino acid sequence homologous to a polypeptide of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST is utilized as described in Altschul et al. (Nucleic Acids. Res. 25:3389-3402, 1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) are used. See
25 <http://www.ncbi.nlm.nih.gov>.

Further embodiments of the present invention include polynucleotides encoding laminin 8 chain polypeptides having at least 70% identity, preferably at least 80% identity, and most preferably at least 90% identity to one or more of the polypeptide sequences contained in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, or
30 fragments thereof.

As used herein, " α 4 polynucleotide" refers to polynucleotides encoding an α 4 laminin chain of the same name. Such polynucleotides can be characterized by one or

more of the following: (a) the nucleotides of said polynucleotide may encode an amino acid sequence substantially similar to the sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12 or fragments thereof; (b) polynucleotides that encode polypeptides which share at least 70% identity, preferably 80% identity, and most preferably at least 90% identity with the sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12, or fragments thereof; (c) the $\alpha 4$ polynucleotides hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 1, 3, 5, 7, 9, 11, or fragments thereof, or complementary sequences thereof; or (d) the $\alpha 4$ polynucleotides encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted $\alpha 4$ chain polypeptides.

As used herein, " $\beta 1$ polynucleotides" refers to polynucleotides encoding a $\beta 1$ laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) the nucleotides of said polynucleotides may encode an amino acid sequence substantially similar to the sequence set forth in SEQ ID NO: 14, 16, 18, 20 or fragments thereof; (b) polynucleotides that encode polypeptides which share at least 70% identity, preferably at least 80%, and most preferably at least 90% identity with one or more of the sequences set forth in SEQ ID NO: 14, 16, 18, 20 or fragments thereof; (c) the $\beta 1$ polynucleotides hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 13, 15, 17, 19, fragments thereof, or complementary sequences thereof; or (d) the $\beta 1$ polynucleotides encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted $\beta 1$ chain polypeptides.

As used herein, " $\gamma 1$ polynucleotides" refers to polynucleotides encoding a $\gamma 1$ laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) the nucleotides of said polynucleotides may encode an amino acid that is substantially similar to one or more of the sequences set forth in SEQ ID NO: 22, 24, 26, 28 or fragments thereof; (b) polynucleotides that encode polypeptides which share at least 70% identity, preferably at least 80%, and most preferably at least

90% identity with at one or more of the sequences set forth in SEQ ID NO: 22, 24, 26, 28 or fragments thereof; (c) the $\gamma 1$ polynucleotides hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 21, 23, 25, 27 or complementary sequences thereof; or (d) the $\gamma 1$ polynucleotides
5 encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted $\gamma 1$ chain polypeptides.

As used herein, the term "epitope tag" refers to a polypeptide sequence that is
10 expressed as part of a chimeric protein, where the epitope tag serves as a recognition site for binding of antibodies generated against the epitope tag, or for binding of other molecules that can be used for affinity purification of sequences containing the tag.

As used herein, the term "increased biocompatibility" refers to reduced induction of acute or chronic inflammatory response, and reduced disruption of the
15 proper differentiation of implant-surrounding tissues for laminin 8-coated biomaterials relative to an analogous, non-coated biomaterial.

As used herein the term "graft" refers to both natural and prosthetic grafts and implants.

In one aspect, the present invention provides r-laminin 8 expressing-cells that
20 have been transfected with an expression vector containing promoter sequences that are operatively linked to nucleic acid sequences encoding at least one polypeptide sequence comprising the $\alpha 4$, $\beta 1$ and $\gamma 1$ chains of laminin 8, or fragments thereof, wherein the transfected cells secrete heterotrimeric laminin 8 containing the recombinant laminin chain. In a preferred embodiment, the cells are systematically transfected with
25 recombinant expression vectors containing promoter sequences that are operatively linked to nucleic acid sequences encoding polypeptide sequences comprising the $\alpha 4$, $\beta 1$ and $\gamma 1$ chains of laminin 8. After the multiple transfections, the cells express each of the recombinant laminin 8 chains, which form the heterotrimer, before r-laminin 8 secretion into the media.

30 In a preferred embodiment, cDNAs encoding the $\alpha 4$, $\beta 1$ and $\gamma 1$ chains, or fragments thereof, are subcloned into an expression vector. Alternatively, laminin 8 $\alpha 4$, $\beta 1$ and/or $\gamma 1$ gene sequences, including one or more introns, can be used.

Any cell capable of expressing and secreting the r-laminin 8 can be used. Preferably, eukaryotic cells are used, and most preferably mammalian cells are used, including but not limited to kidney and epithelial cell lines. In a most preferred embodiment, the mammalian cells do not express all of the laminin 8 chains endogenously. Carbohydrate and disulfide post-translational modifications are believed to be required for laminin 8 protein folding and function. This makes the use of eukaryotic cells preferable for producing functional r-laminin 8, although other systems are useful for obtaining, for example, antigens for antibody production.

"Recombinant expression vector" includes vectors that operatively link a nucleic acid coding region or gene to any promoter capable of effecting expression of the gene product. The promoter sequence used to drive expression of the individual chains or r-laminin 8 may be constitutive (driven by any of a variety of promoters, including but not limited to, CMV, SV40, RSV, actin, EF) or inducible (driven by any of a number of inducible promoters including, but not limited to, tetracycline, ecdysone, steroid-responsive). The expression vector must be replicable in the host organisms either as an episome or by integration into host chromosomal DNA. In a preferred embodiment, the expression vector comprises a plasmid. However, the invention is intended to include other expression vectors that serve equivalent functions, such as viruses.

In one embodiment, at least one of the laminin chain polypeptide sequences, or fragments thereof, is operatively linked to a nucleic acid sequence encoding an "epitope tag", so that at least one of the chains is expressed as a fusion protein with an expressed epitope tag. The epitope tag may be expressed as the amino terminus, the carboxy terminus, or internal to any of the polypeptide chains comprising r-laminin 8, so long as the resulting r-laminin 8 remains functional. Any epitope tag may be utilized, so long as it can be used as the basis for affinity purification of the resulting r-laminin 8. Examples of such epitope tags include, but are not limited to FLAG (Sigma Chemical, St. Louis, MO), myc (9E10) (Invitrogen, Carlsbad, CA), 6-His (Invitrogen; Novagen, Madison, WI), and HA (Boehringer Mannheim Biochemicals).

In another embodiment, one of the r-laminin 8 chains is expressed as a fusion protein with a first epitope tag, and at least one other r-laminin chain is expressed as a fusion protein with a second epitope tag. This permits multiple rounds of purification

to be carried out. Alternatively, the same epitope tag can be used to create fusion proteins with more than one of the r-laminin chains.

In a further embodiment, the epitope tag can be engineered to be cleavable from the r-laminin 8 chain(s). Alternatively, no epitope tag is fused to any of the r-laminin 8 chains, and the r-laminin 8 is purified by standard techniques, including but not limited to affinity chromatography using laminin 8 specific antibodies or other laminin 8 binding molecules.

Transfection of the expression vectors into eukaryotic cells can be accomplished via any technique known in the art, including but not limited to calcium phosphate co-precipitation, electroporation, or liposome mediated-, DEAE dextran mediated-, polycationic mediated-, or viral mediated transfection. Transfection of bacterial cells can be done by standard methods.

In a preferred embodiment, the cells are stably transfected. Methods for stable transfection and selection of appropriate transfected cells are known in the art. In a most preferred embodiment, a CMV promoter driven expression vector is used in a human kidney embryonic 293 cell line.

Media from cells transfected with a single laminin chain are initially analyzed on Western blots using laminin chain-specific antibodies. The expression of single laminin chains following transfection is generally intracellular. Clones showing reactivity against individual transfected chain(s) are verified by any appropriate method, such as PCR, reverse transcription-PCR, or nucleic acid hybridization, to confirm incorporation of the transfected gene. Preferably, analysis of genomic DNA preparations from such clones is done by PCR using laminin chain-specific primer pairs. Media from transfected clones producing all three chains are further analyzed for r-laminin 8 secretion and/or activity, by any appropriate method, including Western blot analysis and cell binding assays. Activity of the r-laminin 8 is preferably analyzed in a cell adhesion assay.

In another aspect, the present invention provides substantially purified laminin 8, preferably r-laminin 8. In one embodiment, the substantially purified laminin 8 comprises a first chain comprising an $\alpha 4$ chain polypeptide; a second chain comprising a $\beta 1$ chain polypeptide; and a third chain comprising a $\gamma 1$ chain polypeptide. Alternatively, the r-laminin 8 comprises a first chain that is substantially similar to at

least one of the sequences shown in SEQ ID NO: 2, 4, 6, 8, 10, 12 or fragments thereof; a second chain that is substantially similar to at least one of the sequence shown in SEQ ID NO: 14, 16, 18, 20 or fragments thereof; and a third chain that is substantially similar to the sequence shown in SEQ ID NO: 22, 24, 26, 28 or fragments thereof.

5 In another embodiment, the substantially purified r-laminin 8 comprises a first chain comprising a polypeptide that is at least about 70% identical to at least one of the sequences shown in SEQ ID NO: 2, 4, 6, 8, 10, 12 or fragments thereof; a second chain comprising a polypeptide that is at least 70% identical to at least one of the sequences shown in SEQ ID NO: 14, 16, 18, 20 or fragments thereof; and a third chain comprising
10 a polypeptide that is at least 70% identical to at least one of the sequences shown in SEQ ID NO: 22, 24, 26, 28 or fragments thereof, wherein the first, second, and third polypeptides are produced recombinantly, and wherein the first, second, and third chains assemble into a recombinant heterotrimeric laminin 8.

In a preferred embodiment, at least one of the first, second, or third chains of the
15 substantially purified human r-laminin 8 is expressed as a fusion protein with an epitope tag.

Alternatively, the r-laminin 8 comprises a heterotrimeric polypeptide structure, wherein each individual chain comprises a general structure selected from the group consisting of: (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-
20 R3(e); (7) R2-R3; and (8) R2-R3(e)

wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or an artificial sequence; R3 is a secreted $\alpha 4$, $\beta 1$, or $\gamma 1$ laminin chain; and
25 R3(e) is a secreted laminin $\alpha 4$, $\beta 1$, and $\gamma 1$ chain that further comprises an epitope tag (such as those described above), which can be placed at any position within the laminin chain amino acid sequence.

In a preferred embodiment, purification of r-laminin 8 is accomplished by passing media from the transfected cells through an antibody affinity column. In one
30 embodiment, antibodies against a peptide epitope expressed on at least one of the recombinant chains are attached to an affinity column, and bind the r-laminin 8 that has been secreted into the media. The r-laminin 8 is removed from the column by passing

excess peptide over the column. Eluted fractions are analyzed by any appropriate method, including gel electrophoresis and Western blot analysis. In a further embodiment, the peptide epitope can be cleaved after purification. In other embodiments, two or three separate r-laminin chains are expressed as fusion proteins, each with a different epitope tag, permitting two or three rounds of purification and a doubly or triply purified r-laminin 8. The epitope tag can be engineered so as to be cleavable from the r-laminin 8 chain(s) after purification. Alternatively, no epitope tag is fused to any of the r-laminin 8 chains, and the r-laminin 8 is purified by standard techniques, including but not limited to affinity chromatography using laminin 8 specific antibodies or other laminin 8 binding molecules.

The present invention further provides pharmaceutical compositions comprising substantially purified laminin 8 and a pharmaceutically acceptable carrier. In a preferred embodiment, the pharmaceutical composition comprises substantially purified r-laminin 8. According to this aspect of the invention, other agents can be included in the pharmaceutical compositions, depending on the condition being treated. The pharmaceutical composition may further comprise one or more other compounds, including but not limited to any of the collagens, other laminin types, fibronectin, vitronectin, cadherins, integrins, α -dystroglycan, entactin/nidogen, α -dystroglycan, glycoproteins, proteoglycans, heparan sulfate proteoglycan, glycosaminoglycans, epidermal growth factor, vascular endothelial growth factor, fibroblast growth factor, or nerve growth factors, and peptide fragments thereof.

Pharmaceutical preparations comprising substantially purified laminin 8 can be prepared in any suitable form, and generally comprise the laminin 8 in combination with any of the well known pharmaceutically acceptable carriers. The carriers can be injectable carriers, topical carriers, transdermal carriers, and the like. The preparation may advantageously be in a form for topical administration, such as an ointment, gel, cream, spray, dispersion, suspension or paste. The preparations may further advantageously include preservatives, antibacterials, antifungals, antioxidants, osmotic agents, and similar materials in composition and quantity as is conventional. Suitable solutions for use in accordance with the invention are sterile, are not harmful for the proposed application, and may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives,

stabilizers, wetting agents, emulsifiers, buffers etc. For assistance in formulating the compositions of the present invention, one may refer to Remington's Pharmaceutical Sciences, 15th Ed., Mack Publishing Co., Easton, Pa. (1975).

In further aspect, the present invention provides methods and kits comprising laminin 8, or pharmaceutical compositions thereof (and instructions for using the laminin 8 in the kits) for accelerating the healing of injuries to tissue of mesenchymal origin, such as bone, cartilage, tendon, and ligament, treating injuries to vascular and neural tissue, and for improving the biocompatibility of grafts used for treating such injuries. In a preferred embodiment of each of the methods disclosed below, r-laminin 8 is used. In specific examples, substantially purified laminin 8, r-laminin 8, or pharmaceutical compositions thereof are used to:

- a. promote re-endothelialization at the site of vascular injuries;
- b. improve the "take" of grafts;
- c. improve the biocompatibility of medical devices;
- d. treat neural injuries (neural regeneration);
- e. regulate angiogenesis; and
- d. promote cell attachment and migration

by providing an amount effective of laminin 8 or pharmaceutical compositions thereof for the various methods.

In one embodiment, laminin 8 is used to promote re-endothelialization, and to thus inhibit abnormal smooth muscle cell proliferation, at the site of a vascular injury. The $\alpha 4$ chain is associated with mesenchymally derived cell populations, including but not limited to endothelium and smooth muscle cells, and laminin 8 has been shown to be a primary laminin of the vascular endothelium.

The value of angioplasty in clearing occluded coronary arteries is limited by a restenosis/reocclusion rate of 50-70%. Several studies have indicated that the insertion of a vascular stent following angioplasty appears to decrease the occurrence of restenosis, but the problem still limits the effectiveness of this treatment. Restenosis appears to arise in part from the proliferation of vascular smooth muscle cells in response to the angioplasty treatment. It is likely that the scraping action of angioplasty removes not only the problematic occlusion, but also sections of the vascular basal lamina. The discontinuous basal lamina that results could contribute to

what appears to be abnormal growth of the vascular smooth muscle cells that leads to restenosis.

The attachment of laminin 8 to vascular stents can be used to limit restenosis, by promoting re-endothelialization. The interaction of vascular endothelial cells with the laminin 8 coated stents promotes their adhesion and attachment, thereby leading to homeostasis and a normal cell growth response, instead of the injury/activation endothelial cell response seen with restenosis. While activated platelets adhere to laminin 8, non-activated platelets do not. Furthermore, it has been shown that soluble laminin 8 does not cause platelet activation, but has an inhibitory effect on platelet activation by classical activators such as thrombin, collagen I, and ADP (unpublished observations). A more normal and controlled rate of re-endothelialization will decrease the incidence of re-occlusions, and improve the outcome of the angioplasty procedure.

Similarly, synthetic vascular grafts can induce blood clotting and thrombosis through interactions of blood clotting factors with the synthetic graft material. Coating vascular grafts with laminin 8 promotes endothelialization of the synthetic vessel, thereby providing for a non-thrombogenic surface. Vascular endothelial cells, like other cells that sit upon a basement membrane, prefer to adhere to an appropriate basement membrane substrate. Laminin-8 has been identified as a component of the vascular basal lamina, and is suspected to be involved in the attachment of vascular endothelial cells to the supporting basal lamina. Providing this substrate in a graft material creates a non-thrombogenic surface, promotes endothelialization, and inhibits intravascular thrombosis and vascular obstruction.

Administration to the injured blood vessel can be accomplished in some cases by simply coating laminin 8 or pharmaceutical compositions thereof into an injured area. In other embodiments, delivery can be accomplished by:

1. Coating a stent;
2. Coating a biodegradable sleeve over the stent; or
3. Forcing a liquid preparation of the laminin 8 or pharmaceutical compositions thereof through a porous catheter to the injured site.

In another embodiment, the present invention provides methods to promote bone and connective tissue repair in a subject. The incorporation of laminin 8 or pharmaceutical compositions thereof into wound repair dressings and matrices as well

as tissue grafts to accelerate the healing of bone and connective tissue repair provides a natural ligand interactive surface to promote normal cell adherence, cell growth and tissue development. Many grafts are used to replace connective tissue that has a cell layer adherent to a basal lamina. When an inappropriate surface is provided to these cells following grafting, the graft is at risk for failure of restoration of the normal cell layer. The advantage of coating these grafts with laminin 8 is to create a surface that sufficiently recapitulates a normal basal lamina surface to promote cell re-population. As used herein the term "graft" refers to both natural and prosthetic grafts.

The methods of the present invention have application in the healing of tendon, cartilage, or ligament tears, deformities and defects, bone fractures, defects, as well as use in the improved fixation of tendon, cartilage, or ligament to bone or other tissues. In addition, bony in-growth into various prosthetic devices can be greatly enhanced so that such artificial parts are firmly and permanently anchored into the surrounding skeletal tissue through a natural osseous bridge.

In a further aspect, the present invention comprises medical devices with improved biocompatibility, wherein the devices are coated with laminin 8 or pharmaceutical compositions thereof, alone or in combination with other proteins or agents that serve to increase the biocompatibility of the device surface. The coated device stimulates cell attachment and provides for diminished inflammation and/or infection at the site of entry of the appliance.

Such medical devices can be of any material used for implantation into the body, and preferably are made of or coated with a biocompatible metal that may be either stainless steel or titanium. Alternatively, the device is made of or coated with a ceramic material, or a polymer including but not limited to polyester, polyglycolic acid or a polygalactose-polyglycolic acid copolymer.

One particular use of the present invention is to increase cell adhesion to target surfaces, including but not limited to endothelial, skeletal muscle, smooth muscle, and other mesenchymally-derived cells. For example, vascular grafts and stents may be coated with laminin 8 or pharmaceutical compositions thereof to stimulate endothelial cell attachment. Alternatively, bone or connective tissue grafts or prostheses may be coated with laminin 8 or pharmaceutical compositions thereof to stimulate adhesion of the appropriate cell type and improved grafting efficiency.

If the device is made of a natural or synthetic biodegradable material in the form of a mesh, sheet or fabric, laminin 8 or pharmaceutical compositions thereof may be applied directly to the surface thereof. Appropriate cells may then be cultured on the matrix to form transplantable or implantable devices, including dental abutment pieces, needles, metal pins or rods, indwelling catheters, colostomy tubes, surgical meshes and any other appliance for which coating with laminin 8 is desirable. Alternatively, the devices may be implanted and cells may be permitted to attach in vivo.

Coupling of the substantially purified laminin 8 may be non-covalent (such as by adsorption), or by covalent means. The device may be immersed in, incubated in, or sprayed with the laminin 8 or pharmaceutical compositions thereof.

The dosage regimen for various treatments using the laminin 8 of the present invention is based on a variety of factors, including the type of injury or condition, the age, weight, sex, medical condition of the individual, the severity of the condition, and the route of administration. Thus, the dosage regimen may vary widely, but can be determined routinely by a physician using standard methods. Laminins are extremely potent molecules, and one or a few molecules per cell could produce an effect. Thus, effective doses in the pico-gram per milliliter range are possible if the delivery is optimized. Laminins are sometimes present in an insoluble form in the basement membrane and have the capability of polymerizing at concentrations as low as about 50 $\mu\text{g/ml}$, depending on the laminin isoform and the conditions. Laminins can also polymerize into a gel at a concentration of about 2-3 mg/ml . Dosage levels of the order of between 1 ng/ml and 10 mg/ml are thus useful for all methods disclosed herein, preferably between about 1 $\mu\text{g/ml}$ and about 3 mg/ml .

The present invention also provides a method for inducing cell attachment to the device (as disclosed above), comprising coating the appliance with laminin 8 or pharmaceutical compositions thereof prior to incubation with cells appropriate for the desired application.

Laminin preparations are known to induce the growth and differentiation of neurons (U.S. Patent No. 5,229,365), and have been used in combination with Type I collagen to coat a hollow conduit and promote nerve regeneration across a gap of severed nerve. (U.S. Patent No. 5,019,087)

Thus, in another embodiment, a method is provided for nerve regeneration, comprising administering to a subject in need thereof an amount effective of laminin 8 or pharmaceutical compositions thereof to promote nerve regeneration. The graft can comprise a nerve graft, or a prosthetic graft. Both bioresorbable and non-resorbable materials have been used in tubes for bridging nerve gaps. (See for example, Nyilas, et al., (Trans. Soc. Biomater., 6, 85, 1983), Molander, et al. (Biomaterials, Vol. 4, pp. 276-280, October, 1983), Colin, et al., (Journal of Dental Research July, 1984, pp. 987-993). The method can be used to treat diseases and injuries characterized by the loss of function and or/degeneration of neurons and nerves.

Laminins, or cell extracts containing laminins have been shown to regulate angiogenesis in a biphasic manner. (See, for example, Nicosia et al., Dev. Biol. 164:197-206 (1994); Bonfil et al., Int. J. Cancer 58:233-239 (1994)). At lower concentrations (30-300 µg/ml), a laminin-entactin complex stimulated angiogenesis in a three-dimensional culture, while at 3000 µg/ml the same complex was inhibitory to angiogenesis. Thus, in another aspect, the present invention provides methods for regulating angiogenesis, comprising contacting a tissue or culture substrate with an amount effective of laminin 8 or pharmaceutical compositions thereof to regulate angiogenesis. In one embodiment, the laminin 8 is used to promote angiogenesis by contacting a tissue or culture substrate with an amount effective of laminin 8 to promote angiogenesis. In another embodiment, the laminin 8 is used to inhibit angiogenesis, by contacting the tissue or culture substrate with an amount effective of laminin 8 to inhibit angiogenesis. An example of culture substrates to be contacted with laminin 8 to regulate angiogenesis are those used for tissue engineering purposes.

In another aspect of the present invention, laminin 8 is used for the culture of cells, including but not limited to endothelial cells, nerve cells, cells of hematopoietic lineage, and mesenchymally-derived cells including but not limited to cells derived from bone, connective tissue, and adipose tissue, skeletal muscle cells, and smooth muscle cells, by contacting the cells with an amount effective of laminin 8 to stimulate attachment and proliferation/differentiation/stasis of cells. The laminin 8 can either be provided in the cell culture medium, or as a cell culture medium supplement, or may be coated on the surface of a cell growth substrate. In a preferred embodiment, the method further includes contacting the cells with other compounds, including but not

limited to any of the collagens, other laminin types, fibronectin, α -dystroglycan, cadherins, integrins, entactin/nidogen, α -dystroglycan, glycoproteins, proteoglycans, heparan sulfate proteoglycan, glycosaminoglycans, epidermal growth factor or nerve growth factors, vascular endothelial growth factor, fibroblast growth factor, and peptide fragments thereof.

The cells may comprise primary cells or cell culture cell lines. The methods of this aspect of the invention can be used in vivo, ex vivo, or in vitro.

In a preferred embodiment, laminin 8 is used to coat the surface of a substrate, to promote cell adhesion to the substrate, and to stimulate cell proliferation/differentiation/stasis. The substrate used herein may be any desired substrate. For laboratory use, the substrate may be as simple as glass or plastic. For use in vivo, the substrate may be any biologically compatible material capable of supporting cell adhesion. Suitable substrate materials include shaped articles made of or coated with such materials as collagen, regenerated collagen, polyglycolic acid, polygalactose, polylactic acid or derivatives thereof; biocompatible metals such as titanium and stainless steel; ceramic materials including prosthetic material such as hydroxylapatite; synthetic polymers including polyesters and nylons; polystyrene; polyacrylates; polytetrafluoroethylene and virtually any other material to which biological molecules can readily adhere. The determination of the ability of a particular material to support adhesion of the r-laminin 8 of the invention requires only routine experimentation by the skilled artisan.

In a further aspect, the present invention provides cell growth substrates for adhesion and culturing of cells, by providing an amount effective of laminin 8 for the attachment of cells to a cell culture device for the attachment and subsequent proliferation/differentiation/stasis of the cells. The substrates may comprise any of the substrates discussed above.

In another aspect of the present invention, an improved cell culture medium is provided, wherein the improvement comprises addition to the cell culture medium of an effective amount of laminin 8 to the cell culture medium to promote the adherence, proliferation, and/or maintenance of cells. Any cell culture media that can support the growth of cells can be used with the present invention. Such cell culture media include, but are not limited to Basal Media Eagle, Dulbecco's Modified Eagle Medium, Iscove's

Modified Dulbecco's Medium, McCoy's Medium, Minimum Essential Medium, F-10 Nutrient Mixtures, Opti-MEM® Reduced-Serum Medium, RPMI Medium, and Macrophage-SFM Medium or combinations thereof.

The improved cell culture medium can be supplied in either a concentrated (ie: 10X) or non-concentrated form, and may be supplied as either a liquid, a powder, or a lyophilizate. The cell culture may be either chemically defined, or may contain a serum supplement. Culture media is commercially available from many sources, such as GIBCO BRL (Gaithersburg, MD) and Sigma (St. Louis, MO). In an alternative embodiment, the laminin 8 is used as a cell culture supplement.

The laminin 8 or pharmaceutical compositions thereof of the present invention can be used for the treatment of a variety of conditions and diseases as described herein, including but not limited to various vascular, neural, and mesenchymal tissue injuries, including but not limited to angioplasty restenosis, tissue ischemia, neural damage, vascular surgical procedures, atherosclerosis, bone fractures, defects, and disorders which result in weakened bones such as osteoporosis, osteoarthritis, and periodontal disease; bone loss resulting from cancer or side effects of other medical treatment; age-related loss of bone mass; articular cartilage tears, deformities and other cartilage defects such as arthritis and cartilaginous tissue damage, tendon or ligament tears, deformities and other tendon or ligament defects such as tendinitis and carpal tunnel syndrome, periodontal ligament injury, and tendon-to-bone detachment.

The amount of laminin 8 or pharmaceutical compositions thereof used in such treatments will, of course, depend upon the type and severity of the condition or disease being treated, the route of administration chosen, and will be determined by the attending physician or veterinarian. The term "therapeutically effective amount" of laminin 8 or pharmaceutical compositions thereof refers to the amount of laminin 8 or pharmaceutical compositions thereof, in the absence of other exogenously applied factors, determined to produce a therapeutic response in a mammal. Such therapeutically effective amounts are readily ascertained by one of ordinary skill in the art.

The present invention may be better understood with reference to the accompanying examples that are intended for purposes of illustration only and should

not be construed to limit the scope of the invention, as defined by the claims appended hereto.

EXAMPLES

5 *Expression Constructs*

For expression of the human laminin $\alpha 4$ chain containing a C-terminal FLAG epitope, the full length cDNA was constructed and modified as follows. Complementary DNA lambda clones subcloned into pBluescriptTM or pCRscriptTM (Stratagene) plasmid vectors from an earlier study (Iivanainen et al., 1995) were used
10 as cDNA source, except for clone FL136. The EcoRI insert from FL136 lambda DNA was cloned into the pBluescriptTM EcoRI site to make FL136E. The 0.78 kb SacI-BamHI fragment from clone FL76 was ligated into SacI-BamHI digested pSL1180 (Pharmacia) to make FL76SB. A sequence corresponding to nucleotides 2378-4274 of human laminin $\alpha 4$ cDNA was PCR-amplified using cDNA library as a template,
15 digested with SacI and cloned into the FL76SB SacI site and its orientation confirmed to make HL4-SB. The FL64 BamHI-SalI fragment was cloned into HL4-SB BamHI-SalI to make HL4-3'.

The Eco72I-XhoI fragment from clone FL117 was ligated into the Eco72I-XhoI sites of FL136E to make HL4-5'. Both mouse and human laminin $\alpha 4$ cDNAs have
20 poorly conserved Kozak-sequences at the translation initiation site, as well as several extra 5' untranslated region (UTR) ATG sequences. To ensure efficient and correct translation initiation, the Kozak sequence was edited to match the consensus and the rest of the 5' UTR was deleted using standard molecular biology techniques. The resulting product was EcoRI-EagI-digested and cloned to the EcoRI-EagI-digested
25 HL4-5' to make HL4Mut-5'. The SpeI-XhoI fragment from HL4Mut-5' was cloned into HL4-3' to make clone HL4-Full with full length cDNA. The EcoRI insert from HL4-Full was cloned into pcDNA3.1/Zeo(-) expression vector (Invitrogen) to make HL4-Full.pcDNA. (SEQ ID NO:1)

The sequence encoding the FLAG epitope (SEQ ID NO:3) was inserted as
30 follows. The FL64 BamHI-HindIII fragment was cloned into pUC19 to make FL64BH. PCR was performed using primers to introduce the FLAG epitope, using HL4-3' as template. The product was digested with XbaI and HindIII and cloned into

XbaI-HindIII digested FL64BH to make HL4FLAG-3'. This also resulted in deletion of the original 3' UTR. The BamHI-HindIII fragment from HL4FLAG-3' was cloned into BamHI-HindIII-digested HL4-Full.pcDNA vector, replacing the original BamHI-HindIII fragment to make HL4FLAG-B, which lacked the BamHI-BamHI fragment.

5 The final expression construct named HL4FLAG-Full was made by inserting the missing BamHI fragment in the correct orientation. All PCR-derived parts of the cDNA sequence were sequenced to ensure that no mutations had occurred during amplification.

The construct used for expression of the mouse laminin β 1 chain (SEQ ID NO:15) has been previously described (Yurchenco et al., *Proc. Natl. Acad. Sci. U. S. A.* **94**(19), 10189-94 (1997)).

To make the construct named HG1 for expression of the human laminin γ 1 chain, full length cDNA (SEQ ID NO:19) encoding the human laminin γ 1 chain was released with BamHI from a baculovirus expression vector pVL941 (unpublished) and
15 cloned into the BamHI site of a pcDNA3.1/Hygro(-) mammalian expression vector (Invitrogen).

Antibodies, control proteins, and cell lines

Affinity purified polyclonal anti-laminin α 4 antibody (Ab) S8 was prepared as
20 described previously. (Iivanainen et al., 1997, *J. Biol. Chem.* **272**(44), 27862-8) Polyclonal anti-EHS-laminin Ab, anti-FLAG M2 monoclonal Ab (mAb), purified control mouse IgG, RGDS-peptide and heparin (grade I-A) were purchased from Sigma Chemical Company (St. Louis, MO). Anti-laminin γ 1 (clone 22) mAb was from Transduction Laboratories (Lexington, KY). Mouse function blocking mAbs against
25 integrin α 1 (clone FB12), integrin α 2 (clone P1E6), and integrin α 3 (clone P1B5) were obtained from Chemicon (Temecula, CA). Rat function blocking mAbs anti-integrin α 6 (clone GoH3) and control rat IgG_{2a} were also from Chemicon. Rat function blocking mAbs against integrin α 5 (clone BIIG2) and integrin β 1 (clone AIIB2) were provided by Dr. C. Damsky (Univ. of California, San Francisco) as hybridoma
30 supernatants. Immunoglobulins were purified from the supernatants using GAMMABIND PLUSTM Sepharose (Pharmacia; Stockholm, Sweden) according to the manufacturer's instructions. Secondary Ab conjugates anti-rabbit IgG-HRP and anti-

mouse IgG-HRP were from Dakopatts (Denmark). Laminin 1 from EHS-tumor, collagen type IV from EHS-tumor, and human placental laminin were obtained from Sigma. Fibronectin and some of the laminin 1 from EHS-tumor were purchased from Gibco BRL (Rockville, MD). EHS-derived laminin 1/nidogen complex was kindly
5 provided by Dr. J. Engel (Univ. of Basel, Switzerland). Human fibrosarcoma HT-1080 (CCL-121) cells were from the American Type Tissue Collection. (Manassas, VA) IMMORTOMOUSETM brain capillary endothelial (IBE, Kanda et al., 1999, *Exp. Cell Res.* 248(1), 203-13) and bovine adrenal microvascular (BCE, Folkman et al., 1979) cells were kindly provided by Dr. L. Claesson-Welsh (Medical Biochemistry and
10 Microbiology, Univ. of Uppsala) and K. Olausson (Medical Cell Biology, Univ. of Uppsala). Three human erythroleukemic K562 cell lines transfected to express integrins $\alpha 3$ (Delwel et al., 1994, *Mol. Biol. Cell* 5(2), 203-15), $\alpha 6$ (Delwel et al., 1993, *J. Biol. Chem.* 268(34), 25865-75), or both $\alpha 6$ and $\alpha 4$ (Niessen et al., 1994, *Exp. Cell Res.* 211(2), 360-7 *Mol. Biol. Cell*) were provided by Dr. A. Sonnenberg (Netherlands
15 Cancer Institute, Amsterdam, Netherlands).

Production and purification of recombinant laminin 8

Recombinant laminin 8 ("r-laminin 8") was produced in human embryonic kidney cells (HEK-293, ATCC CRL-1573) cultured in DME/pyruvate/10% fetal calf
20 serum (FCS) at 37°C in a humidified 5% CO₂ atmosphere. Wild-type cells were stably transfected with the laminin $\beta 1$ expression construct as previously described (Yurchenco et al., 1997) and selected using 500 μ g/ml G418. All further cell culture and clonal expansion was carried out in the continuous presence of relevant selection antibiotics. A highly expressing clone was then transfected with the HL4FLAG-Full
25 construct using standard calcium-phosphate transfection methods, and stable colonies were selected using 300 μ g/ml Zeocin. Clones were isolated using cloning rings, expanded, and analyzed for laminin $\alpha 4$ secretion by Western blotting of medium using the anti-laminin $\alpha 4$ Ab S8. The clone with the highest expression was transfected with the HG1 construct, and stable clones were selected using 100 μ g/ml hygromycin.
30 These clones were then screened via Western blotting using a mAb against laminin $\gamma 1$, and clones showing the highest secretion were expanded further.

For production of r-laminin 8, cells were grown in the culture medium for up to four days, after which the medium was collected and centrifuged to remove cell debris. After collection, Tris-Cl pH 7.5 was added to 50 mM and EDTA was added to a concentration of 10 mM. If not used immediately, the medium was stored at -70°C.

5 For protein production into serum-free medium, confluent cultures were washed twice with PBS and the medium was changed to DME supplemented with pyruvate, insulin-transferrin-selen supplement (Sigma) and 1 µg/ml aprotinin (Sigma).

r-laminin 8 was affinity purified using an anti-FLAG M2 matrix (Sigma).

Before use, the matrix was washed with 0.1M glycine (pH 3.5) and TBS (50 mM Tris-

10 HCl pH 7.5/150 mM NaCl) according to the manufacturer's instructions. Brij-20

(Fluka, Milwaukee, Wisconsin) was added to the medium to a final concentration of

0.05% (v/v), and the medium was incubated in batch mode with the matrix (25 µl

matrix/ml) overnight at 4°C with agitation. The matrix was collected by passing the

medium through a sintered column, and washed extensively in the column first with

15 TBS/1 mM EDTA and then PBS/1 mM EDTA. Bound r-laminin 8 was competitively

eluted with 100 µg/ml FLAG peptide (Sigma) in PBS/1mM EDTA at room

temperature. The matrix was then regenerated as recommended by the manufacturer.

The eluate was diluted 1:1 with 20 mM NaPO₄/1 mM EDTA (pH 7.5), and injected into

a UNO-Q ion-exchange column (Bio-Rad, Hercules, CA). At this salt concentration,

20 the FLAG peptide passes through, but r-laminin 8 is bound. The column was then

washed with 20 mM phosphate/1 mM EDTA, and the r-laminin 8 was eluted with 20

mM NaPO₄/1.5M NaCl/1 mM EDTA. The eluate was diluted 1:10 with 20 mM NaPO₄

(pH 7.5)/1 mM EDTA to a final salt concentration of 150 mM and concentrated using

100 kD cut-off ultrafiltration (Gelman; Ann Arbor, Michigan) to approximately 0.5

25 mg/ml.

Characterization of r-laminin 8

Secreted r-laminin 8 in cell medium and after purification was characterized using linear 5% or 6% SDS-PAGE and 3-12% gradient SDS-PAGE under reducing and

30 non-reducing conditions. Proteins were visualized using silver staining or blotted to PVDF membranes using a semi-dry blotting system (Bio-Rad). For immunodetection, Renaissance ECL-System (Dupont, Waltham, MA) was used in conjunction with the

Abs described above. Protein quantitation was done by measuring absorbance at 280 nm or using the Bradford method (Bio-Rad protein assay kit).

Rotary shadowing electron microscopy (EM) was performed as described previously. (Yurchenco and Chen, 1993) When purifying for rotary shadowing, the
5 matrix was equilibrated with 0.15 M NH_4HCO_3 -acetate buffer (pH 7.4), and the r-laminin 8 was then eluted with FLAG-peptide in the same buffer.

Adhesion assays and cell culture

For adhesion assays, flat-bottom 96 well plates (Maxi-Sorp, Nunc; Rochester,
10 NY) were coated by incubating with proteins diluted in PBS overnight at 4°C (50 μl /well). The remaining protein-binding capacity was saturated by addition of 2% heat-inactivated BSA in PBS (50 μl /well) and further incubation for at least 4 hours. Prior to assaying, the coating/blocking solution was aspirated, and the wells were washed with the binding medium (100 μl /well). Drying of coated protein was avoided, since
15 this was found to be detrimental to adhesion in some cases.

All cells were cultured in humidified 5% CO_2 atmosphere. HT-1080 and BCE cells were cultured in DME/10% FCS/pyruvate at 37°C, BCE on gelatin-coated plastic. IBE cells were cultured in F12/10% FCS/2 U/ml γ -interferon on gelatin-coated plastic at 33°C. Transfected K562 cells were grown in suspension in RPMI/10%FCS
20 supplemented with 1 mg/ml G418 at 37°C. For K562 cells transfected with both $\alpha 4$ and $\beta 4$ integrins, 0.7 mg/ml hygromycin was included in the medium. Prior to dissociation, the cells were washed twice with PBS. HT-1080 cells were disassociated using 5 mM EDTA in PBS, while the others were disassociated using trypsin-EDTA (Gibco-BRL). To remove trypsin, cells were pelleted and resuspended twice in serum-
25 free medium. Cells were counted and suspended in buffered serum-free medium at $2-3 \times 10^5$ cells/ml. K562 cells were washed twice with serum-free medium and resuspended at 10^6 cells/ml. DME/25 mM HEPES/pyruvate was used for HT-1080 cells; F12/25 mM HEPES/0.25% BSA was used for other cell types.

K562 cell stimulation was done using 5 ng/ml PMA (Sigma). Antibodies or
30 other test compounds were added to the cell suspension and the cells were allowed to recover at 37°C for 30 minutes. The cells were then added to the protein-coated 96-

well plates (100 μ l/well) and allowed to adhere for 30 (K562) or 60 (other cells) minutes at 37°C. To remove unbound cells, wells were washed by two or three cycles of careful addition of 100 μ l of binding medium followed by aspiration. The remaining cells were fixed with 1% glutaraldehyde in PBS for 10 minutes at room temperature.

5 Cells were stained with 0.1% crystal violet (Sigma) for 30 minutes and unbound stain was removed by four washes with water. Bound stain was solubilized in 2% SDS (100 μ l/well) and quantitated by measuring the absorbance at 595 nm using a microplate reader.

None of the cell lines bound appreciably to BSA. When the quantitative results were calculated, binding to BSA was given a value of zero, while the relevant control was given the value of 100. The mean and SEM were calculated from results obtained from parallel wells.

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RESULTS

Production and characterization of r-laminin 8

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Unconcentrated medium from wild-type HEK-293 cells did not react in Western blots with the anti-laminin α 4, anti-laminin γ 1, anti-EHS-laminin, or anti-FLAG antibodies, indicating that these cells express endogenous laminins at very low amounts if at all. The transfected α 4 chain could be secreted to some extent even when expressed alone, but secretion of the other chains required simultaneous expression of all three chains. Cells transfected with laminin α 4, β 1, and γ 1 chain expression constructs secreted large amounts of all three chains to the medium. The best cell clones (“G1-2” and “G1-3”) were estimated to produce 3-5 milligrams of r-laminin 8 per liter of medium.

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The r-laminin 8 bound to anti-FLAG M2 matrix with high specificity. When eluted competitively with the FLAG peptide, only laminin α 4, β 1, and γ 1 bands were seen in silver-stained 3-12% gradient SDS-PAGE gels. (**Figure 1**) Under non-reducing conditions, the purified protein hardly entered the gel, which was to be expected as the predicted molecular weight for the mature trimer is at least 570 kD. A minor fraction of the purified trimer appeared as non-covalently associated (see discussion). In this fraction, the β 1 and γ 1 chains appeared as covalently associated dimers, whereas the α 4 chain was non-covalently associated. Under reducing conditions, the protein appeared

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as a broad band at around 200 kD, which reacted on Western blots with $\alpha 4$, EHS, $\gamma 1$, and anti-FLAG antibodies. The predicted molecular weights for mature $\alpha 4$, $\beta 1$, and $\gamma 1$ polypeptides are 200, 195, and 174 kD respectively. Laminins are heavily glycosylated, which may account for the slight discrepancy in molecular weight observed in SDS-PAGE. The $\beta 1$ and $\gamma 1$ chains of laminin 1 purified from EHS-tumor showed similar or slightly slower mobility than those of r-laminin 8.

Rotary shadowing EM revealed r-laminin 8 to be a Y-shaped molecule with two short and one long arm in accordance with the predicted structure. (**Figure 2**) In many cases, a very short (5-10 nm) rod-like stub could be seen at the junction of the arms. The G-domains could sometimes be seen as consisting of two moieties.

Cell binding to r-laminin 8 and receptor identification

We assayed the binding of human fibrosarcoma (HT-1080) and transfected K562 cells to r-laminin 8 in the presence of different blocking anti-integrin antibodies to identify integrin receptors binding to r-laminin 8. Immortomouse brain capillary endothelial (IBE) and bovine adrenal microvascular endothelial (BCE) cells were also used to study the adhesion of endothelial cells to r-laminin 8. The BCE cells express at least integrins $\alpha 6\beta 1$, $\alpha 6\beta 4$, $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha 5\beta 1$, $\alpha v\beta 1$, $\alpha v\beta 3$, and $\alpha 5\beta 5$ (Klein et al., 1993, *Mol. Biol. Cell* 4(10), 973-82), whereas IBE cells have been reported to express integrins $\alpha 3$, $\alpha 5$ and $\beta 1$, but not $\alpha 1$, $\alpha 2$, or $\alpha 6$ (Kanda et al., 1999)

When compared to laminin 1, the adhesiveness of r-laminin 8 was quantitatively similar or slightly weaker for the cell lines studied, as approximately the same number of cells bound to both substrates after washing. (Figure 3) Similar results were obtained with IBE and BCE cells (data not shown). In further cell adhesion assays (**Figures 4-8**), cells were allowed to bind to either-laminin 8 or laminin 1 coated at 10 $\mu\text{g/ml}$ on 96 well plates. Prior to the assay, different components were added to the cell medium. Values indicated are relative to that of control antibody (normal mouse IgG for mouse antibodies and rat IgG_{2a} for rat monoclonal antibodies), which was designated as 100. For other substances, the same volume of buffer was added. Adhesion to bovine serum albumin (BSA) was designated zero. The text under the columns indicate the integrin subunit blocked or the added substance. Error bars

indicate SEM. Integrin monoclonal antibodies were used at 10 µg/ml, heparin at 2 mg/ml, and EDTA at 5 mM.

Monoclonal antibodies against integrins $\alpha 1$ and $\alpha 2$ were tested only in the HT-1080 cell line, where they had no or only small effects on cell binding, indicating that these integrins were not major mediators of adhesion to r-laminin 8 (**Figure 4**). Adhesion to Type IV collagen was reduced to about 50% by the anti-integrin $\alpha 2$ mAb, demonstrating the presence of active $\alpha 2$ integrin (data not shown). Integrin $\alpha 1$ mAb had only a slight effect on adhesion to collagen IV when used alone, but it had a synergistic effect when used in combination with the $\alpha 2$ mAb (not shown). The Ab against integrin $\alpha 3$ had only minor effects on adhesion of HT-1080 when used alone, but it had a synergistic effect when used in combination with the $\alpha 2$ mAb (data not shown). The monoclonal antibody to $\alpha 2$ integrin had only minor effects on adhesion of HT 1080 (**Figure 4**) cells to fibronectin or laminin, even though the cells have been shown to express high levels of $\alpha 3\beta 1$ (Wayner et al., 1993, *J. Cell Biol.* **121**(5), 1141-52). The blocking of integrin $\alpha 5$ had a slight stimulating effect on HT-1080 adhesion to both laminin 1 and laminin 8 (**Figure 4**), whereas adhesion of BCE cells to r-laminin 8 was slightly reduced (**Figure 5**). The mAb did block adhesion of HT-1080 cells to fibronectin almost completely, indicating the presence of active $\alpha 5$ integrin in these cells (not shown).

α -6 subunit containing integrin(s) were identified as the major mediators of adhesion to r-laminin 8. The integrin $\alpha 6$ subunit is known to associate with either $\beta 1$ or $\beta 4$ (Sonnenberg et al., 1990, *J. Cell Sci.* 96(Pt 2), 207-17). By using a mAb (GoH3) that blocks $\alpha 6\beta 1$ - and $\alpha 6\beta 4$ -mediated binding, we could completely abolish binding of HT-1080 and BCE cells to r-laminin 8. An anti- $\beta 1$ integrin mAb (AIIB2) also completely blocked the binding of HT-1080 cells to r-laminin 8 indicating that integrin $\alpha 6\beta 1$ is crucial for adhesion of these cells to r-laminin 8 (**Figure 4**). In contrast, binding of BCE cells was blocked only partially (about 70%) by the anti- $\beta 1$ mAb, suggesting that these endothelial cells use both $\alpha 6\beta 1$ and $\alpha 6\beta 4$ to adhere to r-laminin 8 (**Figure 5**). In another endothelial cell line, the mouse IBE cells, the anti- $\alpha 6$ subunit mAb blocked the binding to r-laminin 8 only partially (about 60%), suggesting that the

cells are using, in addition to $\alpha 6$ -subunit containing integrins, also other receptors (Figure 6).

Interestingly, when adhesion to r-laminin 8 was compared to that of laminin 1, it was observed that the adhesion was quite differently affected by the blocking anti- $\alpha 6$ and anti- $\alpha 1$ integrin mAbs. HT-1080 cells interacted with laminin 1 not only via $\alpha 6\beta 1$ integrin, but also via other $\beta 1$ -subunit-containing integrin(s), since the blocking was only partial with anti- $\alpha 6$, but complete with anti- $\beta 1$. (Figure 4) Furthermore, the adhesion of BCE cells to laminin 1 was mediated by $\beta 1$ integrin(s) other than $\alpha 6\beta 1$, since the adhesion was completely blocked by anti- $\beta 1$, but was only minimally affected by anti- $\alpha 6$. (Figure 5) Similarly, in IBE cells, the adhesion to laminin 1 was mediated by receptors other than $\alpha 6$ integrin(s), since it was not affected by anti- $\alpha 6$. (Figure 6)

To verify the role of $\alpha 6\beta 1$ and $\alpha 6\beta 4$ integrins as r-laminin 8 receptors, transfected K562 cells were used. Parental K562 cells endogenously express only integrin $\alpha 5\beta 1$, which is in an inactive state. The cells normally grow in suspension but can be made adherent with an activating anti- $\beta 1$ Ab or stimulation with PMA. K562 cells transfected with the $\alpha 6$ subunit express $\alpha 6\beta 1$ on the cell surface (Delwel et al., 1993). Interestingly, while these cells bound laminin 1 efficiently only after stimulation with PMA, they bound r-laminin 8 strongly even without stimulation (Figure 8). This finding demonstrates that the adhesive properties of r-laminin 8 are different from those of laminin 1. The cell adhesion to both laminin isoforms could be blocked with either anti-integrin $\alpha 6$ or $\beta 1$ mAbs, which agrees with results obtained with other cell lines (Figure 4-5). In addition to inactive $\alpha 6\beta 1$, K562 cells transfected with $\alpha 6$ and $\beta 4$ subunits express constitutively active $\alpha 6\beta 4$ complex, and can bind laminin 1 even without stimulation (Niessen et al., 1994). We found that these cells bound to both laminin 1 and laminin 8 without stimulation, although activation of the $\beta 1$ integrins with PMA resulted in increased adhesion. The adhesion of non-stimulated cells could be completely inhibited with anti-integrin $\alpha 6$, but only partially with anti- $\beta 1$, again indicating that $\alpha 6\beta 4$ is able to mediate adhesion to r-laminin 8 (Figure 7). In contrast, K562 cells expressing $\alpha 3\beta 1$ adhered poorly to both laminin isoforms (not shown). This agrees with an earlier study where $\alpha 3$ -transfected K562 cells were found to bind efficiently to laminin 8, but poorly to laminin 1 (Delwel et al., 1994).

Cell adhesion to both laminin 1 and r-laminin 8 was found to be dependent on divalent cations, since it could be abolished by 5 mM EDTA in all cell lines tested (**Figures 4-8**). Heparin, when used at 2 mg/ml, had no effect on the adhesion of HT-1080, BCE, and IBE to r-laminin 8 (**Figures 4-6**). On laminin 1, however, there was a slight decrease in adhesion of BCE cells (**Figure 5**), while the other cell lines were unaffected (**Figures 4,6**). The RGDS-peptide that is reported to block the function of various integrins (Pierschbacher and Ruoslahti, 1984, *Nature* **309**(5963), 30-3) had no effect at 1 mM concentration on adhesion of HT-1080, BCE, or IBE cells to the laminins (data not shown).

It was further observed that the cell-binding activity of r-laminin 8 was sensitive to air-drying. When the coated protein was allowed to air dry for 15 minutes at room temperature before adding the cells, the cell-binding activity of r-laminin 8 was completely lost (**Figure 4**). Even shorter than a 15 minute exposure could abolish the cell-binding activity (not shown). A drop of buffer was allowed to sit on the plastic, while the rest of the well was briefly exposed to air drying. On the dried area, the BCE cells were rounded, and only a few of them showed any signs of spreading. On the area kept wet, practically all cells were well spread and tightly adhered to the surface. Accordingly, all cells on the dried area were lost during washing. Laminin 1 was not as sensitive to this effect, but drying still reduced the cell binding activity by half (**Figure 4**).

DISCUSSION

The present work provides significant advances concerning the recently described laminin 8 isoform and its $\alpha 4$ chain. Large quantities of r-laminin 8 could be produced as native trimeric protein in cultured human cells, and the r-laminin 8 was shown to be biologically active and to have cell adhesive properties. Furthermore, r-laminin 8 was shown to have a preference for binding to the $\alpha 6$ integrins.

The r-laminin 8 produced in this study is a species hybrid of two human ($\alpha 4$ and $\gamma 1$) and one mouse ($\beta 1$) chains, and it contained a FLAG epitope tag attached to the C-terminus of the $\alpha 4$ chain. Despite these modifications, r-laminin 8 assembled into trimers in a manner expected from a native laminin protein, as demonstrated by rotary shadowing EM. The amount of r-laminin 8 produced by the HEK-293 cells in

monolayer cultures was quite high considering the size and complexity of the protein. An amount of 3-5 mg/L of culture medium is similar to what is frequently obtained in eukaryotic systems, such as the baculovirus insect cell system.

Similarly to other laminin isoforms characterized to date, all the chains of the r-laminin 8 trimer were disulfide linked to each other. Only a minor fraction consisted of disulfide-linked $\beta 1/\gamma 1$ containing dimers and non-crosslinked $\alpha 4$. These chains were also associated into trimers, since the dimers followed the FLAG-tagged $\alpha 4$ chain in immunoprecipitations using the anti-FLAG mAb. The presence of the $\alpha 4$ chain in r-laminin 8 trimers was also demonstrated by showing that all of the $\alpha 4$ could be immunoprecipitated after several rounds of immunoprecipitation with the anti-laminin 1 Ab that recognizes the $\alpha 1$, $\beta 1$, and $\gamma 1$ chains (data not shown).

The reason for the two minor r-laminin 8 bands of different size reacting with EHS and $\gamma 1$ antibodies is unclear. The larger one agrees with the size for a dimer, but the smaller one could not be accounted for. The size difference could be as large as 100 kD. It is possible that these dimers and non-covalent trimers are the products of incomplete or incorrect post-translational processing due to overexpression.

The purified r-laminin 8 was shown to have biological activity, as all cell lines tested in this study adhered to and spread equally well on r-laminin 8 as on laminin 1. This activity could be abolished by drying the protein, suggesting that native conformation was important for full cell binding activity. The cell binding in all cases be abolished by EDTA, indicating dependence on divalent cations.

A large variety of integrins have been implicated as receptors for different laminin isoforms. In this study, we demonstrated that integrins $\alpha 6\beta 1$ and $\alpha 6\beta 4$ were major mediators of cell adhesion to r-laminin 8. The adhesion of HT-1080 and BCE cells was completely blocked by anti-integrin $\alpha 6$ mAb, despite the fact that both cell lines express a wide spectrum of $\beta 1$ and αv integrins, including several of those shown to bind to other laminin isoforms. (Conforti et. al., 1994, *Cell Adhes. Commun.* 1(4), 279-93) HT-1080 cell adhesion to r-laminin 8 is mediated solely by integrin $\alpha 6\beta 1$, since the adhesion could be blocked not only by anti- $\alpha 6$ mAb, but also by the $\beta 1$ antibody. In contrast, the $\beta 1$ mAb only partially blocked adhesion to BCE cells, suggesting that $\alpha 6\beta 4$ contributed to the binding of BCE cells to r-laminin 8. The role

of $\alpha 6\beta 4$ as a r-laminin 8 receptor was confirmed by assaying the binding of $\alpha 6$ and $\beta 4$ transfected K562 cells that express both $\alpha 6\beta 1$ and $\alpha 6\beta 4$ on the cell surface. Indeed, adhesion was completely blocked with $\alpha 6$ mAb, but only partially with $\beta 1$ mAb, indicating that the $\alpha 6\beta 4$ complex also binds to r-laminin 8. K562 cells expressing $\alpha 6\beta 1$ bound r-laminin 8 while $\alpha 3\beta 1$ expressing cells did not, thus confirming that integrin $\alpha 6\beta 1$ binds r-laminin 8. Our results somewhat contradict the reported lack of integrin $\alpha 6$ subunit in IBE cells (Kanda et al, 1999), since the adhesion to r-laminin 8 was severely perturbed by the anti-integrin $\alpha 6$ mAb. The result suggests that these cells use yet another receptor(s) in addition to $\alpha 6$ integrins for binding to r-laminin 8. However, in certain cases GoH3 is not able to completely block integrin $\alpha 6$ in $\alpha 6\beta 4$ complexes (Sonnenberg et al., 1993, *J. Cell Sci.* **106**(Pt 4), 1083-102). Thus, the remaining adhesion could be due to incompletely blocked $\alpha 6\beta 4$ complexes.

Interestingly, adhesion of the cell lines tested to r-laminin 8 was found to be more dependent on integrin $\alpha 6$ than adhesion of the cell lines to laminin 1. Another indication of the different adhesive properties of r-laminin 8 and laminin 1 was the finding that $\alpha 6\beta 1$ -expressing K562 cells did bind to r-laminin 8 without stimulation, but, as also previously reported (Delwel et al., 1993), needed to be stimulated by PMA to efficiently bind to laminin 1 coated surfaces. Thus, r-laminin 8 appears to have a higher avidity or affinity than laminin 1 to $\alpha 6\beta 1$. The $\alpha 6\beta 1$ integrin might bind r-laminin 8 even in the conformation that makes it unable to bind to laminin 1, or the cells could be stimulated by the presence of r-laminin 8 via an unknown mechanism. It could be that the avidity/affinity difference is of biological significance, and may well be one reason for the existence of large numbers of laminin isoforms.

In addition to integrins, several other cell surface proteins have been reported to function as laminin receptors. Alpha-dystroglycan is a component of the dystrophin-dystroglycan complex in the skeletal muscle thought to connect the contractile cytoskeleton to the extracellular matrix. Dystroglycan has also been shown to bind laminin 2 and dystrophin, forming a link between the two. (Ervasti and Campbell, 1993, *J. Cell Biol.* **122**(4), 809-23) Indirect evidence suggests that laminin 8 might bind to α -dystroglycan; it has been shown that laminin from laminin α d-deficient dystrophic muscle bound dystroglycan, but, in contrast to laminin from normal muscle,

in a manner that was sensitive to inhibition by heparin. (McDearmon et al., 1998, *J. Biol. Chem.* **273**(37), 24139-44) Since upregulation of laminin $\alpha 4$ has been observed in laminin $\alpha 2$ deficient muscular dystrophy (Patton et al, 1997; Ringelmann et al., 1999), it can be assumed that the laminin $\alpha 4$ chain is involved in the observed interaction. Alpha-dystroglycan is not restricted to skeletal muscle. (Durbeej et al. 1998, *J. Histochem. Cytochem.* **46**(4), 449-57) It was recently shown to be a receptor for laminin 1 in bovine aorta endothelial cells, binding in a manner sensitive to heparin, dextran sulfate, and fucoidan. (Shimizu et al., 1999, *J. Biol. Chem.* **274**(17), 11995-2000) Heparin-sensitive interactions were not detected in this study, but this does not rule out the possibility of such interactions in other cell types or in vivo. We did observe that the r-laminin 8 binds heparin-sepharose at physiological salt concentration (data not shown).

In this study, integrins $\alpha 6\beta 1$ and $\alpha 6\beta 4$ were identified as receptors for r-laminin 8 in cultured cells, and thus it is likely that these integrins mediate binding of laminin 8 in vivo, such as to endothelial and muscle cells. Endothelial cells express a wide variety of integrins depending on developmental stage, activation state, and location. At least integrins $\alpha 2\beta 1$, $\alpha 5\beta 1$, $\alpha 6\beta 1$, $\alpha 6\beta 4$, and $\alpha v\beta 3$ have been found in endothelial cells in vivo (Sonnenberg 1990; Conforti 1992), whereas the main laminin isoforms in endothelial basement membranes (BM) are laminins 8 and 10. Other cells besides endothelial cells are likely to interact with the laminin 8 in endothelial BM; platelets contain and secrete laminin 8 when stimulated and adhere to it using the $\alpha 6\beta 1$ integrin.

Laminins 8 and 9 are also found in developing muscle and in the peripheral nervous system, overlapping in expression with integrin $\alpha 6$. In laminin $\alpha 2$ -deficient muscle, both the laminin $\alpha 4$ and integrin $\alpha 6$ are upregulated. (Vachon et al, 1997, *J. Clin. Invest.* **100**(7), 1870-81) Interestingly, integrin $\alpha 6$ and integrin $\beta 4$ knock-outs result in epidermolysis bullosa (Georges-Labouesse et al, 1996, *Nat. Genet.* **13**(3), 370-3; van der Neut et al., 1996, *Nat. Genet.* **13**(3), 366-9), but no muscular or vascular phenotype was reported.

The present invention is not limited by the aforementioned particular preferred embodiments. It will occur to those ordinarily skilled in the art that various modifications may be made to the disclosed preferred embodiments without diverting

from the concept of the invention. All such modifications are intended to be within the scope of the present invention.

We claim

1. Substantially purified laminin 8.
2. The substantially purified laminin 8 of claim 1, comprising recombinant laminin
- 5 8.
3. The substantially purified recombinant laminin 8 of claim 2 comprising:
a first chain comprising a polypeptide that is substantially similar to an $\alpha 4$
laminin chain;
a second chain comprising a polypeptide that is substantially similar to a $\beta 1$
10 laminin chain; and
a third chain comprising a polypeptide that is substantially similar to a $\gamma 1$
laminin chain;
wherein the first, second, and third chains are assembled into recombinant
heterotrimeric laminin 8.
- 15 4. The substantially purified recombinant laminin 8 of claim 2 comprising:
a first chain encoded by a polynucleotide that hybridizes under high stringency
conditions to a coding region of one or more of SEQ ID NO:1, 3, 5, 7, 9, or fragments
thereof;
20 a second chain encoded by a polynucleotide that hybridizes under high
stringency conditions to a coding region of one or more of SEQ ID NO:11, 13, 15, 17,
or fragments thereof; and
a third chain encoded by a polynucleotide that hybridizes under high stringency
conditions to a coding region of one or more of SEQ ID NO: 19, 21, 23, 25, or
25 fragments thereof;
wherein the first, second, and third chains are assembled into recombinant
heterotrimeric laminin 8.
5. The substantially purified recombinant laminin 8 of claim 2 comprising:
30 a first chain comprising a polypeptide at least 70% identical to one or more of
SEQ ID NO:2, 4, 6, 8, 10 or fragments thereof;
a second chain comprising a polypeptide at least 70% identical to one or more

of SEQ ID NO:12, 14, 16, 18 or fragments thereof; and

a third chain comprising a polypeptide at least 70% identical to one or more of SEQ ID NO:20, 22, 24, 26, or fragments thereof;

wherein the first, second, and third chains are assembled into recombinant heterotrimeric laminin 8.

6. The substantially purified recombinant laminin 8 of claim 2 comprising a first, second, and third polypeptide chain, wherein the first, second, and third polypeptide chains each comprise a general structure selected from the group consisting of: (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e)

wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or it may be an artificial sequence; R3 is a secreted $\alpha 4$ laminin chain for the first polypeptide chain, a secreted $\beta 1$ laminin chain for the second polypeptide chain, and $\gamma 1$ laminin chain for the third polypeptide chain; and R3(e) is identical to R3, but further comprises an epitope tag.

7. Recombinant laminin 8-expressing host cells.

8. The recombinant laminin 8-expressing host cells of claim 7, wherein the cells express recombinant laminin 8 comprising:

a first chain comprising a recombinant polypeptide that is substantially similar to an $\alpha 4$ laminin polypeptide;

a second chain comprising a recombinant polypeptide that is substantially similar to a $\beta 1$ laminin polypeptide sequence; and

a third chain comprising a recombinant polypeptide that is substantially similar to a $\gamma 1$ laminin polypeptide sequence;

wherein the cell expresses the first, second, and third chains, and wherein the first, second, and third chains assemble into recombinant laminin 8 that is secreted into the media by the cultured cell.

9. The recombinant laminin 8-expressing host cells of claim 7, wherein the cells express recombinant laminin 8 comprising:

a first chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO:1, 3, 5, 7, or 9, or fragments thereof;

a second chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO:11, 13, or fragments thereof; and

a third chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO: 15, 17, or fragments thereof;

wherein the cell expresses the first, second, and third chains, and wherein the first, second, and third chains assemble into recombinant laminin 8 that is secreted into the media by the cultured cell.

10. The recombinant laminin 8-expressing host cells of claim 7, wherein the cells express recombinant laminin 8 comprising:

a first chain comprising a polypeptide at least 70% identical to one or more of SEQ ID NO:2, 4, 6, 8, 10 or fragments thereof;

a second chain comprising a polypeptide at least 70% identical to one or more of SEQ ID NO:12, 14, 16, 18 or fragments thereof; and

a third chain comprising a recombinant polypeptide at least 70% identical to one or more of SEQ ID NO:20, 22, 24, 26, or fragments thereof;

wherein the cell expresses the first, second, and third chains, and wherein the first, second, and third chains assemble into recombinant laminin 8 that is secreted into the media by the cultured cell.

11. The recombinant laminin 8-expressing host cells of claim 7, wherein the cells express recombinant laminin 8 comprising a first, second, and third polypeptide chain, wherein the first, second, and third polypeptide chains each comprise a general

structure selected from the group consisting of: (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e)

wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or it may be an artificial sequence; R3 is a secreted $\alpha 4$ laminin chain for the first polypeptide chain, a secreted $\beta 1$ laminin chain for the second polypeptide chain, and $\gamma 1$ laminin chain for the third polypeptide chain; and R3(e) is identical to R3, but further comprises an epitope tag .

12. The host cells of any of claims 7-11, wherein the host cell is a mammalian cell.

13. The host cells of claim 12, wherein at least one of the first, second, or third chains is expressed as a fusion protein with an epitope tag.

14. A method of purifying recombinant laminin 8, comprising:

a. providing the host cells of claim 12;

b. growing the cells in cell culture medium under conditions to stimulate expression of the recombinant laminin 8 chains;

c. passing the cell culture medium through an affinity chromatography column, wherein the column contains a compound that binds to the recombinant laminin 8;

d. washing the affinity column to remove unbound materials; and

e. eluting the bound recombinant laminin 8 from the column.

15. Substantially purified recombinant laminin 8 isolated according to the method of claim 14.

16. A pharmaceutical composition comprising:

- a. laminin 8; and
- b. a pharmaceutically acceptable carrier.

5 17. The pharmaceutical composition of claim 16, wherein the laminin 8 comprises recombinant laminin 8.

18. A method to accelerate healing of a vascular tissue injury in a subject, comprising contacting the site of the vascular tissue injury of the subject with an
10 amount effective of laminin 8 to promote re-endothelialization at the vascular tissue injury site.

19. The method of claim 18, wherein the vascular injury is selected from the group consisting of angioplasty restenosis, vascular surgical procedures, aneurysm, and
15 atherosclerosis.

20. A method to accelerate healing of a bone or connective tissue injury in a subject comprising contacting the site of the bone or connective tissue injury in the subject with an amount effective of laminin 8 to accelerate healing of the bone or connective tissue
20 injury.

21. The method of claim 20 wherein healing is accomplished by incorporation of recombinant laminin 8 into wound repair dressings, matrices, or tissue grafts.

25 22. The method of claim 20 wherein the bone or connective tissue injury is selected from the group consisting of fractures, tears, deformities, or defects of bone, tendon, cartilage, and ligament.

23. A method to improve the biocompatibility of a medical device or graft, comprising contacting the medical device or graft with an amount effective of laminin
30 8 to improve the biocompatibility of the medical device or graft.

24. An improved medical device or graft, wherein the improvement consists of providing a medical device or graft with an amount effective of laminin 8 to improve the biocompatibility of the medical device or graft.
- 5 25. A method to regulate angiogenesis in a subject, comprising contacting a site in need of angiogenesis in the subject with an amount effective of laminin 8 to regulate angiogenesis.
26. A method to promote neural regeneration in a subject, comprising contacting a
10 site in need of neural regeneration in the subject with an amount effective of laminin 8 to promote neural regeneration.
27. A method to promote cell adhesion to a surface, comprising contacting cells with an amount effective of the laminin 8 to promote cell adhesion to the surface.
15
28. An improved cell growth substrate, wherein the improvement consists of providing a cell growth substrate that has been coated with an amount effective of laminin 8 to promote cell attachment to the cell growth substrate.
- 20 29. The method of any of claims 18-28, wherein the laminin 8 comprises recombinant laminin 8.
30. A method to accelerate healing of a vascular tissue injury in a subject, comprising contacting the site of the vascular tissue injury of the subject with an
25 amount effective of the pharmaceutical composition of claim 16 or 17 to promote re-endothelialization at the vascular tissue injury site.
31. The method of claim 30, wherein the vascular injury is selected from the group consisting of angioplasty restenosis, vascular surgical procedures, aneurysm, and
30 atherosclerosis

32. A method to accelerate healing of a bone or connective tissue injury in a subject comprising contacting the site of the bone or connective tissue injury in the subject with an amount effective of the pharmaceutical composition of claim 16 or 17 to accelerate healing of the bone or connective tissue injury.

5

33. The method of claim 32 wherein healing is accomplished by incorporation of recombinant laminin 8 into wound repair dressings, matrices, or tissue grafts.

34. The method of claim 32 wherein the bone or connective tissue injury is selected from the group consisting of fractures, tears, deformities, or defects of bone, tendon, cartilage, and ligament.

35. A method to improve the biocompatibility of a medical device or graft, comprising contacting the medical device or graft with an amount effective of the pharmaceutical composition of claim 16 or 17 to improve the biocompatibility of the medical device or graft.

36. An improved medical device or graft, wherein the improvement consists of providing a medical device or graft with an amount effective of the pharmaceutical composition of claim 16 or 17 to improve the biocompatibility of the medical device or graft.

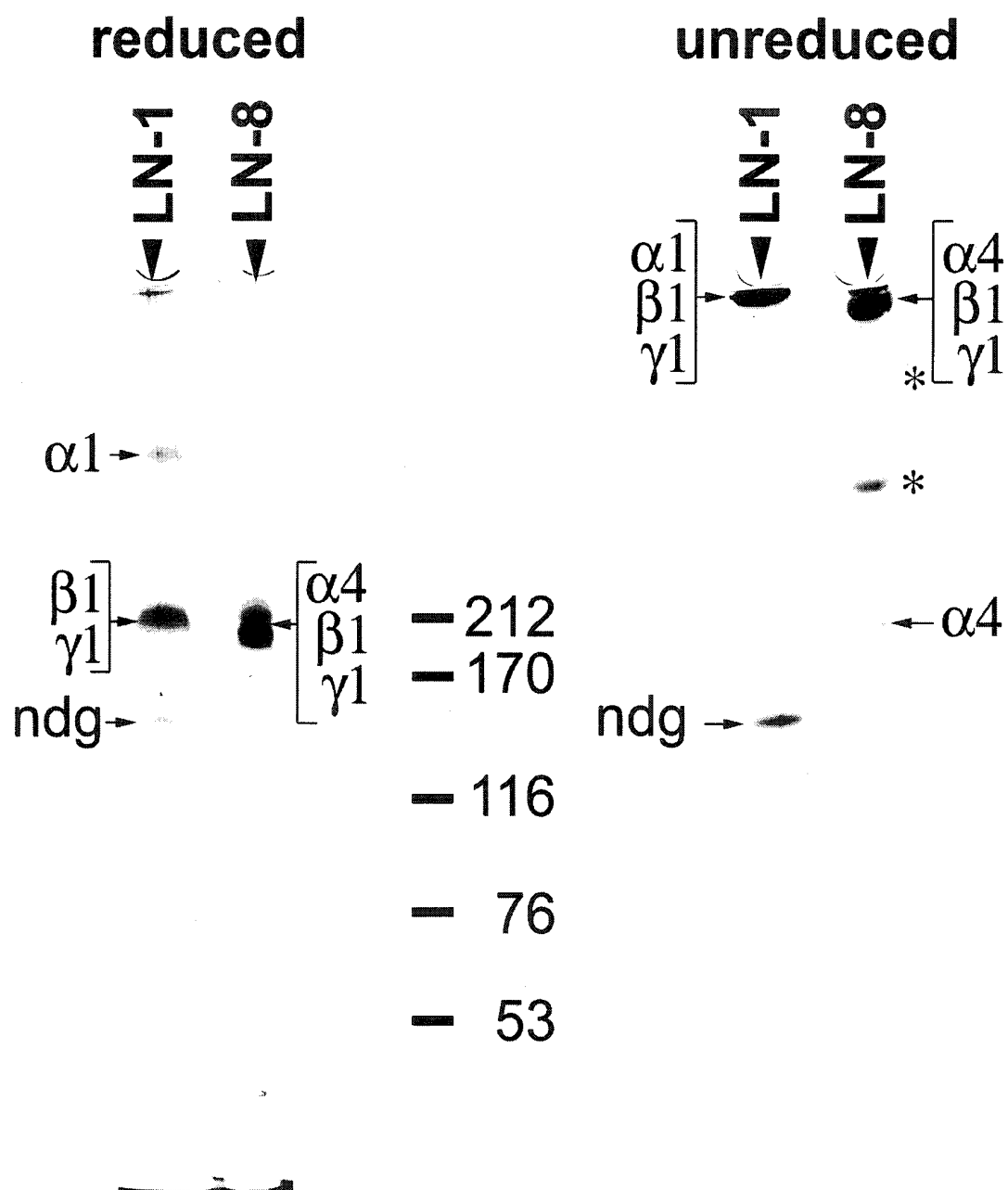
37. A method to promote angiogenesis in a subject, comprising contacting a site in need of angiogenesis in the subject with an amount effective of the pharmaceutical composition of claim 16 or 17 to promote angiogenesis.

38. A method to promote neural regeneration in a subject, comprising contacting a site in need of neural regeneration in the subject with an amount effective of the pharmaceutical composition of claim 16 or 17 to promote neural regeneration.

30

39. A method to promote cell adhesion to a surface, comprising contacting cells with an amount effective of the pharmaceutical composition of claim 16 or 17 to promote cell adhesion to the surface.
- 5 40. An improved cell growth substrate, wherein the improvement consists of providing a cell growth substrate that has been coated with an amount effective of the pharmaceutical composition of claim 16 or 17 to promote cell attachment to the cell growth substrate.
- 10 41. A kit for carrying out the method of any of claims 18-28, comprising:
- (a) an amount effective of laminin 8 for carrying out the method; and
 - (b) instructions for using the laminin 8 for carrying out the method.
- 15 42. A method to inhibit cell adhesion to laminin 8, comprising contacting the cell with an amount effective of an antagonist of at least one of integrin $\alpha 6\beta 1$ and $\alpha 6\beta 4$ to inhibit cell adhesion to laminin 8.

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FIG. 1

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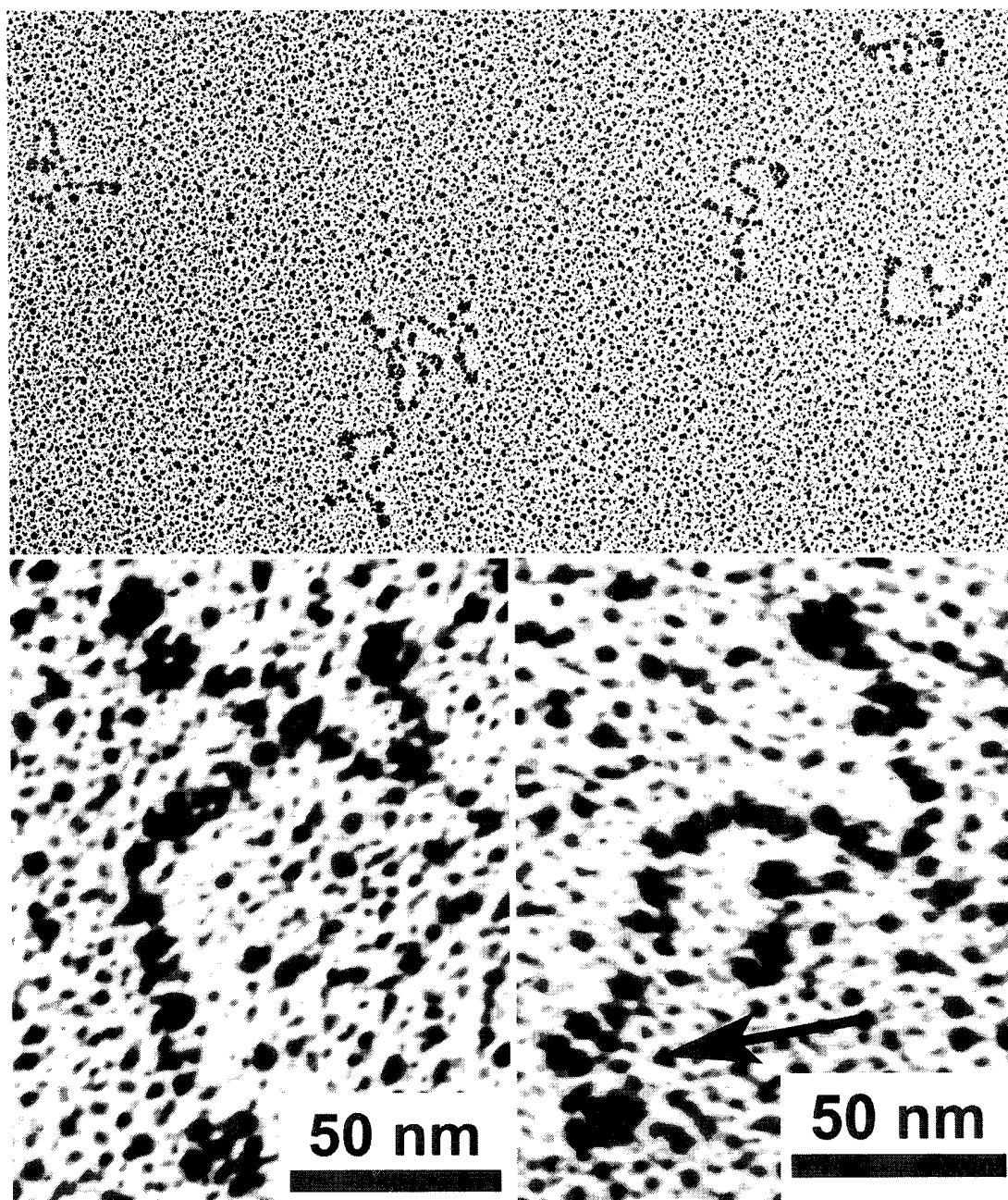
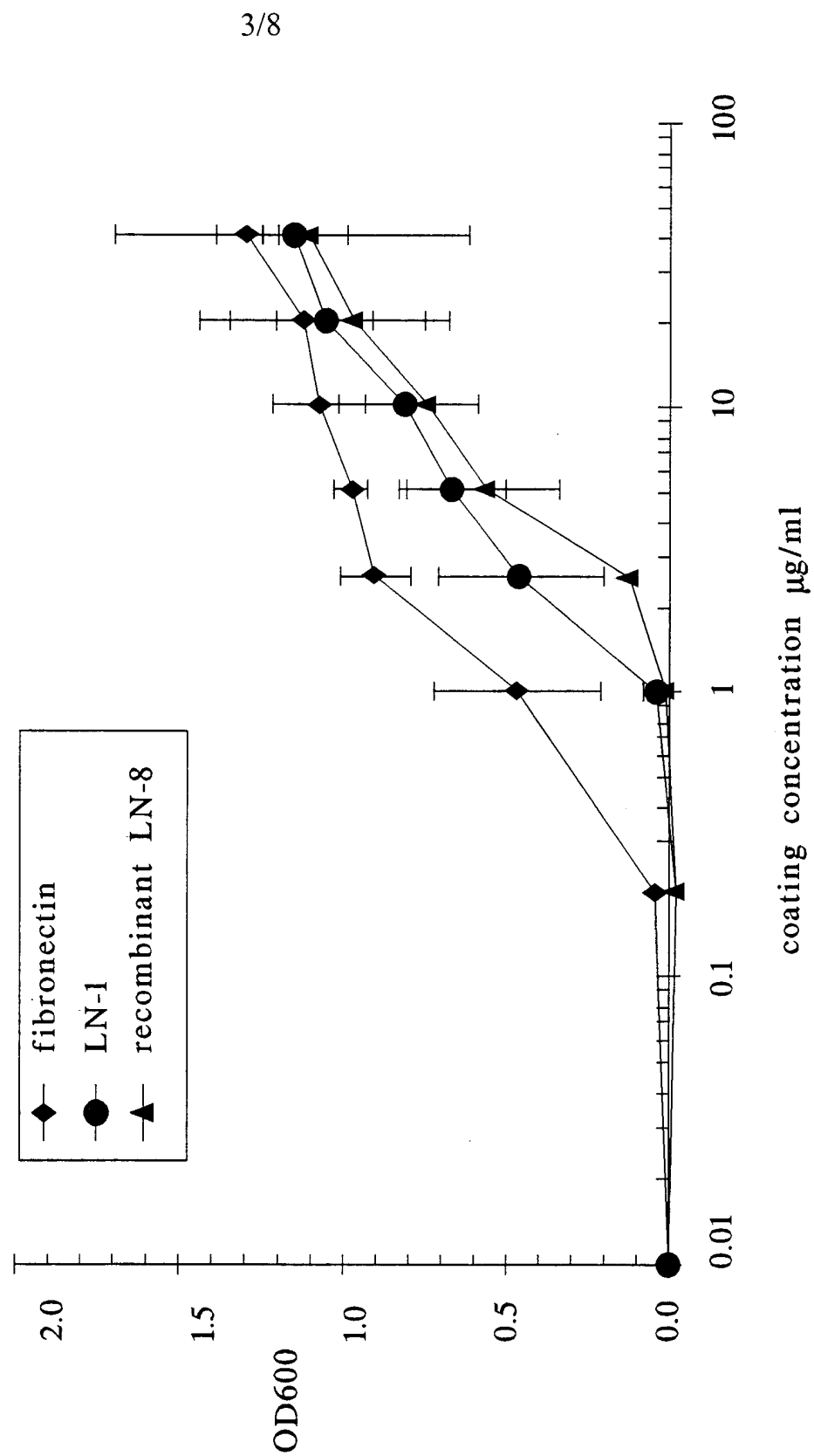
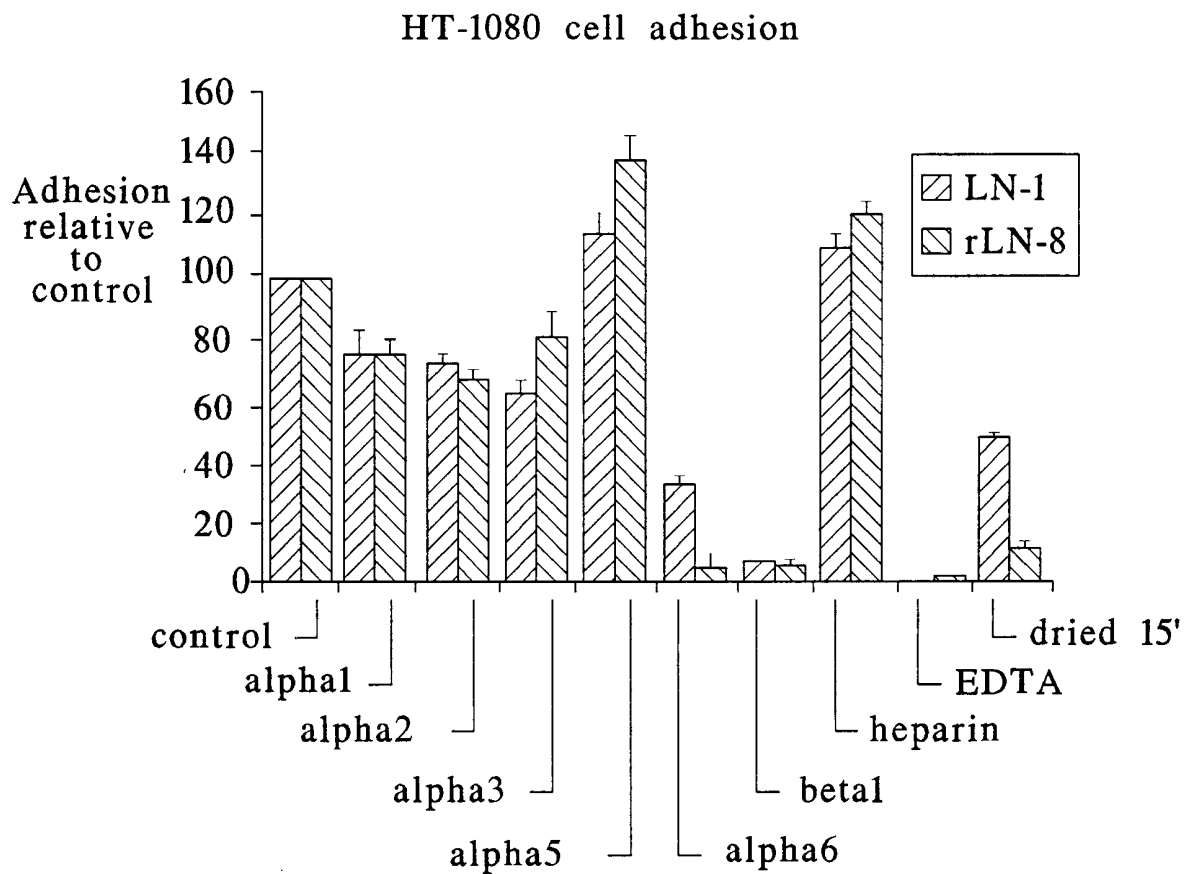
FIG. 2

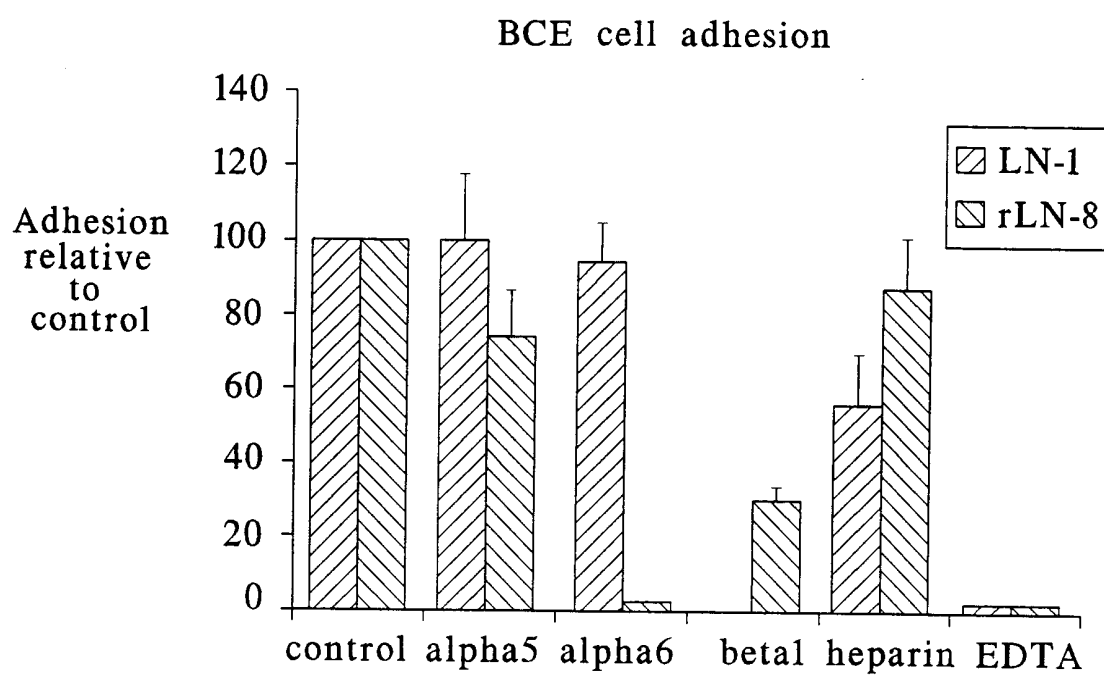
FIG. 3



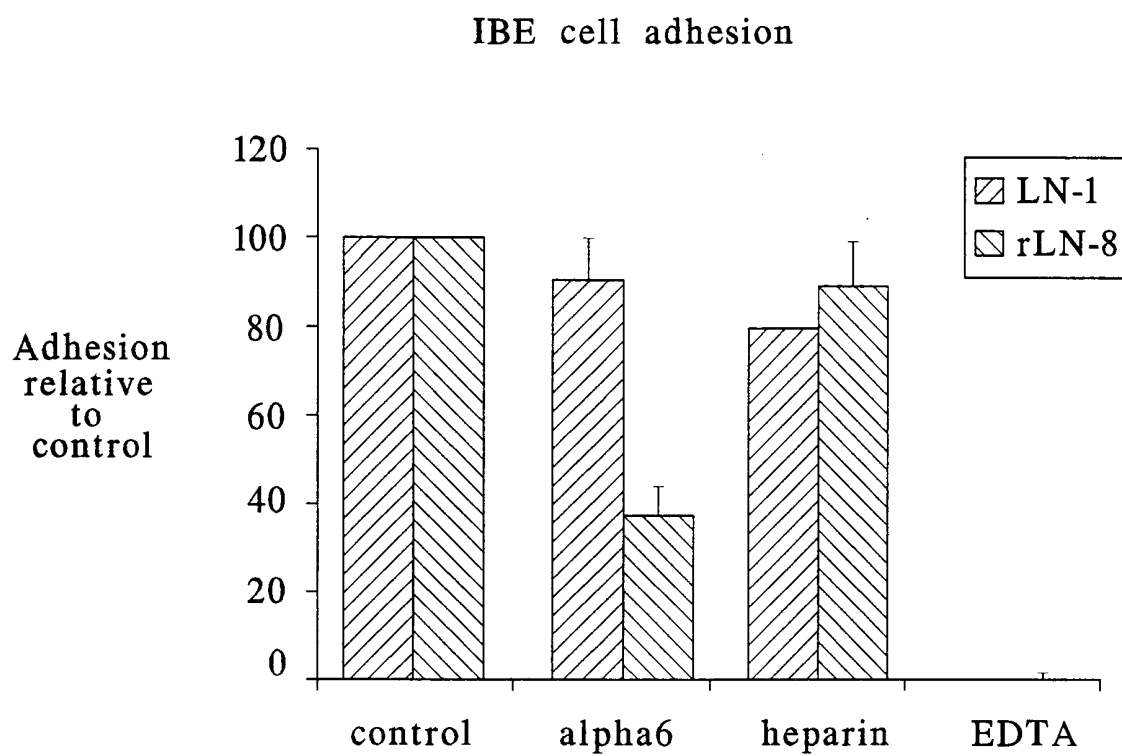
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FIG. 4

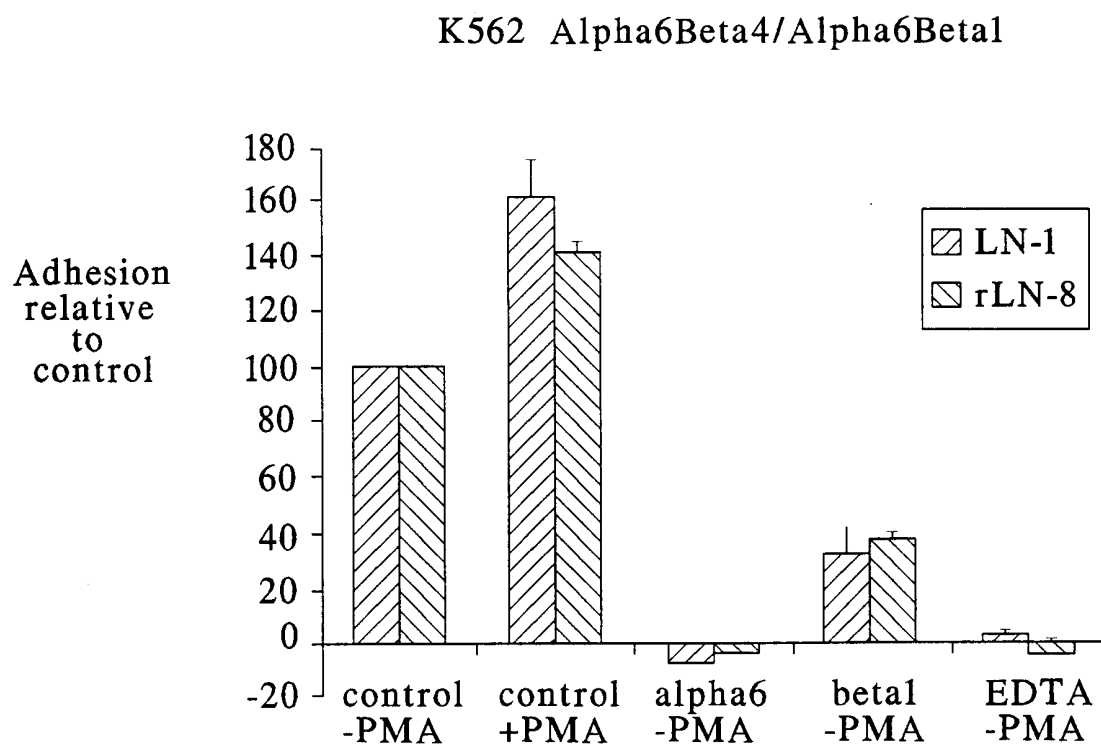
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FIG. 5

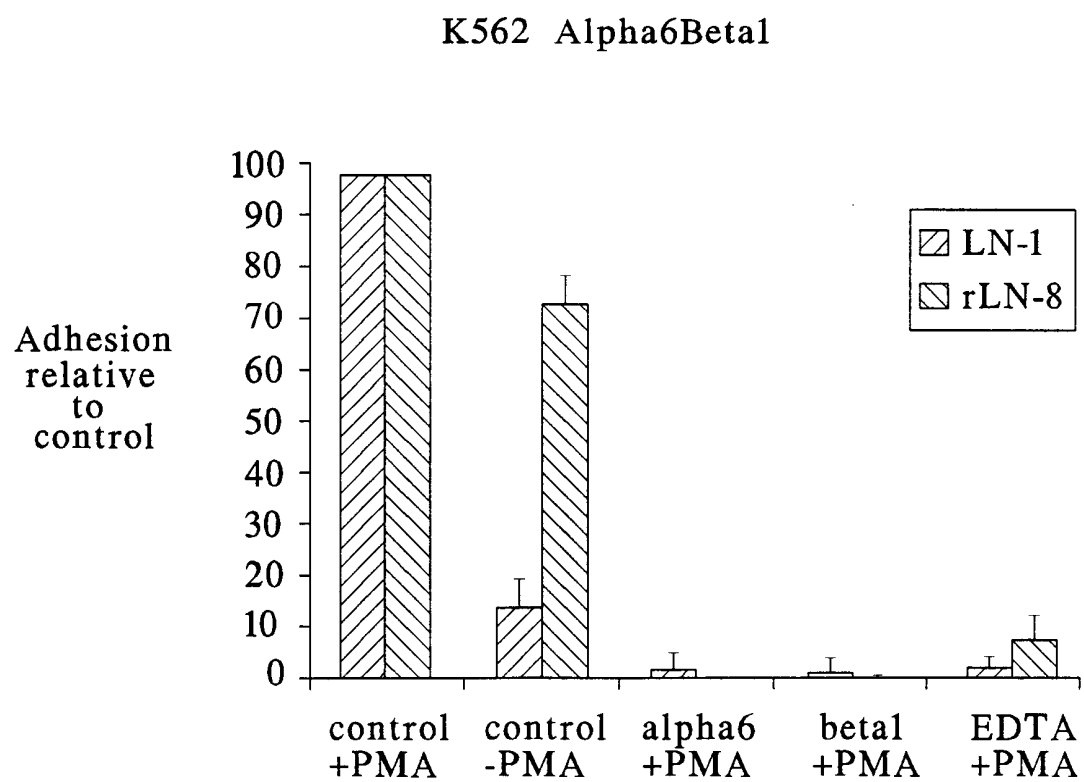
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FIG. 6

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FIG. 7

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FIG. 8

SEQUENCE LISTING

<110> Korttesmaa, Jarrko
Tryggvason, Karl

<120> Laminin 8 and Methods For Its Use

<130> 99,274-D1

<140> To Be Assigned

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cagcggagaaa atg gct ttg agc tca gcc tgg cgc tcg gtt ctg cct ctg      229
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	480	485	490
gat gcc gaa gac atg aac agg gcc aca gca gcc agg cag cgg gac cat			1717
Asp Ala Glu Asp Met Asn Arg Ala Thr Ala Ala Arg Gln Arg Asp His			
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Glu Lys Gln Gln Glu Arg Val Arg Glu Gln Met Glu Val Val Asn Met			
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Ser Leu Ser Thr Ser Ala Asp Ser Leu Thr Thr Pro Arg Leu Thr Leu			
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Ser Glu Leu Asp Asp Ile Ile Lys Asn Ala Ser Gly Ile Tyr Ala Glu			
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ata gat gga gcc aaa agt gaa cta caa gta aaa cta tct aac cta agt			1909
Ile Asp Gly Ala Lys Ser Glu Leu Gln Val Lys Leu Ser Asn Leu Ser			
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aac ctc agc cat gat tta gtc caa gaa gct att gac cat gca cag gac			1957
Asn Leu Ser His Asp Leu Val Gln Glu Ala Ile Asp His Ala Gln Asp			
	575	580	585

ctt caa caa gaa gct aat gaa ttg agc agg aag ttg cac agt tca gat	2005
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atg aac ggg ctg gta cag aag gct ttg gat gca tca aat gtc tat gaa	2053
Met Asn Gly Leu Val Gln Lys Ala Leu Asp Ala Ser Asn Val Tyr Glu	
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Asn Ile Val Asn Tyr Val Ser Glu Ala Asn Glu Thr Ala Glu Phe Ala	
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Leu Asn Thr Thr Asp Arg Ile Tyr Asp Ala Val Ser Gly Ile Asp Thr	
640 645 650	
caa atc att tac cat aaa gat gaa agt gag aac ctc ctc aat caa gcc	2197
Gln Ile Ile Tyr His Lys Asp Glu Ser Glu Asn Leu Leu Asn Gln Ala	
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Arg Glu Leu Gln Ala Lys Ala Glu Ser Ser Ser Asp Glu Ala Val Ala	
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Asp Thr Ser Arg Arg Val Gly Gly Ala Leu Ala Arg Lys Ser Ala Leu	
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Lys Thr Arg Leu Ser Asp Ala Val Lys Gln Leu Gln Ala Ala Glu Arg	
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Gly Asp Ala Gln Gln Arg Leu Gly Gln Ser Arg Leu Ile Thr Glu Glu	
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gcc aac agg acg acg atg gag gtg cag cag gcc act gcc ccc atg gcc	2437
Ala Asn Arg Thr Thr Met Glu Val Gln Gln Ala Thr Ala Pro Met Ala	
735 740 745	
aac aat cta acc aac tgg tca cag aat ctt caa cat ttt gac tct tct	2485
Asn Asn Leu Thr Asn Trp Ser Gln Asn Leu Gln His Phe Asp Ser Ser	
750 755 760 765	
gct tac aac act gca gtg aac tct gct agg gat gca gta aga aat ctg	2533
Ala Tyr Asn Thr Ala Val Asn Ser Ala Arg Asp Ala Val Arg Asn Leu	
770 775 780	
acc gag gtt gtc cct cag ctc ctg gat cag ctt cgt acg gtt gag cag	2581
Thr Glu Val Val Pro Gln Leu Leu Asp Gln Leu Arg Thr Val Glu Gln	
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Lys Arg Pro Ala Ser Asn Val Ser Ala Ser Ile Gln Arg Ile Arg Glu	
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ctc att gct cag acc aga agt gtt gcc agc aag atc caa gtc tcc atg	2677
Leu Ile Ala Gln Thr Arg Ser Val Ala Ser Lys Ile Gln Val Ser Met	
815 820 825	

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Met Phe Asp Gly Gln Ser Ala Val Glu Val His Ser Arg Thr Ser Met	
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Asp Asp Leu Lys Ala Phe Thr Ser Leu Ser Leu Tyr Met Lys Pro Pro	
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Val Lys Arg Pro Glu Leu Thr Glu Thr Ala Asp Gln Phe Ile Leu Tyr	
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Val Pro Ser Leu Ser Ser Thr Ala Glu Glu Lys Phe Ile Lys Lys Gly	
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Asn Asp Val Ile Ser Leu Tyr Asn Phe Lys His Ile Tyr Asn Met Asp	
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Pro Ser Thr Ser Val Pro Cys Ala Arg Asp Lys Leu Ala Phe Thr Gln	
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Ser Arg Ala Ala Ser Tyr Phe Phe Asp Gly Ser Gly Tyr Ala Val Val	
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Ile Glu Val Arg Thr Pro Ala Asp Asn Gly Leu Ile Leu Leu Met Val 1070	1075	1080	1085	
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Ser Glu Lys Lys Phe Tyr Phe Gly Gly Ser Pro Ile Ser Ala Gln Tyr				
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Ala Asn Phe Thr Gly Cys Ile Ser Asn Ala Tyr Phe Thr Arg Val Asp				
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Arg Asp Val Glu Val Glu Asp Phe Gln Arg Tyr Thr Glu Lys Val His				
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Thr Ser Leu Tyr Glu Cys Pro Ile Glu Ser Ser Pro Leu Phe Leu Leu				
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His Lys Lys Gly Lys Asn Leu Ser Lys Pro Lys Ala Ser Gln Asn Lys				
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Lys Leu Pro Glu Arg Asn Thr Pro Arg Asn Ser His Cys His Leu Ser				
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Asn Ser Pro Arg Ala Ile Glu His Ala Tyr Gln Tyr Gly Gly Thr Ala				
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Asn Ser Arg Gln Glu Phe Glu His Leu Lys Gly Asp Phe Gly Ala Lys				
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Phe Tyr Val Ser Asp Gln Glu Glu Asn Asp Phe Met Thr Leu Phe Leu				
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gcc cat ggc cgc ttg gtt tac atg ttt aat gtt ggt cac aaa aaa ctg				4789
Ala His Gly Arg Leu Val Tyr Met Phe Asn Val Gly His Lys Lys Leu				
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Lys Ile Arg Ser Gln Glu Lys Tyr Asn Asp Gly Leu Trp His Asp Val				
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Ile Phe Ile Arg Glu Arg Ser Ser Gly Arg Leu Val Ile Asp Gly Leu				
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Arg Val Leu Glu Glu Ser Leu Pro Pro Thr Glu Ala Thr Trp Lys Ile	
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Ser Thr Ser Val Thr Pro Lys Gln Ser Leu Cys Asp Gly Arg Trp His	
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His Arg Glu Pro Val Phe Val Gly Gly Val Pro Glu Ser Leu Leu Thr	
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<212> PRT

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Pro	Phe	Asp	Ile	Glu	Gly	Ser	Ser	Ala	Val	Gly	Arg	Gln	Asp	Pro	Pro
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Cys	Gln	Pro	Cys	Pro	Cys	Pro	Leu	Pro	His	Leu	Ala	Asn	Phe	Pro	Glu
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 Pro Phe Leu Ile Gly Ser Thr Cys Lys Lys Cys Asp Cys Ser Gly Asn
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 Asp Thr Ile Asn His Ala Ser Gln Leu Val Glu Gln Ala His Asp Met
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 His Thr Leu Ser Gly Glu Cys Val Pro Cys Asp Cys Asn Gly Asn Ser
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 Thr Thr Gly Glu His Cys Glu Lys Cys Leu Asp Gly Tyr Ile Gly Asp
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 Ser Ile Arg Gly Ala Pro Gln Phe Cys Gln Pro Cys Pro Cys Pro Leu
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Thr	Gly	Phe	Lys	Cys	Glu	Arg	Cys	Ala	Pro	Gly	Tyr	Tyr	Gly	Asp	Ala	
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Gln	Leu	Val	Gln	Lys	Glu	Ser	Met	Asp	Thr	Ile	Asn	His	Ala	Ser	Gln	
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Asn	Lys	Met	Leu	Tyr	Tyr	Gly	Glu	Glu	His	Glu	Leu	Ser	Pro	Lys	Glu	
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Ser	Arg	Gln	Pro	Phe	Phe	Thr	Gln	Arg	Glu	Leu	Val	Asp	Glu	Glu	Ala	
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Glu Val Val Asn Met Ser Leu Ser Thr Ser Ala Asp Ser Leu Thr Thr	
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Pro His Leu Ala Asn Phe Pro Glu Ser Cys Tyr Arg Lys Asn Gly Ala
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Cys Ala Pro Gly Tyr Tyr Gly Asn Pro Phe Leu Ile Gly Ser Thr Cys
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Lys Lys Cys Asp Cys Ser Gly Asn Ser Asp Pro Asn Leu Ile Phe Glu
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gag gaa ggc aaa tcc ggg gtg ctg agc gta tcc tct ggg gcc gcc gct	916
Glu Glu Gly Lys Ser Gly Val Leu Ser Val Ser Ser Gly Ala Ala Ala	
285 290 295 300	
cat agg cac gtg aat gaa atc aac gcc acc atc tac ctc ctc aaa aca	964
His Arg His Val Asn Glu Ile Asn Ala Thr Ile Tyr Leu Leu Lys Thr	
305 310 315	
aaa ttg tca gaa aga gaa aac caa tac gcc cta aga aag ata caa atc	1012
Lys Leu Ser Glu Arg Glu Asn Gln Tyr Ala Leu Arg Lys Ile Gln Ile	
320 325 330	
aac aat gct gag aac acg atg aaa agc ctt ctg tct gac gta gag gaa	1060
Asn Asn Ala Glu Asn Thr Met Lys Ser Leu Leu Ser Asp Val Glu Glu	
335 340 345	
tta gtt gaa aag gaa aat caa gcc tcc aga aaa gga caa ctt gtt cag	1108
Leu Val Glu Lys Glu Asn Gln Ala Ser Arg Lys Gly Gln Leu Val Gln	
350 355 360	
aag gaa agc atg gac acc att aac cac gca agt cag ctg gta gag caa	1156
Lys Glu Ser Met Asp Thr Ile Asn His Ala Ser Gln Leu Val Glu Gln	
365 370 375 380	
gcc cat gat atg agg gat aaa atc caa gag atc aac aac aag atg ctc	1204
Ala His Asp Met Arg Asp Lys Ile Gln Glu Ile Asn Asn Lys Met Leu	
385 390 395	
tat tat ggg gaa gag cat gaa ctt agc ccc aag gaa atc tct gag aag	1252
Tyr Tyr Gly Glu Glu His Glu Leu Ser Pro Lys Glu Ile Ser Glu Lys	
400 405 410	
ctg gtg ttg gcc cag aag atg ctt gaa gag att aga agc cgt caa cca	1300
Leu Val Leu Ala Gln Lys Met Leu Glu Glu Ile Arg Ser Arg Gln Pro	
415 420 425	
ttt ttc acc caa cgg gag ctc gtg gat gag gag gca gat gag gct tac	1348
Phe Phe Thr Gln Arg Glu Leu Val Asp Glu Glu Ala Asp Glu Ala Tyr	
430 435 440	
gaa cta ctg agc cag gct gag agc tgg cag cgg ctg cac aat gag acc	1396
Glu Leu Leu Ser Gln Ala Glu Ser Trp Gln Arg Leu His Asn Glu Thr	
445 450 455 460	
cgc act ctg ttt cct gtc gtc ctg gag cag ctg gat gac tac aat gct	1444
Arg Thr Leu Phe Pro Val Val Leu Glu Gln Leu Asp Asp Tyr Asn Ala	
465 470 475	
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Lys Leu Ser Asp Leu Gln Glu Ala Leu Asp Gln Ala Leu Asn Tyr Val	
480 485 490	
agg gat gcc gaa gac atg aac agg gcc aca gca gcc agg cag cgg gac	1540
Arg Asp Ala Glu Asp Met Asn Arg Ala Thr Ala Ala Arg Gln Arg Asp	
495 500 505	

cat gag aaa caa cag gaa aga gtg agg gaa caa atg gaa gtg gtg aac	1588
His Glu Lys Gln Gln Glu Arg Val Arg Glu Gln Met Glu Val Val Asn	
510 515 520	
atg tct ctg agc aca tct gcg gac tct ctg aca aca cct cgt cta act	1636
Met Ser Leu Ser Thr Ser Ala Asp Ser Leu Thr Thr Pro Arg Leu Thr	
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ctt tca gaa ctt gat gat ata ata aag aat gcg tca ggg att tat gca	1684
Leu Ser Glu Leu Asp Asp Ile Ile Lys Asn Ala Ser Gly Ile Tyr Ala	
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gaa ata gat gga gcc aaa agt gaa cta caa gta aaa cta tct aac cta	1732
Glu Ile Asp Gly Ala Lys Ser Glu Leu Gln Val Lys Leu Ser Asn Leu	
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agt aac ctc agc cat gat tta gtc caa gaa gct att gac cat gca cag	1780
Ser Asn Leu Ser His Asp Leu Val Gln Glu Ala Ile Asp His Ala Gln	
575 580 585	
gac ctt caa caa gaa gct aat gaa ttg agc agg aag ttg cac agt tca	1828
Asp Leu Gln Gln Glu Ala Asn Glu Leu Ser Arg Lys Leu His Ser Ser	
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Asp Met Asn Gly Leu Val Gln Lys Ala Leu Asp Ala Ser Asn Val Tyr	
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gaa aat att gtt aat tat gtt agt gaa gcc aat gaa aca gca gaa ttt	1924
Glu Asn Ile Val Asn Tyr Val Ser Glu Ala Asn Glu Thr Ala Glu Phe	
625 630 635	
gct ttg aac acc act gac cga att tat gat gcg gtg agt ggg att gat	1972
Ala Leu Asn Thr Thr Asp Arg Ile Tyr Asp Ala Val Ser Gly Ile Asp	
640 645 650	
act caa atc att tac cat aaa gat gaa agt gag aac ctc ctc aat caa	2020
Thr Gln Ile Ile Tyr His Lys Asp Glu Ser Glu Asn Leu Leu Asn Gln	
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gcc aga gaa ctg caa gca aag gca gag tct agc agt gat gaa gca gtg	2068
Ala Arg Glu Leu Gln Ala Lys Ala Glu Ser Ser Ser Asp Glu Ala Val	
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gct gac act agc agg cgt gtg ggt gga gcc cta gca agg aaa agt gcc	2116
Ala Asp Thr Ser Arg Val Gly Gly Ala Leu Ala Arg Lys Ser Ala	
685 690 695 700	
ctt aaa acc aga ctc agt gat gcc gtt aag caa cta caa gca gca gag	2164
Leu Lys Thr Arg Leu Ser Asp Ala Val Lys Gln Leu Gln Ala Ala Glu	
705 710 715	
aga ggg gat gcc cag cag cgc ctg ggg cag tct aga ctg atc acc gag	2212
Arg Gly Asp Ala Gln Gln Arg Leu Gly Gln Ser Arg Leu Ile Thr Glu	
720 725 730	
gaa gcc aac agg acg acg atg gag gtg cag cag gcc act gcc ccc atg	2260
Glu Ala Asn Arg Thr Thr Met Glu Val Gln Gln Ala Thr Ala Pro Met	
735 740 745	
gcc aac aat cta acc aac tgg tca cag aat ctt caa cat ttt gac tct	2308

Ala Asn Asn Leu Thr Asn Trp Ser Gln Asn Leu Gln His Phe Asp Ser	
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tct gct tac aac act gca gtg aac tct gct agg gat gca gta aga aat	2356
Ser Ala Tyr Asn Thr Ala Val Asn Ser Ala Arg Asp Ala Val Arg Asn	
765 770 775 780	
ctg acc gag gtt gtc cct cag ctc ctg gat cag ctt cgt acg gtt gag	2404
Leu Thr Glu Val Val Pro Gln Leu Leu Asp Gln Leu Arg Thr Val Glu	
785 790 795	
cag aag cga cct gca agc aac gtt tct gcc agc atc cag agg atc cga	2452
Gln Lys Arg Pro Ala Ser Asn Val Ser Ala Ser Ile Gln Arg Ile Arg	
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Glu Leu Ile Ala Gln Thr Arg Ser Val Ala Ser Lys Ile Gln Val Ser	
815 820 825	
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Met Met Phe Asp Gly Gln Ser Ala Val Glu Val His Ser Arg Thr Ser	
830 835 840	
atg gat gac tta aag gcc ttc acg tct ctg agc ctg tac atg aaa ccc	2596
Met Asp Asp Leu Lys Ala Phe Thr Ser Leu Ser Leu Tyr Met Lys Pro	
845 850 855 860	
cct gtg aag cgg ccg gaa ctg acc gag act gca gat cag ttt atc ctg	2644
Pro Val Lys Arg Pro Glu Leu Thr Glu Thr Ala Asp Gln Phe Ile Leu	
865 870 875	
tac ctc gga agc aaa aac gcc aaa aaa gag tat atg ggt ctt gca atc	2692
Tyr Leu Gly Ser Lys Asn Ala Lys Lys Glu Tyr Met Gly Leu Ala Ile	
880 885 890	
aaa aat gat aat ctg gta tac gtc tat aat ttg gga act aaa gat gtg	2740
Lys Asn Asp Asn Leu Val Tyr Val Tyr Asn Leu Gly Thr Lys Asp Val	
895 900 905	
gag att ccc ctg gac tcc aag ccc gtc agt tcc tgg cct gct tac ttc	2788
Glu Ile Pro Leu Asp Ser Lys Pro Val Ser Ser Trp Pro Ala Tyr Phe	
910 915 920	
agc att gtc aag att gaa agg gtg gga aaa cat gga aag gtg ttt tta	2836
Ser Ile Val Lys Ile Glu Arg Val Gly Lys His Gly Lys Val Phe Leu	
925 930 935 940	
aca gtc ccg agt cta agt agc aca gca gag gaa aag ttc att aaa aag	2884
Thr Val Pro Ser Leu Ser Ser Thr Ala Glu Glu Lys Phe Ile Lys Lys	
945 950 955	
ggg gaa ttt tcg gga gat gac tct ctg ctg gac ctg gac cct gag gac	2932
Gly Glu Phe Ser Gly Asp Asp Ser Leu Leu Asp Leu Asp Pro Glu Asp	
960 965 970	
aca gtg ttt tat gtt ggt gga gtg cct tcc aac ttc aag ctc cct acc	2980
Thr Val Phe Tyr Val Gly Gly Val Pro Ser Asn Phe Lys Leu Pro Thr	
975 980 985	
agc tta aac ctg cct ggc ttt gtt ggc tgc ctg gaa ctg gcc act ttg	3028
Ser Leu Asn Leu Pro Gly Phe Val Gly Cys Leu Glu Leu Ala Thr Leu	

990	995	1000	
aat aat gat gtg atc agc ttg tac aac ttt aag cac atc tat aat atg			3076
Asn Asn Asp Val Ile Ser Leu Tyr Asn Phe Lys His Ile Tyr Asn Met			
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gac ccc tcc aca tca gtg cca tgt gcc cga gat aag ctg gcc ttc act			3124
Asp Pro Ser Thr Ser Val Pro Cys Ala Arg Asp Lys Leu Ala Phe Thr			
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cag agt cgg gct gcc agt tac ttc ttc gat ggc tcc ggt tat gcc gtg			3172
Gln Ser Arg Ala Ala Ser Tyr Phe Phe Asp Gly Ser Gly Tyr Ala Val			
	1040	1045	1050
gtg aga gac ata cca agg aga ggg aaa ttt ggt cag gtg act cgc ttt			3220
Val Arg Asp Ile Pro Arg Arg Gly Lys Phe Gly Gln Val Thr Arg Phe			
	1055	1060	1065
gac ata gaa gtt cga aca cca gct gac aac ggc ctt att ctc ctg atg			3268
Asp Ile Glu Val Arg Thr Pro Ala Asp Asn Gly Leu Ile Leu Leu Met			
	1070	1075	1080
gtc aat gga agt atg ttt ttc aga ctg gaa atg cgc aat ggt tac cta			3316
Val Asn Gly Ser Met Phe Phe Arg Leu Glu Met Arg Asn Gly Tyr Leu			
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cat gtg ttc tat gat ttt gga ttc agc agt ggc cgt gtg cat ctt gaa			3364
His Val Phe Tyr Asp Phe Gly Phe Ser Ser Gly Arg Val His Leu Glu			
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gat acg tta aag aaa gct caa att aat gat gca aaa tac cat gag atc			3412
Asp Thr Leu Lys Lys Ala Gln Ile Asn Asp Ala Lys Tyr His Glu Ile			
	1120	1125	1130
tca atc att tac cac aat gat aag aaa atg atc ttg gta gtt gac aga			3460
Ser Ile Ile Tyr His Asn Asp Lys Lys Met Ile Leu Val Val Asp Arg			
	1135	1140	1145
agg cat gtc aag agc atg gat aat gaa aag atg aaa ata cct ttt aca			3508
Arg His Val Lys Ser Met Asp Asn Glu Lys Met Lys Ile Pro Phe Thr			
	1150	1155	1160
gat ata tac att gga gga gct cct cca gaa atc tta caa tcc agg gcc			3556
Asp Ile Tyr Ile Gly Gly Ala Pro Pro Glu Ile Leu Gln Ser Arg Ala			
	1165	1170	1175
ctc aga gca cac ctt ccc cta gat atc aac ttc aga gga tgc atg aag			3604
Leu Arg Ala His Leu Pro Leu Asp Ile Asn Phe Arg Gly Cys Met Lys			
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ggc ttc cag ttc caa aag aag gac ttc aat tta ctg gag cag aca gaa			3652
Gly Phe Gln Phe Gln Lys Lys Asp Phe Asn Leu Leu Glu Gln Thr Glu			
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acc ctg gga gtt ggt tat gga tgc cca gaa gac tca ctt ata tct cgc			3700
Thr Leu Gly Val Gly Tyr Gly Cys Pro Glu Asp Ser Leu Ile Ser Arg			
	1215	1220	1225
aga gca tat ttc aat gga cag agc ttc att gct tca att cag aaa ata			3748
Arg Ala Tyr Phe Asn Gly Gln Ser Phe Ile Ala Ser Ile Gln Lys Ile			
	1230	1235	1240

tct ttc ttt gat ggc ttt gaa gga ggt ttt aat ttc cga aca tta caa	3796
Ser Phe Phe Asp Gly Phe Glu Gly Gly Phe Asn Phe Arg Thr Leu Gln	
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cca aat ggg tta cta ttc tat tat gct tca ggg tca gac gtg ttc tcc	3844
Pro Asn Gly Leu Leu Phe Tyr Tyr Ala Ser Gly Ser Asp Val Phe Ser	
1265 1270 1275	
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Ile Ser Leu Asp Asn Gly Thr Val Ile Met Asp Val Lys Gly Ile Lys	
1280 1285 1290	
gtt cag tca gta gat aag cag tac aat gat ggg ctg tcc cac ttc gtc	3940
Val Gln Ser Val Asp Lys Gln Tyr Asn Asp Gly Leu Ser His Phe Val	
1295 1300 1305	
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Ile Ser Ser Val Ser Pro Thr Arg Tyr Glu Leu Ile Val Asp Lys Ser	
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Arg Val Gly Ser Lys Asn Pro Thr Lys Gly Lys Ile Glu Gln Thr Gln	
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Ala Ser Glu Lys Lys Phe Tyr Phe Gly Gly Ser Pro Ile Ser Ala Gln	
1345 1350 1355	
tat gct aat ttc act ggc tgc ata agt aat gcc tac ttt acc agg gtg	4132
Tyr Ala Asn Phe Thr Gly Cys Ile Ser Asn Ala Tyr Phe Thr Arg Val	
1360 1365 1370	
gat aga gat gtg gag gtt gaa gat ttc caa cgg tat act gaa aag gtc	4180
Asp Arg Asp Val Glu Val Glu Asp Phe Gln Arg Tyr Thr Glu Lys Val	
1375 1380 1385	
cac act tct ctt tat gag tgt ccc att gag tct tca cca ttg ttt ctc	4228
His Thr Ser Leu Tyr Glu Cys Pro Ile Glu Ser Ser Pro Leu Phe Leu	
1390 1395 1400	
ctc cat aaa aaa gga aaa aat tta tcc aag cct aaa gca agt cag aat	4276
Leu His Lys Lys Gly Lys Asn Leu Ser Lys Pro Lys Ala Ser Gln Asn	
1405 1410 1415 1420	
aaa aag gga ggg aaa agt aaa gat gca cct tca tgg gat cct gtt gct	4324
Lys Lys Gly Gly Lys Ser Lys Asp Ala Pro Ser Trp Asp Pro Val Ala	
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ctg aaa ctc cca gag cgg aat act cca aga aac tct cat tgc cac ctt	4372
Leu Lys Leu Pro Glu Arg Asn Thr Pro Arg Asn Ser His Cys His Leu	
1440 1445 1450	
tcc aac agc cct aga gca ata gag cac gcc tat caa tat gga gga aca	4420
Ser Asn Ser Pro Arg Ala Ile Glu His Ala Tyr Gln Tyr Gly Gly Thr	
1455 1460 1465	
gcc aac agc cgc caa gag ttt gaa cac tta aaa gga gat ttt ggt gcc	4468
Ala Asn Ser Arg Gln Glu Phe Glu His Leu Lys Gly Asp Phe Gly Ala	
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His Arg Ile Thr Val Ile Arg Asp Ser Asn Val Val Gln Leu Asp Val
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 Asp Ser Glu Val Asn His Val Val Gly Pro Leu Asn Pro Lys Pro Ile
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 Asp His Arg Glu Pro Val Phe Val Gly Gly Val Pro Glu Ser Leu Leu
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 Thr Pro Arg Leu Ala Pro Ser Lys Pro Phe Thr Gly Cys Ile Arg His
 1775 1780 1785
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 Phe Val Ile Asp Gly His Pro Val Ser Phe Ser Lys Ala Ala Leu Val
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 Pro Phe Asp Ile Glu Gly Ser Ser Ala Val Gly Arg Gln Asp Pro Pro
 35 40 45
 Glu Thr Ser Glu Pro Arg Val Ala Leu Gly Arg Leu Pro Pro Ala Ala
 50 55 60
 Glu Lys Cys Asn Ala Gly Phe Phe His Thr Leu Ser Gly Glu Cys Val
 65 70 75 80
 Pro Cys Asp Cys Asn Gly Asn Ser Asn Glu Cys Leu Asp Gly Ser Gly
 85 90 95
 Tyr Cys Val His Cys Gln Arg Asn Thr Thr Gly Glu His Cys Glu Lys
 100 105 110
 Cys Leu Asp Gly Tyr Ile Gly Asp Ser Ile Arg Gly Ala Pro Gln Phe
 115 120 125
 Cys Gln Pro Cys Pro Cys Pro Leu Pro His Leu Ala Asn Phe Pro Glu
 130 135 140
 Ser Cys Tyr Arg Lys Asn Gly Ala Val Arg Cys Ile Cys Asn Glu Asn

His Arg Ile Thr Val Ile Arg Asp Ser Asn Val Val Gln Leu Asp Val
 1725 1730 1735 1740

gac tct gaa gtg aac cat gtg gtt gga ccc ctg aat cca aaa cca att 5284
 Asp Ser Glu Val Asn His Val Val Gly Pro Leu Asn Pro Lys Pro Ile
 1745 1750 1755

gat cac agg gag cct gtg ttt gtt gga ggt gtt cca gaa tct cta ctg 5332
 Asp His Arg Glu Pro Val Phe Val Gly Gly Val Pro Glu Ser Leu Leu
 1760 1765 1770

aca cca cgc ttg gcc ccc agc aaa ccc ttc aca ggc tgc ata cgc cac 5380
 Thr Pro Arg Leu Ala Pro Ser Lys Pro Phe Thr Gly Cys Ile Arg His
 1775 1780 1785

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 Phe Val Ile Asp Gly His Pro Val Ser Phe Ser Lys Ala Ala Leu Val
 1790 1795 1800

agc ggc gcc gta agc atc aac tcc tgt cca gca gcc gac tac aag gac 5476
 Ser Gly Ala Val Ser Ile Asn Ser Cys Pro Ala Ala Asp Tyr Lys Asp
 1805 1810 1815 1820

gac gatgac aag taagcttggc 5498
 Asp Asp Asp Lys

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Pro Phe Asp Ile Glu Gly Ser Ser Ala Val Gly Arg Gln Asp Pro Pro
 35 40 45

Glu Thr Ser Glu Pro Arg Val Ala Leu Gly Arg Leu Pro Pro Ala Ala
 50 55 60

Glu Lys Cys Asn Ala Gly Phe Phe His Thr Leu Ser Gly Glu Cys Val
 65 70 75 80

Pro Cys Asp Cys Asn Gly Asn Ser Asn Glu Cys Leu Asp Gly Ser Gly
 85 90 95

Tyr Cys Val His Cys Gln Arg Asn Thr Thr Gly Glu His Cys Glu Lys
 100 105 110

Cys Leu Asp Gly Tyr Ile Gly Asp Ser Ile Arg Gly Ala Pro Gln Phe
 115 120 125

Cys Gln Pro Cys Pro Cys Pro Leu Pro His Leu Ala Asn Phe Pro Glu
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Ser Cys Tyr Arg Lys Asn Gly Ala Val Arg Cys Ile Cys Asn Glu Asn

145		150		155		160
Tyr Ala Gly Pro	Asn Cys Glu Arg Cys	Ala Pro Gly Tyr Tyr	Gly Asn			
	165	170	175			
Pro Phe Leu Ile	Gly Ser Thr Cys Lys	Lys Cys Asp Cys	Ser Gly Asn			
	180	185	190			
Ser Asp Pro Asn	Leu Ile Phe Glu Asp Cys	Asp Glu Val Thr	Gly Gln			
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Cys Arg Asn Cys	Leu Arg Asn Thr Thr	Gly Phe Lys Cys	Glu Arg Cys			
	210	215	220			
Ala Pro Gly Tyr	Tyr Gly Asp Ala Arg	Ile Ala Lys Asn	Cys Ala Val			
	225	230	235			240
Cys Asn Cys Gly	Gly Gly Pro Cys Asp	Ser Val Thr Gly	Glu Cys Leu			
	245	250	255			
Glu Glu Gly Phe	Glu Pro Pro Thr	Gly Cys Asp Lys	Cys Val Trp	Asp		
	260	265	270			
Leu Thr Asp Asp	Leu Arg Leu Ala	Ala Leu Ser Ile	Glu Glu Gly	Lys		
	275	280	285			
Ser Gly Val Leu	Ser Val Ser Ser	Gly Ala Ala	Ala His Arg	His Val		
	290	295	300			
Asn Glu Ile Asn	Ala Thr Ile Tyr	Leu Leu Lys Thr	Lys Leu Ser	Glu		
	305	310	315			320
Arg Glu Asn Gln	Tyr Ala Leu Arg	Lys Ile Gln Ile	Asn Asn Ala	Glu		
	325	330	335			
Asn Thr Met Lys	Ser Leu Leu Ser	Asp Val Glu Glu	Leu Val Glu	Lys		
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Glu Asn Gln Ala	Ser Arg Lys Gly	Gln Leu Val Gln	Lys Glu Ser	Met		
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Asp Thr Ile Asn	His Ala Ser Gln	Leu Val Glu Gln	Ala His Asp	Met		
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Arg Asp Lys Ile	Gln Glu Ile Asn	Asn Lys Met Leu	Tyr Tyr Gly	Glu		
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Glu His Glu Leu	Ser Pro Lys Glu	Ile Ser Glu Lys	Leu Val Leu	Ala		
	405	410	415			
Gln Lys Met Leu	Glu Glu Ile Arg	Ser Arg Gln Pro	Phe Phe Thr	Gln		
	420	425	430			
Arg Glu Leu Val	Asp Glu Glu Ala	Asp Glu Ala Tyr	Glu Leu Leu	Ser		
	435	440	445			
Gln Ala Glu Ser	Trp Gln Arg Leu	His Asn Glu Thr	Arg Thr Leu	Phe		
	450	455	460			
Pro Val Val Leu	Glu Gln Leu Asp	Asp Tyr Asn Ala	Lys Leu Ser	Asp		
	465	470	475			480

Leu Gln Glu Ala Leu Asp Gln Ala Leu Asn Tyr Val Arg Asp Ala Glu
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Asp Met Asn Arg Ala Thr Ala Ala Arg Gln Arg Asp His Glu Lys Gln
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Gln Glu Arg Val Arg Glu Gln Met Glu Val Val Asn Met Ser Leu Ser
 515 520 525

Thr Ser Ala Asp Ser Leu Thr Thr Pro Arg Leu Thr Leu Ser Glu Leu
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Asp Asp Ile Ile Lys Asn Ala Ser Gly Ile Tyr Ala Glu Ile Asp Gly
 545 550 555 560

Ala Lys Ser Glu Leu Gln Val Lys Leu Ser Asn Leu Ser Asn Leu Ser
 565 570 575

His Asp Leu Val Gln Glu Ala Ile Asp His Ala Gln Asp Leu Gln Gln
 580 585 590

Glu Ala Asn Glu Leu Ser Arg Lys Leu His Ser Ser Asp Met Asn Gly
 595 600 605

Leu Val Gln Lys Ala Leu Asp Ala Ser Asn Val Tyr Glu Asn Ile Val
 610 615 620

Asn Tyr Val Ser Glu Ala Asn Glu Thr Ala Glu Phe Ala Leu Asn Thr
 625 630 635 640

Thr Asp Arg Ile Tyr Asp Ala Val Ser Gly Ile Asp Thr Gln Ile Ile
 645 650 655

Tyr His Lys Asp Glu Ser Glu Asn Leu Leu Asn Gln Ala Arg Glu Leu
 660 665 670

Gln Ala Lys Ala Glu Ser Ser Ser Asp Glu Ala Val Ala Asp Thr Ser
 675 680 685

Arg Arg Val Gly Gly Ala Leu Ala Arg Lys Ser Ala Leu Lys Thr Arg
 690 695 700

Leu Ser Asp Ala Val Lys Gln Leu Gln Ala Ala Glu Arg Gly Asp Ala
 705 710 715 720

Gln Gln Arg Leu Gly Gln Ser Arg Leu Ile Thr Glu Glu Ala Asn Arg
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Thr Thr Met Glu Val Gln Gln Ala Thr Ala Pro Met Ala Asn Asn Leu
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Thr Asn Trp Ser Gln Asn Leu Gln His Phe Asp Ser Ser Ala Tyr Asn
 755 760 765

Thr Ala Val Asn Ser Ala Arg Asp Ala Val Arg Asn Leu Thr Glu Val
 770 775 780

Val Pro Gln Leu Leu Asp Gln Leu Arg Thr Val Glu Gln Lys Arg Pro
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Ala Ser Asn Val Ser Ala Ser Ile Gln Arg Ile Arg Glu Leu Ile Ala
 805 810 815
 Gln Thr Arg Ser Val Ala Ser Lys Ile Gln Val Ser Met Met Phe Asp
 820 825 830
 Gly Gln Ser Ala Val Glu Val His Ser Arg Thr Ser Met Asp Asp Leu
 835 840 845
 Lys Ala Phe Thr Ser Leu Ser Leu Tyr Met Lys Pro Pro Val Lys Arg
 850 855 860
 Pro Glu Leu Thr Glu Thr Ala Asp Gln Phe Ile Leu Tyr Leu Gly Ser
 865 870 875 880
 Lys Asn Ala Lys Lys Glu Tyr Met Gly Leu Ala Ile Lys Asn Asp Asn
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 Leu Val Tyr Val Tyr Asn Leu Gly Thr Lys Asp Val Glu Ile Pro Leu
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 Asp Ser Lys Pro Val Ser Ser Trp Pro Ala Tyr Phe Ser Ile Val Lys
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 Ile Glu Arg Val Gly Lys His Gly Lys Val Phe Leu Thr Val Pro Ser
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 Gly Asp Asp Ser Leu Leu Asp Leu Asp Pro Glu Asp Thr Val Phe Tyr
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 Val Gly Gly Val Pro Ser Asn Phe Lys Leu Pro Thr Ser Leu Asn Leu
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 Pro Gly Phe Val Gly Cys Leu Glu Leu Ala Thr Leu Asn Asn Asp Val
 995 1000 1005
 Ile Ser Leu Tyr Asn Phe Lys His Ile Tyr Asn Met Asp Pro Ser Thr
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gat Asp	tgt Cys	gat Asp	gaa Glu	gtc Val	act Thr	ggc Gly	cag Gln	tgt Cys	agg Arg	aat Asn	tgc Cys	tta Leu	cgc Arg	aac Asn	acc Thr	576
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Ser Gly Ile Asp Thr Gln Ile Ile Tyr His Lys Asp Glu Ser Glu Asn				
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Ala Val Arg Asn Leu Thr Glu Val Val Pro Gln Leu Leu Asp Gln Leu	
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Ser Arg Thr Ser Met Asp Asp Leu Lys Ala Phe Thr Ser Leu Ser Leu	
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Tyr Met Lys Pro Pro Val Lys Arg Pro Glu Leu Thr Glu Thr Ala Asp	
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gct acc tgg aaa atc aag ggt ccc att tat ttg gga ggt gtg gct cct			4704
Ala Thr Trp Lys Ile Lys Gly Pro Ile Tyr Leu Gly Gly Val Ala Pro			
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Gly Lys Ala Val Lys Asn Val Gln Ile Asn Ser Ile Tyr Ser Phe Ser			
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ggc tgt ctc agc aat ctc cag ctc aat ggg gcc tcc atc acc tct gct			4800
Gly Cys Leu Ser Asn Leu Gln Leu Asn Gly Ala Ser Ile Thr Ser Ala			
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tct cag aca ttc agt gtg acc cct tgc ttt gaa ggc ccc atg gaa aca			4848
Ser Gln Thr Phe Ser Val Thr Pro Cys Phe Glu Gly Pro Met Glu Thr			
1605	1610	1615	

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 Gly Thr Tyr Phe Ser Thr Glu Gly Gly Tyr Val Val Leu Asp Glu Ser
 1620 1625 1630

ttc aat att gga ttg aag ttt gaa att gca ttt gaa gtc cgt ccc aga 4944
 Phe Asn Ile Gly Leu Lys Phe Glu Ile Ala Phe Glu Val Arg Pro Arg
 1635 1640 1645

agc agt tcc gga acc ctg gtc cac ggc cac agt gtc aat ggg gag tac 4992
 Ser Ser Ser Gly Thr Leu Val His Gly His Ser Val Asn Gly Glu Tyr
 1650 1655 1660

cta aat gtt cac atg aaa aat gga cag gtc ata gtg aaa gtc aat aat 5040
 Leu Asn Val His Met Lys Asn Gly Gln Val Ile Val Lys Val Asn Asn
 1665 1670 1675 1680

ggc atc aga gat ttt tcc acc tca gta aca ccc aag cag agt ctc tgt 5088
 Gly Ile Arg Asp Phe Ser Thr Ser Val Thr Pro Lys Gln Ser Leu Cys
 1685 1690 1695

gat ggc aga tgg cac aga att aca gtt att aga gat tct aat gtg gtt 5136
 Asp Gly Arg Trp His Arg Ile Thr Val Ile Arg Asp Ser Asn Val Val
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cag ttg gat gtg gac tct gaa gtg aac cat gtg gtt gga ccc ctg aat 5184
 Gln Leu Asp Val Asp Ser Glu Val Asn His Val Val Gly Pro Leu Asn
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cca aaa cca att gat cac agg gag cct gtg ttt gtt gga ggt gtt cca 5232
 Pro Lys Pro Ile Asp His Arg Glu Pro Val Phe Val Gly Gly Val Pro
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gaa tct cta ctg aca cca cgc ttg gcc ccc agc aaa ccc ttc aca ggc 5280
 Glu Ser Leu Leu Thr Pro Arg Leu Ala Pro Ser Lys Pro Phe Thr Gly
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tgc ata cgc cac ttt gtg att gat gga cac cca gtg agc ttc agt aaa 5328
 Cys Ile Arg His Phe Val Ile Asp Gly His Pro Val Ser Phe Ser Lys
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gca gcc ctg gtc agc ggc gcc gta agc atc aac tcc tgt cca gca gcc 5376
 Ala Ala Leu Val Ser Gly Ala Val Ser Ile Asn Ser Cys Pro Ala Ala
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 Asp Tyr Lys Asp Asp Asp Asp Lys
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 <212> PRT
 <213> Homo sapiens

<400> 8
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 20 25 30

Leu Gly Arg Leu Pro Pro Ala Ala Glu Lys Cys Asn Ala Gly Phe Phe
 35 40 45

His Thr Leu Ser Gly Glu Cys Val Pro Cys Asp Cys Asn Gly Asn Ser
 50 55 60

Asn Glu Cys Leu Asp Gly Ser Gly Tyr Cys Val His Cys Gln Arg Asn
 65 70 75 80

Thr Thr Gly Glu His Cys Glu Lys Cys Leu Asp Gly Tyr Ile Gly Asp
 85 90 95

Ser Ile Arg Gly Ala Pro Gln Phe Cys Gln Pro Cys Pro Cys Pro Leu
 100 105 110

Pro His Leu Ala Asn Phe Pro Glu Ser Cys Tyr Arg Lys Asn Gly Ala
 115 120 125

Val Arg Cys Ile Cys Asn Glu Asn Tyr Ala Gly Pro Asn Cys Glu Arg
 130 135 140

Cys Ala Pro Gly Tyr Tyr Gly Asn Pro Phe Leu Ile Gly Ser Thr Cys
 145 150 155 160

Lys Lys Cys Asp Cys Ser Gly Asn Ser Asp Pro Asn Leu Ile Phe Glu
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Asp Cys Asp Glu Val Thr Gly Gln Cys Arg Asn Cys Leu Arg Asn Thr
 180 185 190

Thr Gly Phe Lys Cys Glu Arg Cys Ala Pro Gly Tyr Tyr Gly Asp Ala
 195 200 205

Arg Ile Ala Lys Asn Cys Ala Val Cys Asn Cys Gly Gly Gly Pro Cys
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Asp Ser Val Thr Gly Glu Cys Leu Glu Glu Gly Phe Glu Pro Pro Thr
 225 230 235 240

Gly Cys Asp Lys Cys Val Trp Asp Leu Thr Asp Asp Leu Arg Leu Ala
 245 250 255

Ala Leu Ser Ile Glu Glu Gly Lys Ser Gly Val Leu Ser Val Ser Ser
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Gly Ala Ala Ala His Arg His Val Asn Glu Ile Asn Ala Thr Ile Tyr
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Leu Leu Lys Thr Lys Leu Ser Glu Arg Glu Asn Gln Tyr Ala Leu Arg
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Lys Ile Gln Ile Asn Asn Ala Glu Asn Thr Met Lys Ser Leu Leu Ser
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Asp Val Glu Glu Leu Val Glu Lys Glu Asn Gln Ala Ser Arg Lys Gly
 325 330 335

Gln Leu Val Gln Lys Glu Ser Met Asp Thr Ile Asn His Ala Ser Gln
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Leu Val Glu Gln Ala His Asp Met Arg Asp Lys Ile Gln Glu Ile Asn
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 Asn Lys Met Leu Tyr Tyr Gly Glu Glu His Glu Leu Ser Pro Lys Glu
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 Ser Arg Gln Pro Phe Phe Thr Gln Arg Glu Leu Val Asp Glu Glu Ala
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 His Asn Glu Thr Arg Thr Leu Phe Pro Val Val Leu Glu Gln Leu Asp
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 Asp Tyr Asn Ala Lys Leu Ser Asp Leu Gln Glu Ala Leu Asp Gln Ala
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 Leu Asn Tyr Val Arg Asp Ala Glu Asp Met Asn Arg Ala Thr Ala Ala
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 Arg Gln Arg Asp His Glu Lys Gln Gln Glu Arg Val Arg Glu Gln Met
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 Glu Val Val Asn Met Ser Leu Ser Thr Ser Ala Asp Ser Leu Thr Thr
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 Pro Arg Leu Thr Leu Ser Glu Leu Asp Asp Ile Ile Lys Asn Ala Ser
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 Gly Ile Tyr Ala Glu Ile Asp Gly Ala Lys Ser Glu Leu Gln Val Lys
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 Leu His Ser Ser Asp Met Asn Gly Leu Val Gln Lys Ala Leu Asp Ala
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 Ser Asn Val Tyr Glu Asn Ile Val Asn Tyr Val Ser Glu Ala Asn Glu
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 Thr Ala Glu Phe Ala Leu Asn Thr Thr Asp Arg Ile Tyr Asp Ala Val
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 Ser Gly Ile Asp Thr Gln Ile Ile Tyr His Lys Asp Glu Ser Glu Asn
 625 630 635 640
 Leu Leu Asn Gln Ala Arg Glu Leu Gln Ala Lys Ala Glu Ser Ser Ser
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 Asp Glu Ala Val Ala Asp Thr Ser Arg Arg Val Gly Gly Ala Leu Ala
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 Arg Lys Ser Ala Leu Lys Thr Arg Leu Ser Asp Ala Val Lys Gln Leu

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690					695					700					
Leu	Ile	Thr	Glu	Glu	Ala	Asn	Arg	Thr	Thr	Met	Glu	Val	Gln	Gln	Ala
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Thr	Ala	Pro	Met	Ala	Asn	Asn	Leu	Thr	Asn	Trp	Ser	Gln	Asn	Leu	Gln
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His	Phe	Asp	Ser	Ser	Ala	Tyr	Asn	Thr	Ala	Val	Asn	Ser	Ala	Arg	Asp
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Gln	Arg	Ile	Arg	Glu	Leu	Ile	Ala	Gln	Thr	Arg	Ser	Val	Ala	Ser	Lys
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Ile	Gln	Val	Ser	Met	Met	Phe	Asp	Gly	Gln	Ser	Ala	Val	Glu	Val	His
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Ser	Arg	Thr	Ser	Met	Asp	Asp	Leu	Lys	Ala	Phe	Thr	Ser	Leu	Ser	Leu
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Tyr	Met	Lys	Pro	Pro	Val	Lys	Arg	Pro	Glu	Leu	Thr	Glu	Thr	Ala	Asp
		835					840					845			
Gln	Phe	Ile	Leu	Tyr	Leu	Gly	Ser	Lys	Asn	Ala	Lys	Lys	Glu	Tyr	Met
	850					855					860				
Gly	Leu	Ala	Ile	Lys	Asn	Asp	Asn	Leu	Val	Tyr	Val	Tyr	Asn	Leu	Gly
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Thr	Lys	Asp	Val	Glu	Ile	Pro	Leu	Asp	Ser	Lys	Pro	Val	Ser	Ser	Trp
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Pro	Ala	Tyr	Phe	Ser	Ile	Val	Lys	Ile	Glu	Arg	Val	Gly	Lys	His	Gly
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Lys	Val	Phe	Leu	Thr	Val	Pro	Ser	Leu	Ser	Ser	Thr	Ala	Glu	Glu	Lys
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Phe	Ile	Lys	Lys	Gly	Glu	Phe	Ser	Gly	Asp	Asp	Ser	Leu	Leu	Asp	Leu
	930					935					940				
Asp	Pro	Glu	Asp	Thr	Val	Phe	Tyr	Val	Gly	Gly	Val	Pro	Ser	Asn	Phe
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Ile	Tyr	Asn	Met	Asp	Pro	Ser	Thr	Ser	Val	Pro	Cys	Ala	Arg	Asp	Lys
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 Asn Gly Tyr Leu His Val Phe Tyr Asp Phe Gly Phe Ser Ser Gly Arg
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 Val His Leu Glu Asp Thr Leu Lys Lys Ala Gln Ile Asn Asp Ala Lys
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 Tyr His Glu Ile Ser Ile Ile Tyr His Asn Asp Lys Lys Met Ile Leu
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 Leu Ile Ser Arg Arg Ala Tyr Phe Asn Gly Gln Ser Phe Ile Ala Ser
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 Lys Gly Ile Lys Val Gln Ser Val Asp Lys Gln Tyr Asn Asp Gly Leu
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 Ser His Phe Val Ile Ser Ser Val Ser Pro Thr Arg Tyr Glu Leu Ile
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 Val Asp Lys Ser Arg Val Gly Ser Lys Asn Pro Thr Lys Gly Lys Ile
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 Phe Thr Arg Val Asp Arg Asp Val Glu Val Glu Asp Phe Gln Arg Tyr
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 Thr Glu Lys Val His Thr Ser Leu Tyr Glu Cys Pro Ile Glu Ser Ser
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 Asp Pro Val Ala Leu Lys Leu Pro Glu Arg Asn Thr Pro Arg Asn Ser
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 His Cys His Leu Ser Asn Ser Pro Arg Ala Ile Glu His Ala Tyr Gln
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 Tyr Gly Gly Thr Ala Asn Ser Arg Gln Glu Phe Glu His Leu Lys Gly
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 Asp Phe Gly Ala Lys Ser Gln Phe Ser Ile Arg Leu Arg Thr Arg Ser
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 Ser His Gly Met Ile Phe Tyr Val Ser Asp Gln Glu Glu Asn Asp Phe
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 Met Thr Leu Phe Leu Ala His Gly Arg Leu Val Tyr Met Phe Asn Val
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 Gly His Lys Lys Leu Lys Ile Arg Ser Gln Glu Lys Tyr Asn Asp Gly
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 Val Ile Asp Gly Leu Arg Val Leu Glu Glu Ser Leu Pro Pro Thr Glu
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 Ala Thr Trp Lys Ile Lys Gly Pro Ile Tyr Leu Gly Gly Val Ala Pro
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 Gly Thr Tyr Phe Ser Thr Glu Gly Gly Tyr Val Val Leu Asp Glu Ser
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 Phe Asn Ile Gly Leu Lys Phe Glu Ile Ala Phe Glu Val Arg Pro Arg
 1635 1640 1645
 Ser Ser Ser Gly Thr Leu Val His Gly His Ser Val Asn Gly Glu Tyr

55

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Val Val Gly Arg Gln Asp Pro Ser Glu Thr Ser Asp Ser Gly Val Thr	
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Leu Gly Arg Leu Pro Pro Ala Ala Glu Arg Cys Asp Ala Gly Phe Phe	
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Arg Thr Leu Ser Gly Glu Cys Ala Pro Cys Asp Cys Asn Gly Asn Ser	
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His Glu Cys Leu Asp Gly Ser Gly Phe Cys Leu His Cys Gln Arg Asn	
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Thr Thr Gly Glu His Cys Glu Lys Cys Leu Asp Gly Tyr Ile Gly Asp	
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Ser Ile Arg Gly Thr Pro Arg Phe Cys Gln Pro Cys Pro Cys Pro Leu	
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Pro His Leu Ala Asn Phe Ala Glu Ser Cys Tyr Arg Lys Asn Gly Ala	
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Val Arg Cys Ile Cys Lys Glu Asn Tyr Val Gly Pro Asn Cys Glu Arg	
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Cys Ala Pro Gly Tyr Tyr Glu Asn Pro Leu Leu Ile Gly Ser Thr Cys	
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Lys Lys Cys Asp Cys Ser Gly Asn Ser Asp Pro Asn Leu Ile Phe Glu	
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Asp Cys Asp Glu Ile Thr Gly Gln Cys Arg Asn Cys Leu Arg Asn Thr	
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Arg Thr Ala Lys Asn Cys Ala Val Cys Asn Cys Gly Gly Gly Pro Arg	
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Asp Ser Val Thr Gly Glu Cys Leu Glu Glu Gly Phe Glu Val Pro Thr	
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Ile Ala Glu Lys Leu Val Leu Ala Gln Lys Met Leu Glu Glu Ile Arg	
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Ser Arg Gln Pro Phe Leu Thr His Arg Glu Leu Val Asp Glu Glu Ala	
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Asp Glu Ala Gln Glu Leu Leu Ser Gln Ala Glu Asn Trp Gln Arg Leu	
445 450 455	
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His Asn Asp Thr Arg Ser Leu Phe Pro Val Val Leu Glu Gln Leu Asp	
460 465 470	
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Asp Tyr Asn Ala Lys Leu Ser Asp Leu Gln Glu Ser Ile Asn Gln Ala	
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Leu Asp His Val Arg Asp Ala Glu Asp Met Asn Arg Ala Ile Thr Phe	
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Lys Gln Arg Asp His Glu Lys Gln His Glu Arg Val Lys Glu Gln Met	
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Pro	Gln	Leu	Thr	Leu	Glu	Glu	Leu	Asp	Glu	Ile	Ile	Lys	Asn	Ala	Ser	
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Asp	Glu	Ala	Val	Ala	Asp	Thr	Ser	Arg	Arg	Val	Gly	Gly	Ala	Leu	Trp	
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Gln	Ala	Ala	Glu	Arg	Gly	Asp	Ala	His	Gln	Arg	Leu	Gly	Gln	Ser	Lys	
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ctc	ttc	att	gag	gaa	gct	aac	aag	acg	aca	gcg	gct	gtc	caa	cag	gtt	2440
Leu	Phe	Ile	Glu	Glu	Ala	Asn	Lys	Thr	Thr	Ala	Ala	Val	Gln	Gln	Val	
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Thr	Thr	Pro	Met	Ala	Asn	Asn	Leu	Ser	Asn	Trp	Ser	Gln	Asn	Leu	Gln	
745				750					755					760		
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Thr	Phe	Asp	Ser	Ser	Ala	Tyr	Asn	Thr	Ala	Val	Asp	Ser	Ala	Arg	Asp	

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Arg	Thr	Val	Glu	Gln	Lys	Arg	Pro	Ala	Ser	Asn	Ile	Ser	Ala	Ser	Ile														
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Gln	Ser	Ile	Arg	Glu	Leu	Ile	Ala	Gln	Thr	Arg	Ser	Val	Ala	Ser	Lys														
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Ile	Gln	Val	Ser	Met	Met	Phe	Asp	Gly	Gln	Ser	Ala	Val	Glu	Val	His														
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ccc	aaa	gtc	agt	gtg	gat	gac	ctg	aag	gcc	ttc	aca	tcc	atc	agc	ttg	2776													
Pro	Lys	Val	Ser	Val	Asp	Asp	Leu	Lys	Ala	Phe	Thr	Ser	Ile	Ser	Leu														
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Tyr	Met	Lys	Pro	Pro	Pro	Lys	Pro	Ala	Glu	Pro	Thr	Gly	Ala	Trp	Val														
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gca	gat	cag	ttt	gtc	ctc	tac	ctc	gga	agc	aaa	aac	gcc	aaa	aaa	gaa	2872													
Ala	Asp	Gln	Phe	Val	Leu	Tyr	Leu	Gly	Ser	Lys	Asn	Ala	Lys	Lys	Glu														
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Ser	Trp	Pro	Ala	Tyr	Phe	Ser	Ile	Val	Lys	Ile	Glu	Arg	Val	Gly	Glu														
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cac	gga	aag	gtg	ttc	ttg	aca	gtc	ccc	agt	ctc	agt	agc	aca	gca	gaa	3064													
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gaa	aag	ttt	att	aag	aag	ggg	gag	ttt	gca	gga	gat	gac	tcc	ttg	ctg	3112													
Glu	Lys	Phe	Ile	Lys	Lys	Gly	Glu	Phe	Ala	Gly	Asp	Asp	Ser	Leu	Leu														
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Asp	Val	Thr	Pro	Glu	Asp	Thr	Val	Phe	Tyr	Val	Gly	Gly	Val	Pro	Ala														
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Lys His Ile Tyr Asn Met Asp Pro Ser Lys Ser Val Pro Cys Ala Arg	
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Gly Ser Ser Tyr Ala Val Val Arg Asp Ile Thr Arg Arg Gly Lys Phe	
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Gly Gln Val Thr Arg Phe Asp Ile Glu Ile Arg Thr Pro Ala Asp Asn	
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Gly Leu Val Leu Leu Met Val Asn Gly Ser Met Phe Phe Ser Leu Glu	
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Met Arg Asn Gly Tyr Leu His Val Phe Tyr Asp Phe Gly Phe Ser Asn	
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Gly Pro Val His Leu Glu Asp Thr Leu Lys Lys Ala Gln Ile Asn Asp	
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Ala Lys Tyr His Glu Ile Ser Ile Ile Tyr His Asn Asp Lys Lys Met	
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Ile Leu Val Val Asp Arg Arg His Val Lys Ser Thr Asp Asn Glu Lys	
1145 1150 1155 1160	
aaa aag att cct ttc acg gac atc tac atc gga ggt gcg ccc caa gaa	3736
Lys Lys Ile Pro Phe Thr Asp Ile Tyr Ile Gly Gly Ala Pro Gln Glu	
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Val Leu Gln Ser Arg Thr Leu Arg Ala His Leu Pro Leu Asp Ile Asn	
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Phe Arg Gly Cys Met Lys Gly Phe Gln Phe Gln Lys Lys Asp Phe Asn	
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Asn Phe Arg Thr Leu Gln Pro Asn Gly Leu Leu Phe Tyr Tyr Thr Ser	
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Asp Val Lys Gly Ile Lys Val Met Ser Thr Asp Lys Gln Tyr His Asp	
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Gly Leu Pro His Phe Val Val Thr Ser Ile Ser Asp Thr Arg Tyr Glu	
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Leu Val Val Asp Lys Ser Arg Leu Arg Gly Lys Asn Pro Thr Lys Gly	
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Lys Ala Glu Gln Thr Gln Thr Thr Glu Lys Lys Phe Tyr Phe Gly Gly	
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Ser Pro Ile Ser Pro Gln Tyr Ala Asn Phe Thr Gly Cys Ile Ser Asn	
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Ala Tyr Phe Thr Arg Leu Asp Arg Asp Val Glu Val Glu Asp Phe Gln	
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Arg Tyr Ser Glu Lys Val His Thr Ser Leu Tyr Glu Cys Pro Ile Glu	
1385 1390 1395 1400	
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Ser Ser Pro Leu Phe Leu Leu His Lys Lys Gly Lys Asn Ser Ser Lys	
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Pro Lys Thr Asn Lys Gln Gly Glu Lys Ser Lys Asp Ala Pro Ser Trp	
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Asp Pro Ile Gly Leu Lys Phe Leu Glu Gln Lys Ala Pro Arg Asp Ser	
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His Cys His Leu Ser Ser Ser Pro Arg Ala Ile Glu His Ala Tyr Gln	
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tat ggc ggc acg gcc aac agt cgc cag gag ttt gaa cac gaa caa gga	4648
Tyr Gly Gly Thr Ala Asn Ser Arg Gln Glu Phe Glu His Glu Gln Gly	
1465 1470 1475 1480	
gat ttt ggt gaa aaa tcc cag ttt gcc att cgt ctg aag acc cgt tcc	4696
Asp Phe Gly Glu Lys Ser Gln Phe Ala Ile Arg Leu Lys Thr Arg Ser	
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Ser His Gly Met Ile Phe Tyr Val Ser Asp Gln Glu Glu Asn Asp Phe	
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Met Thr Leu Phe Leu Ala His Gly Arg Leu Val Phe Met Phe Asn Val	
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ggc cat aag aaa ctg aag att aga agc cag gag aaa tac aat gat gga	4840
Gly His Lys Lys Leu Lys Ile Arg Ser Gln Glu Lys Tyr Asn Asp Gly	
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Leu Trp His Asp Val Ile Phe Ile Arg Glu Lys Ser Ser Gly Arg Leu	
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Val Ile Asp Gly Leu Arg Val Leu Glu Glu Arg Leu Pro Pro Ser Gly	
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Ala Ala Trp Lys Ile Lys Gly Pro Ile Tyr Leu Gly Gly Val Ala Pro	
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Gly Arg Ala Val Lys Asn Val Gln Ile Thr Ser Val Tyr Ser Phe Ser	
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Gly Thr Tyr Phe Ser Thr Glu Gly Gly Tyr Val Val Leu Asp Glu Ser	
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Phe Asn Ile Gly Leu Lys Phe Glu Ile Ala Phe Glu Val Arg Pro Arg	
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Ser Ser Ser Gly Thr Leu Val His Gly His Ser Val Asn Gly Glu Tyr	
1675 1680 1685	
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Leu Asn Val His Met Arg Asn Gly Gln Val Ile Val Lys Val Asn Asn	
1690 1695 1700	
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Gly Val Arg Asp Phe Ser Thr Ser Val Thr Pro Lys Gln Asn Leu Cys	
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Asp Gly Arg Trp His Arg Ile Thr Val Ile Arg Asp Ser Asn Val Val	
1725 1730 1735	
cag ttg gat gta gac tca gaa gtg aac cat gta gtt ggg ccg ttg aat	5464
Gln Leu Asp Val Asp Ser Glu Val Asn His Val Val Gly Pro Leu Asn	

1740	1745	1750	
cca aag cca gtt gat cac agg gag cct gtg ttt gtt gga ggt gtt cca			5512
Pro Lys Pro Val Asp His Arg Glu Pro Val Phe Val Gly Gly Val Pro			
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gag tct tta ctg aca cca cgt ttg gct ccc agc aaa ccc ttc acc ggc			5560
Glu Ser Leu Leu Thr Pro Arg Leu Ala Pro Ser Lys Pro Phe Thr Gly			
1770	1775	1780	
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Cys Ile Arg His Phe Val Ile Asp Ser Arg Pro Val Ser Phe Ser Lys			
1785	1790	1795	1800
gct gcc ctg gtc agt ggt gct gtg agc atc aac tcc tgt ccc aca gcc			5656
Ala Ala Leu Val Ser Gly Ala Val Ser Ile Asn Ser Cys Pro Thr Ala			
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Trp Cys Ala Val Cys Ser Asn Ala Ala Ser Gly Asp Gly Asn Ala Phe			
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Pro Phe Asp Ile Glu Gly Ser Ala Val Val Gly Arg Gln Asp Pro Ser			
35	40	45	
Glu Thr Ser Asp Ser Gly Val Thr Leu Gly Arg Leu Pro Pro Ala Ala			
50	55	60	
Glu Arg Cys Asp Ala Gly Phe Phe Arg Thr Leu Ser Gly Glu Cys Ala			
65	70	75	80
Pro Cys Asp Cys Asn Gly Asn Ser His Glu Cys Leu Asp Gly Ser Gly			
85	90	95	
Phe Cys Leu His Cys Gln Arg Asn Thr Thr Gly Glu His Cys Glu Lys			
100	105	110	
Cys Leu Asp Gly Tyr Ile Gly Asp Ser Ile Arg Gly Thr Pro Arg Phe			
115	120	125	
Cys Gln Pro Cys Pro Cys Pro Leu Pro His Leu Ala Asn Phe Ala Glu			
130	135	140	
Ser Cys Tyr Arg Lys Asn Gly Ala Val Arg Cys Ile Cys Lys Glu Asn			
145	150	155	160

Tyr Val Gly Pro Asn Cys Glu Arg Cys Ala Pro Gly Tyr Tyr Gly Asn
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 Pro Leu Leu Ile Gly Ser Thr Cys Lys Lys Cys Asp Cys Ser Gly Asn
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 Ser Asp Pro Asn Leu Ile Phe Glu Asp Cys Asp Glu Ile Thr Gly Gln
 195 200 205
 Cys Arg Asn Cys Leu Arg Asn Thr Thr Gly Phe Lys Cys Glu Arg Cys
 210 215 220
 Ala Pro Gly Tyr Tyr Gly Asp Ala Arg Thr Ala Lys Asn Cys Ala Val
 225 230 235 240
 Cys Asn Cys Gly Gly Gly Pro Arg Asp Ser Val Thr Gly Glu Cys Leu
 245 250 255
 Glu Glu Gly Phe Glu Val Pro Thr Gly Cys Asp Lys Cys Val Trp Asp
 260 265 270
 Leu Thr Asp Asp Leu Arg Leu Ala Ala Leu Ser Ile Glu Glu Ser Lys
 275 280 285
 Ser Gly Leu Leu Ser Val Ser Ser Ala Ala Ala His Arg His Val
 290 295 300
 Thr Asp Met Asn Ser Thr Ile His Leu Leu Arg Thr Arg Leu Ser Glu
 305 310 315 320
 Arg Glu Asn Gln Tyr Thr Leu Arg Lys Ile Gln Ile Asn Asn Ser Glu
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 Asn Thr Leu Arg Ser Leu Leu Pro Asp Val Glu Gly Leu His Glu Lys
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 Arg Asp Lys Ile Gln Glu Ile Asn Ser Lys Met Leu Tyr Tyr Gly Glu
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 Arg Glu Leu Val Asp Glu Glu Ala Asp Glu Ala Gln Glu Leu Leu Ser
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 Pro Val Val Leu Glu Gln Leu Asp Asp Tyr Asn Ala Lys Leu Ser Asp
 465 470 475 480
 Leu Gln Glu Ser Ile Asn Gln Ala Leu Asp His Val Arg Asp Ala Glu

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His	Glu	Arg	Val	Lys	Glu	Gln	Met	Glu	Val	Val	Gly	Ala	Ser	Leu	Ser
		515					520					525			
Met	Ser	Ala	Asp	Ser	Leu	Thr	Ile	Pro	Gln	Leu	Thr	Leu	Glu	Glu	Leu
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Asp	Glu	Ile	Ile	Lys	Asn	Ala	Ser	Gly	Ile	Tyr	Ala	Glu	Ile	Asp	Gly
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Ala	Lys	Asn	Glu	Leu	Gln	Gly	Lys	Leu	Ser	Asn	Leu	Ser	Asn	Leu	Ser
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His	Asp	Leu	Val	Gln	Glu	Ala	Thr	Asp	His	Ala	Tyr	Asn	Leu	Gln	Gln
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Glu	Ala	Asp	Glu	Leu	Ser	Arg	Asn	Leu	His	Ser	Ser	Asp	Met	Asn	Gly
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Leu	Val	Gln	Lys	Ala	Leu	Asp	Ala	Ser	Asn	Val	Tyr	Glu	Asn	Ile	Ala
	610					615					620				
Asn	Tyr	Val	Ser	Glu	Ala	Asn	Glu	Thr	Ala	Glu	Leu	Ala	Leu	Asn	Ile
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Thr	Asp	Arg	Ile	Tyr	Asp	Ala	Val	Ser	Gly	Ile	Asp	Thr	Gln	Ile	Ile
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Tyr	His	Lys	Asp	Glu	Ser	Asp	Asn	Leu	Leu	Asn	Gln	Ala	Arg	Glu	Leu
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Gln	Ala	Lys	Ala	Asp	Ser	Cys	Asn	Asp	Glu	Ala	Val	Ala	Asp	Thr	Ser
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Arg	Arg	Val	Gly	Gly	Ala	Leu	Trp	Arg	Lys	Gly	Ala	Leu	Arg	Asp	Arg
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Leu	Asn	Asp	Ala	Val	Lys	Gln	Leu	Gln	Ala	Ala	Glu	Arg	Gly	Asp	Ala
705					710					715					720
His	Gln	Arg	Leu	Gly	Gln	Ser	Lys	Leu	Phe	Ile	Glu	Glu	Ala	Asn	Lys
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Thr	Thr	Ala	Ala	Val	Gln	Gln	Val	Thr	Thr	Pro	Met	Ala	Asn	Asn	Leu
		740						745					750		
Ser	Asn	Trp	Ser	Gln	Asn	Leu	Gln	Thr	Phe	Asp	Ser	Ser	Ala	Tyr	Asn
		755					760					765			
Thr	Ala	Val	Asp	Ser	Ala	Arg	Asp	Ala	Val	Arg	Asn	Leu	Thr	Glu	Val
		770				775					780				
Val	Pro	Gln	Leu	Leu	Asp	Gln	Leu	Arg	Thr	Val	Glu	Gln	Lys	Arg	Pro
785					790					795					800
Ala	Ser	Asn	Ile	Ser	Ala	Ser	Ile	Gln	Ser	Ile	Arg	Glu	Leu	Ile	Ala
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Gln Thr Arg Ser Val Ala Ser Lys Ile Gln Val Ser Met Met Phe Asp
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 Gly Gln Ser Ala Val Glu Val His Pro Lys Val Ser Val Asp Asp Leu
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 Lys Ala Phe Thr Ser Ile Ser Leu Tyr Met Lys Pro Pro Pro Lys Pro
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 Ala Glu Pro Thr Gly Ala Trp Val Ala Asp Gln Phe Val Leu Tyr Leu
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 Asp Asn Leu Val Tyr Val Tyr Asn Leu Gly Met Lys Asp Val Glu Ile
 900 905 910
 Leu Leu Asp Ser Lys Pro Val Ser Ser Trp Pro Ala Tyr Phe Ser Ile
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 Val Lys Ile Glu Arg Val Gly Glu His Gly Lys Val Phe Leu Thr Val
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 Pro Ser Leu Ser Ser Thr Ala Glu Glu Lys Phe Ile Lys Lys Gly Glu
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Ile Tyr His Asn Asp Lys Lys Met Ile Leu Val Val Asp Arg Arg His
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 Val Lys Ser Thr Asp Asn Glu Lys Lys Lys Ile Pro Phe Thr Asp Ile
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 Tyr Ile Gly Gly Ala Pro Gln Glu Val Leu Gln Ser Arg Thr Leu Arg
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 Ala His Leu Pro Leu Asp Ile Asn Phe Arg Gly Cys Met Lys Gly Phe
 185 1190 1195 1200
 Gln Phe Gln Lys Lys Asp Phe Asn Leu Leu Glu Gln Thr Glu Thr Leu
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 Tyr Phe Asn Gly Gln Ser Phe Ile Ala Ser Ile Gln Lys Ile Ser Phe
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1380 1385 1390	

cct aaa aca aac aaa cag gga gag aag agt aag gat gcg cct tca tgg 4224
 Pro Lys Thr Asn Lys Gln Gly Glu Lys Ser Lys Asp Ala Pro Ser Trp
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gat cct att ggc ctg aag ttt ctg gaa cag aaa gct cca aga gat tcc 4272
 Asp Pro Ile Gly Leu Lys Phe Leu Glu Gln Lys Ala Pro Arg Asp Ser
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 His Cys His Leu Ser Ser Ser Pro Arg Ala Ile Glu His Ala Tyr Gln
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 Tyr Gly Gly Thr Ala Asn Ser Arg Gln Glu Phe Glu His Glu Gln Gly
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gat ttt ggt gaa aaa tcc cag ttt gcc att cgt ctg aag acc cgt tcc 4416
 Asp Phe Gly Glu Lys Ser Gln Phe Ala Ile Arg Leu Lys Thr Arg Ser
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 Ser His Gly Met Ile Phe Tyr Val Ser Asp Gln Glu Glu Asn Asp Phe
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 Met Thr Leu Phe Leu Ala His Gly Arg Leu Val Phe Met Phe Asn Val
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 Gly His Lys Lys Leu Lys Ile Arg Ser Gln Glu Lys Tyr Asn Asp Gly
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 Val Ile Asp Gly Leu Arg Val Leu Glu Glu Arg Leu Pro Pro Ser Gly
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 Ala Ala Trp Lys Ile Lys Gly Pro Ile Tyr Leu Gly Gly Val Ala Pro
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 Ser Ser Ser Gly Thr Leu Val His Gly His Ser Val Asn Gly Glu Tyr
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 Glu Ser Leu Leu Thr Pro Arg Leu Ala Pro Ser Lys Pro Phe Thr Gly
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 Cys Ile Arg His Phe Val Ile Asp Ser Arg Pro Val Ser Phe Ser Lys
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 His Glu Cys Leu Asp Gly Ser Gly Phe Cys Leu His Cys Gln Arg Asn
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 Ser Ile Arg Gly Thr Pro Arg Phe Cys Gln Pro Cys Pro Cys Pro Leu
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 Pro His Leu Ala Asn Phe Ala Glu Ser Cys Tyr Arg Lys Asn Gly Ala
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 Cys Ala Pro Gly Tyr Tyr Gly Asn Pro Leu Leu Ile Gly Ser Thr Cys
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 Lys Lys Cys Asp Cys Ser Gly Asn Ser Asp Pro Asn Leu Ile Phe Glu
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 Arg Thr Ala Lys Asn Cys Ala Val Cys Asn Cys Gly Gly Gly Pro Arg
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 Asp Ser Val Thr Gly Glu Cys Leu Glu Glu Gly Phe Glu Val Pro Thr
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 Gly Cys Asp Lys Cys Val Trp Asp Leu Thr Asp Asp Leu Arg Leu Ala
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 Ala Leu Ser Ile Glu Glu Ser Lys Ser Gly Leu Leu Ser Val Ser Ser
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 Ala Ala Ala Ala His Arg His Val Thr Asp Met Asn Ser Thr Ile His
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 Lys Ile Gln Ile Asn Asn Ser Glu Asn Thr Leu Arg Ser Leu Leu Pro
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 Asp Val Glu Gly Leu His Glu Lys Gly Ser Gln Ala Ser Arg Lys Gly
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 Met Leu Val Glu Lys Glu Ser Met Asp Thr Ile Asp Gln Ala Thr His
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 Ser Lys Met Leu Tyr Tyr Gly Glu Asn Gln Glu Leu Gly Pro Glu Glu

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His	Asn	Asp	Thr	Arg	Ser	Leu	Phe	Pro	Val	Val	Leu	Glu	Gln	Leu	Asp
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Glu	Val	Val	Gly	Ala	Ser	Leu	Ser	Met	Ser	Ala	Asp	Ser	Leu	Thr	Ile
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Asp	Glu	Ala	Val	Ala	Asp	Thr	Ser	Arg	Arg	Val	Gly	Gly	Ala	Leu	Trp
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Arg	Lys	Gly	Ala	Leu	Arg	Asp	Arg	Leu	Asn	Asp	Ala	Val	Lys	Gln	Leu
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Gln	Ala	Ala	Glu	Arg	Gly	Asp	Ala	His	Gln	Arg	Leu	Gly	Gln	Ser	Lys
	690					695					700				

Leu	Phe	Ile	Glu	Glu	Ala	Asn	Lys	Thr	Thr	Ala	Ala	Val	Gln	Gln	Val	705	710	715	720
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Ile	Gln	Val	Ser	Met	Met	Phe	Asp	Gly	Gln	Ser	Ala	Val	Glu	Val	His	805	810	815	
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Tyr	Met	Lys	Pro	Pro	Pro	Lys	Pro	Ala	Glu	Pro	Thr	Gly	Ala	Trp	Val	835	840	845	
Ala	Asp	Gln	Phe	Val	Leu	Tyr	Leu	Gly	Ser	Lys	Asn	Ala	Lys	Lys	Glu	850	855	860	
Tyr	Met	Gly	Leu	Ala	Ile	Lys	Asn	Asp	Asn	Leu	Val	Tyr	Val	Tyr	Asn	865	870	875	880
Leu	Gly	Met	Lys	Asp	Val	Glu	Ile	Leu	Leu	Asp	Ser	Lys	Pro	Val	Ser	885	890	895	
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His	Gly	Lys	Val	Phe	Leu	Thr	Val	Pro	Ser	Leu	Ser	Ser	Thr	Ala	Glu	915	920	925	
Glu	Lys	Phe	Ile	Lys	Lys	Gly	Glu	Phe	Ala	Gly	Asp	Asp	Ser	Leu	Leu	930	935	940	
Asp	Val	Thr	Pro	Glu	Asp	Thr	Val	Phe	Tyr	Val	Gly	Gly	Val	Pro	Ala	945	950	955	960
Asn	Phe	Lys	Leu	Pro	Ala	Ser	Leu	Asn	Leu	Pro	Ser	Tyr	Ser	Gly	Cys	965	970	975	
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 Leu Val Val Asp Lys Ser Arg Leu Arg Gly Lys Asn Pro Thr Lys Gly
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 Ser Pro Ile Ser Pro Gln Tyr Ala Asn Phe Thr Gly Cys Ile Ser Asn
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 Ala Tyr Phe Thr Arg Leu Asp Arg Asp Val Glu Val Glu Asp Phe Gln

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Pro Lys Thr Asn Lys Gln Gly Glu Lys Ser Lys Asp Ala Pro Ser Trp			
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His Cys His Leu Ser Ser Ser Pro Arg Ala Ile Glu His Ala Tyr Gln			
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Gly Thr Tyr Phe Ser Thr Glu Gly Gly Tyr Val Val Leu Asp Glu Ser			
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Phe Asn Ile Gly Leu Lys Phe Glu Ile Ala Phe Glu Val Arg Pro Arg			
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Leu Asn Val His Met Arg Asn Gly Gln Val Ile Val Lys Val Asn Asn			
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Gln Leu Asp Val Asp Ser Glu Val Asn His Val Val Gly Pro Leu Asn
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 Met Gly Leu Leu Gln Leu Leu Ala Phe Ser Phe Leu Ala Leu Cys Arg
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Glu Asn Val Val Thr Thr Phe Ala Pro Asn Arg Leu Lys Ile Trp Trp	
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Gln Ser Glu Asn Gly Val Glu Asn Val Thr Ile Gln Leu Asp Leu Glu	
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Gly Val Tyr Arg Tyr Phe Ala Tyr Asp Cys Glu Ala Ser Phe Pro Gly	
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Ile Ser Thr Gly Pro Met Lys Lys Val Asp Asp Ile Ile Cys Asp Ser	
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Arg Tyr Ser Asp Ile Glu Pro Ser Thr Glu Gly Glu Val Ile Phe Arg	
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Gln Asn Leu Leu Lys Ile Thr Asn Leu Arg Ile Lys Phe Val Lys Leu	
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His Thr Leu Gly Asp Asn Leu Leu Asp Ser Arg Met Glu Ile Arg Glu	
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Lys Tyr Tyr Tyr Ala Val Tyr Asp Met Val Val Arg Gly Asn Cys Phe	
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Glu Val Glu Gly Met Val His Gly His Cys Met Cys Arg His Asn Thr	
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Lys Gly Leu Asn Cys Glu Leu Cys Met Asp Phe Tyr His Asp Leu Pro	
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Phe	Ser	Thr	Gly	Leu	Ile	Ala	Gly	Gln	Cys	Arg	Cys	Lys	Leu	Asn	Val		
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gaa	gga	gaa	cat	tgt	gat	gtt	tgc	aaa	gaa	ggc	ttc	tat	gat	tta	agc	1461	
Glu	Gly	Glu	His	Cys	Asp	Val	Cys	Lys	Glu	Gly	Phe	Tyr	Asp	Leu	Ser		
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agt	gaa	gat	cca	ttt	ggc	tgt	aaa	tct	tgt	gct	tgc	aat	cct	ctg	gga	1509	
Ser	Glu	Asp	Pro	Phe	Gly	Cys	Lys	Ser	Cys	Ala	Cys	Asn	Pro	Leu	Gly		
	450					455					460						
aca	att	cct	gga	ggg	aat	cct	tgt	gat	tcc	gag	aca	ggc	cac	tgc	tac	1557	
Thr	Ile	Pro	Gly	Gly	Asn	Pro	Cys	Asp	Ser	Glu	Thr	Gly	His	Cys	Tyr		
465					470				475					480			
tgc	aag	cgt	ctg	gtg	aca	gga	cag	cat	tgt	gac	cag	tgc	ctg	cca	gag	1605	
Cys	Lys	Arg	Leu	Val	Thr	Gly	Gln	His	Cys	Asp	Gln	Cys	Leu	Pro	Glu		
			485				490						495				
cac	tgg	ggc	tta	agc	aat	gat	ttg	gat	gga	tgt	cga	cca	tgt	gac	tgt	1653	
His	Trp	Gly	Leu	Ser	Asn	Asp	Leu	Asp	Gly	Cys	Arg	Pro	Cys	Asp	Cys		
			500				505						510				
gac	ctt	ggg	gga	gcc	tta	aac	aac	agt	tgc	ttt	gcg	gag	tca	ggc	cag	1701	
Asp	Leu	Gly	Gly	Ala	Leu	Asn	Asn	Ser	Cys	Phe	Ala	Glu	Ser	Gly	Gln		
		515				520						525					
tgc	tca	tgc	cgg	cct	cac	atg	att	gga	cgt	cag	tgc	aac	gaa	gtg	gaa	1749	
Cys	Ser	Cys	Arg	Pro	His	Met	Ile	Gly	Arg	Gln	Cys	Asn	Glu	Val	Glu		
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cct	ggc	tac	tac	ttt	gcc	acc	ctg	gat	cac	tac	ctc	tat	gaa	gcg	gag	1797	
Pro	Gly	Tyr	Tyr	Phe	Ala	Thr	Leu	Asp	His	Tyr	Leu	Tyr	Glu	Ala	Glu		
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gaa	gcc	aac	ttg	ggg	cct	ggg	gtt	agc	ata	gtg	gag	cgg	caa	tat	atc	1845	
Glu	Ala	Asn	Leu	Gly	Pro	Gly	Val	Ser	Ile	Val	Glu	Arg	Gln	Tyr	Ile		

85

gga tgc aaa cct tgt gag tgc cat ctg caa gga tct gtc aat gcc ttc	2613
Gly Cys Lys Pro Cys Glu Cys His Leu Gln Gly Ser Val Asn Ala Phe	
820 825 830	
tgc aat ccc gtc act ggc cag tgc cac tgt ttc cag gga gtg tat gct	2661
Cys Asn Pro Val Thr Gly Gln Cys His Cys Phe Gln Gly Val Tyr Ala	
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cgg cag tgt gat cgg tgc tta cct ggg cac tgg ggc ttt cca agt tgc	2709
Arg Gln Cys Asp Arg Cys Leu Pro Gly His Trp Gly Phe Pro Ser Cys	
850 855 860	
cag ccc tgc cag tgc aat ggc cac gcc gat gac tgc gac cca gtg act	2757
Gln Pro Cys Gln Cys Asn Gly His Ala Asp Asp Cys Asp Pro Val Thr	
865 870 875 880	
ggg gag tgc ttg aac tgc cag gac tac acc atg ggt cat aac tgt gaa	2805
Gly Glu Cys Leu Asn Cys Gln Asp Tyr Thr Met Gly His Asn Cys Glu	
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agg tgc ttg gct ggt tac tat ggc gac ccc atc att ggg tca ggt gat	2853
Arg Cys Leu Ala Gly Tyr Tyr Gly Asp Pro Ile Ile Gly Ser Gly Asp	
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cac tgc cgc cct tgc cct tgc cca gat ggt ccc gac agt gga cgc cag	2901
His Cys Arg Pro Cys Pro Cys Pro Asp Gly Pro Asp Ser Gly Arg Gln	
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Phe Ala Arg Ser Cys Tyr Gln Asp Pro Val Thr Leu Gln Leu Ala Cys	
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Val Cys Asp Pro Gly Tyr Ile Gly Ser Arg Cys Asp Asp Cys Ala Ser	
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Gly Tyr Phe Gly Asn Pro Ser Glu Val Gly Gly Ser Cys Gln Pro Cys	
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Gln Cys His Asn Asn Ile Asp Thr Thr Asp Pro Glu Ala Cys Asp Lys	
980 985 990	
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Glu Thr Gly Arg Cys Leu Lys Cys Leu Tyr His Thr Glu Gly Glu His	
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Cys Gln Phe Cys Arg Phe Gly Tyr Tyr Gly Asp Ala Leu Arg Gln Asp	
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Cys Arg Lys Cys Val Cys Asn Tyr Leu Gly Thr Val Gln Glu His Cys	
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Asn Gly Ser Asp Cys Gln Cys Asp Lys Ala Thr Gly Gln Cys Leu Cys	
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ctt cct aat gtg atc ggg cag aac tgt gac cgc tgt gcg ccc aat acc 3333
 Leu Pro Asn Val Ile Gly Gln Asn Cys Asp Arg Cys Ala Pro Asn Thr
 1060 1065 1070

tgg cag ctg gcc agt ggc act ggc tgt gac cca tgc aac tgc aat gct 3381
 Trp Gln Leu Ala Ser Gly Thr Gly Cys Asp Pro Cys Asn Cys Asn Ala
 1075 1080 1085

gct cat tcc ttc ggg cca tct tgc aat gag ttc acg ggg cag tgc cag 3429
 Ala His Ser Phe Gly Pro Ser Cys Asn Glu Phe Thr Gly Gln Cys Gln
 1090 1095 1100

tgc atg cct ggg ttt gga ggc cgc acc tgc agc gag tgc cag gaa ctc 3477
 Cys Met Pro Gly Phe Gly Gly Arg Thr Cys Ser Glu Cys Gln Glu Leu
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 Phe Trp Gly Asp Pro Asp Val Glu Cys Arg Ala Cys Asp Cys Asp Pro
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 1140 1145 1150

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 Cys Val Glu Gly Val Glu Gly Pro Arg Cys Asp Lys Cys Thr Arg Gly
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 Tyr Ser Gly Val Phe Pro Asp Cys Thr Pro Cys His Gln Cys Phe Ala
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 Leu Trp Asp Val Ile Ile Ala Glu Leu Thr Asn Arg Thr His Arg Phe
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 Leu Glu Lys Ala Lys Ala Leu Lys Ile Ser Gly Val Ile Gly Pro Tyr
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cgt gag act gtg gac tcg gtg gag agg aaa gtc agc gag ata aaa gac 3813
 Arg Glu Thr Val Asp Ser Val Glu Arg Lys Val Ser Glu Ile Lys Asp
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atc ctg gcg cag agc ccc gca gca gag cca ctg aaa aac att ggg aat 3861
 Ile Leu Ala Gln Ser Pro Ala Ala Glu Pro Leu Lys Asn Ile Gly Asn
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ctc ttt gag gaa gca gag aaa ctg att aaa gat gtt aca gaa atg atg 3909
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 1250 1255 1260

gct caa gta gaa gtg aaa tta tct gac aca act tcc caa agc aac agc 3957
 Ala Gln Val Glu Val Lys Leu Ser Asp Thr Thr Ser Gln Ser Asn Ser
 1265 1270 1275 1280

aca gcc aaa gaa ctg gat tct cta cag aca gaa gcc gaa agc cta gac 4005
 Thr Ala Lys Glu Leu Asp Ser Leu Gln Thr Glu Ala Glu Ser Leu Asp
 1285 1290 1295

aac act gtg aaa gaa ctt gct gaa caa ctg gaa ttt atc aaa aac tca 4053

Asn Thr Val Lys Glu Leu Ala Glu Gln Leu Glu Phe Ile Lys Asn Ser	
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Asp Ile Arg Gly Ala Leu Asp Ser Ile Thr Lys Tyr Phe Gln Met Ser	
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ctt gag gca gag gag agg gtg aat gcc tcc acc aca gaa ccc aac agc	4149
Leu Glu Ala Glu Glu Arg Val Asn Ala Ser Thr Thr Glu Pro Asn Ser	
1330 1335 1340	
act gtg gag cag tca gcc ctc atg aga gac aga gta gaa gac gtg atg	4197
Thr Val Glu Gln Ser Ala Leu Met Arg Asp Arg Val Glu Asp Val Met	
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atg gag cga gaa tcc cag ttc aag gaa aaa caa gag gag cag gct cgc	4245
Met Glu Arg Glu Ser Gln Phe Lys Glu Lys Gln Glu Glu Gln Ala Arg	
1365 1370 1375	
ctc ctt gat gaa ctg gca ggc aag cta caa agc cta gac ctt tca gcc	4293
Leu Leu Asp Glu Leu Ala Gly Lys Leu Gln Ser Leu Asp Leu Ser Ala	
1380 1385 1390	
gct gcc gaa atg acc tgt gga aca ccc cca ggg gcc tcc tgt tcc gag	4341
Ala Ala Glu Met Thr Cys Gly Thr Pro Pro Gly Ala Ser Cys Ser Glu	
1395 1400 1405	
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Thr Glu Cys Gly Gly Pro Asn Cys Arg Thr Asp Glu Gly Glu Arg Lys	
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Cys Gly Gly Pro Gly Cys Gly Gly Leu Val Thr Val Ala His Asn Ala	
1425 1430 1435 1440	
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Trp Gln Lys Ala Met Asp Leu Asp Gln Asp Val Leu Ser Ala Leu Ala	
1445 1450 1455	
gaa gtg gaa cag ctc tcc aag atg gtc tct gaa gca aaa ctg agg gca	4533
Glu Val Glu Gln Leu Ser Lys Met Val Ser Glu Ala Lys Leu Arg Ala	
1460 1465 1470	
gat gag gca aaa caa agt gct gaa gac att ctg ttg aag aca aat gct	4581
Asp Glu Ala Lys Gln Ser Ala Glu Asp Ile Leu Leu Lys Thr Asn Ala	
1475 1480 1485	
acc aaa gaa aaa atg gac aag agc aat gag gag ctg aga aat cta atc	4629
Thr Lys Glu Lys Met Asp Lys Ser Asn Glu Glu Leu Arg Asn Leu Ile	
1490 1495 1500	
aag caa atc aga aac ttt ttg acc cag gat agt gct gat ttg gac agc	4677
Lys Gln Ile Arg Asn Phe Leu Thr Gln Asp Ser Ala Asp Leu Asp Ser	
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att gaa gca gtt gct aat gaa gta ttg aaa atg gag atg cct agc acc	4725
Ile Glu Ala Val Ala Asn Glu Val Leu Lys Met Glu Met Pro Ser Thr	
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cca cag cag tta cag aac ttg aca gaa gat ata cgt gaa cga gtt gaa	4773
Pro Gln Gln Leu Gln Asn Leu Thr Glu Asp Ile Arg Glu Arg Val Glu	

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Ser Leu Ser Gln Val Glu Val Ile Leu Gln His Ser Ala Ala Asp Ile			
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gcc aga gct gag atg ttg tta gaa gaa gct aaa aga gca agc aaa agt			4869
Ala Arg Ala Glu Met Leu Leu Glu Glu Ala Lys Arg Ala Ser Lys Ser			
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gca aca gat gtt aaa gtc act gca gat atg gta aag gaa gct ctg gaa			4917
Ala Thr Asp Val Lys Val Thr Ala Asp Met Val Lys Glu Ala Leu Glu			
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gaa gca gaa aag gcc cag gtc gca gca gag aag gca att aaa caa gca			4965
Glu Ala Glu Lys Ala Gln Val Ala Ala Glu Lys Ala Ile Lys Gln Ala			
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Asp Glu Asp Ile Gln Gly Thr Gln Asn Leu Leu Thr Ser Ile Glu Ser			
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gaa aca gca gct tct gag gaa acc ttg ttc aac gcg tcc cag cgc atc			5061
Glu Thr Ala Ala Ser Glu Glu Thr Leu Phe Asn Ala Ser Gln Arg Ile			
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agc gag tta gag agg aat gtg gaa gaa ctt aag cgg aaa gct gcc caa			5109
Ser Glu Leu Glu Arg Asn Val Glu Glu Leu Lys Arg Lys Ala Ala Gln			
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Asn Ser Gly Glu Ala Glu Tyr Ile Glu Lys Val Val Tyr Thr Val Lys			
1665	1670	1675	1680
caa agt gca gaa gat gtt aag aag act tta gat ggt gaa ctt gat gaa			5205
Gln Ser Ala Glu Asp Val Lys Lys Thr Leu Asp Gly Glu Leu Asp Glu			
1685	1690	1695	
aag tat aaa aaa gta gaa aat tta att gcc aaa aaa act gaa gag tca			5253
Lys Tyr Lys Lys Val Glu Asn Leu Ile Ala Lys Lys Thr Glu Glu Ser			
1700	1705	1710	
gct gat gcc aga agg aaa gcc gaa atg cta caa aat gaa gca aaa act			5301
Ala Asp Ala Arg Arg Lys Ala Glu Met Leu Gln Asn Glu Ala Lys Thr			
1715	1720	1725	
ctt tta gct caa gca aat agc aag ctg caa ctg ctc aaa gat tta gaa			5349
Leu Leu Ala Gln Ala Asn Ser Lys Leu Gln Leu Leu Lys Asp Leu Glu			
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aga aaa tat gaa gac aat caa aga tac tta gaa gat aaa gct caa gaa			5397
Arg Lys Tyr Glu Asp Asn Gln Arg Tyr Leu Glu Asp Lys Ala Gln Glu			
1745	1750	1755	1760
tta gca aga ctg gaa gga gaa gtc cgt tca ctc cta aag gat ata agc			5445
Leu Ala Arg Leu Glu Gly Glu Val Arg Ser Leu Leu Lys Asp Ile Ser			
1765	1770	1775	
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Gln Lys Val Ala Val Tyr Ser Thr Cys Leu			
1780	1785		

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<212> PRT

<213> Homo sapiens

<400> 14

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20 25 30

Gly Ser Cys Tyr Pro Ala Thr Gly Asp Leu Leu Ile Gly Arg Ala Gln
35 40 45

Lys Leu Ser Val Thr Ser Thr Cys Gly Leu His Lys Pro Glu Pro Tyr
50 55 60

Cys Ile Val Ser His Leu Gln Glu Asp Lys Lys Cys Phe Ile Cys Asn
65 70 75 80

Ser Gln Asp Pro Tyr His Glu Thr Leu Asn Pro Asp Ser His Leu Ile
85 90 95

Glu Asn Val Val Thr Thr Phe Ala Pro Asn Arg Leu Lys Ile Trp Trp
100 105 110

Gln Ser Glu Asn Gly Val Glu Asn Val Thr Ile Gln Leu Asp Leu Glu
115 120 125

Ala Glu Phe His Phe Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg
130 135 140

Pro Ala Ala Met Leu Ile Glu Arg Ser Ser Asp Phe Gly Lys Thr Trp
145 150 155 160

Gly Val Tyr Arg Tyr Phe Ala Tyr Asp Cys Glu Ala Ser Phe Pro Gly
165 170 175

Ile Ser Thr Gly Pro Met Lys Lys Val Asp Asp Ile Ile Cys Asp Ser
180 185 190

Arg Tyr Ser Asp Ile Glu Pro Ser Thr Glu Gly Glu Val Ile Phe Arg
195 200 205

Ala Leu Asp Pro Ala Phe Lys Ile Glu Asp Pro Tyr Ser Pro Arg Ile
210 215 220

Gln Asn Leu Leu Lys Ile Thr Asn Leu Arg Ile Lys Phe Val Lys Leu
225 230 235 240

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

Lys Tyr Tyr Tyr Ala Val Tyr Asp Met Val Val Arg Gly Asn Cys Phe

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Cys	Tyr	Gly	His	Ala	Ser	Glu	Cys	Ala	Pro	Val	Asp	Gly	Phe	Asn	Glu
		275					280					285			
Glu	Val	Glu	Gly	Met	Val	His	Gly	His	Cys	Met	Cys	Arg	His	Asn	Thr
		290					295					300			
Lys	Gly	Leu	Asn	Cys	Glu	Leu	Cys	Met	Asp	Phe	Tyr	His	Asp	Leu	Pro
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Trp	Arg	Pro	Ala	Glu	Gly	Arg	Asn	Ser	Asn	Ala	Cys	Lys	Lys	Cys	Asn
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Cys	Asn	Glu	His	Ser	Ile	Ser	Cys	His	Phe	Asp	Met	Ala	Val	Tyr	Leu
			340					345					350		
Ala	Thr	Gly	Asn	Val	Ser	Gly	Gly	Val	Cys	Asp	Asp	Cys	Gln	His	Asn
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Thr	Met	Gly	Arg	Asn	Cys	Glu	Gln	Cys	Lys	Pro	Phe	Tyr	Tyr	Gln	His
		370					375					380			
Pro	Glu	Arg	Asp	Ile	Arg	Asp	Pro	Asn	Phe	Cys	Glu	Arg	Cys	Thr	Cys
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Asp	Pro	Ala	Gly	Ser	Gln	Asn	Glu	Gly	Ile	Cys	Asp	Ser	Tyr	Thr	Asp
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Phe	Ser	Thr	Gly	Leu	Ile	Ala	Gly	Gln	Cys	Arg	Cys	Lys	Leu	Asn	Val
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Glu	Gly	Glu	His	Cys	Asp	Val	Cys	Lys	Glu	Gly	Phe	Tyr	Asp	Leu	Ser
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Cys	Lys	Arg	Leu	Val	Thr	Gly	Gln	His	Cys	Asp	Gln	Cys	Leu	Pro	Glu
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Asp	Leu	Gly	Gly	Ala	Leu	Asn	Asn	Ser	Cys	Phe	Ala	Glu	Ser	Gly	Gln
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Cys	Ser	Cys	Arg	Pro	His	Met	Ile	Gly	Arg	Gln	Cys	Asn	Glu	Val	Glu
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Pro	Gly	Tyr	Tyr	Phe	Ala	Thr	Leu	Asp	His	Tyr	Leu	Tyr	Glu	Ala	Glu
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Glu	Ala	Asn	Leu	Gly	Pro	Gly	Val	Ser	Ile	Val	Glu	Arg	Gln	Tyr	Ile
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Gln	Asp	Arg	Ile	Pro	Ser	Trp	Thr	Gly	Ala	Gly	Phe	Val	Arg	Val	Pro
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 Glu Tyr Asp Ile Leu Ile Arg Tyr Glu Pro Gln Leu Pro Asp His Trp
 610 615 620
 Glu Lys Ala Val Ile Thr Val Gln Arg Pro Gly Arg Ile Pro Thr Ser
 625 630 635 640
 Ser Arg Cys Gly Asn Thr Ile Pro Asp Asp Asp Asn Gln Val Val Ser
 645 650 655
 Leu Ser Pro Gly Ser Arg Tyr Val Val Leu Pro Arg Pro Val Cys Phe
 660 665 670
 Glu Lys Gly Thr Asn Tyr Thr Val Arg Leu Glu Leu Pro Gln Tyr Thr
 675 680 685
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 Tyr Arg Cys Leu Glu Asn Ser Arg Ser Val Val Lys Thr Pro Met Thr
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 Asp Val Cys Arg Asn Ile Ile Phe Ser Ile Ser Ala Leu Leu His Gln
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 Thr Gly Leu Ala Cys Glu Cys Asp Pro Gln Gly Ser Leu Ser Ser Val
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 Cys Asp Pro Asn Gly Gly Gln Cys Gln Cys Arg Pro Asn Val Val Gly
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 Arg Gln Cys Asp Arg Cys Leu Pro Gly His Trp Gly Phe Pro Ser Cys
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 Arg Cys Leu Ala Gly Tyr Tyr Gly Asp Pro Ile Ile Gly Ser Gly Asp
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His Cys Arg Pro Cys Pro Cys Pro Asp Gly Pro Asp Ser Gly Arg Gln
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 Phe Ala Arg Ser Cys Tyr Gln Asp Pro Val Thr Leu Gln Leu Ala Cys
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Ala Gln Val Glu Val Lys Leu Ser Asp Thr Thr Ser Gln Ser Asn Ser		
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Thr Ala Lys Glu Leu Asp Ser Leu Gln Thr Glu Ala Glu Ser Leu Asp		
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Asn Thr Val Lys Glu Leu Ala Glu Gln Leu Glu Phe Ile Lys Asn Ser		
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Leu Glu Ala Glu Glu Arg Val Asn Ala Ser Thr Thr Glu Pro Asn Ser		
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Thr Glu Cys Gly Gly Pro Asn Cys Arg Thr Asp Glu Gly Glu Arg Lys		
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Cys Gly Gly Pro Gly Cys Gly Gly Leu Val Thr Val Ala His Asn Ala		
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Trp Gln Lys Ala Met Asp Leu Asp Gln Asp Val Leu Ser Ala Leu Ala		
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Glu Val Glu Gln Leu Ser Lys Met Val Ser Glu Ala Lys Leu Arg Ala		
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Asp Glu Ala Lys Gln Ser Ala Glu Asp Ile Leu Leu Lys Thr Asn Ala		
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Thr Lys Glu Lys Met Asp Lys Ser Asn Glu Glu Leu Arg Asn Leu Ile		
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Lys Gln Ile Arg Asn Phe Leu Thr Gln Asp Ser Ala Asp Leu Asp Ser		
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Ile Glu Ala Val Ala Asn Glu Val Leu Lys Met Glu Met Pro Ser Thr		
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Pro Gln Gln Leu Gln Asn Leu Thr Glu Asp Ile Arg Glu Arg Val Glu		
1540	1545	1550
Ser Leu Ser Gln Val Glu Val Ile Leu Gln His Ser Ala Ala Asp Ile		
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Ser Thr Cys Gly Leu His Lys Pro Glu Pro Tyr Cys Ile Val Ser His	
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Leu Gln Glu Asp Lys Lys Cys Phe Ile Cys Asn Ser Gln Asp Pro Tyr	
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His Glu Thr Leu Asn Pro Asp Ser His Leu Ile Glu Asn Val Val Thr	
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Thr Phe Ala Pro Asn Arg Leu Lys Ile Trp Trp Gln Ser Glu Asn Gly	
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Val Glu Asn Val Thr Ile Gln Leu Asp Leu Glu Ala Glu Phe His Phe	
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Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg Pro Ala Ala Met Leu	
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Met Lys Lys Val Asp Asp Ile Ile Cys Asp Ser Arg Tyr Ser Asp Ile	
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Glu Pro Ser Thr Glu Gly Glu Val Ile Phe Arg Ala Leu Asp Pro Ala	
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Phe Lys Ile Glu Asp Pro Tyr Ser Pro Arg Ile Gln Asn Leu Leu Lys	
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Asn Leu Leu Asp Ser Arg Met Glu Ile Arg Glu Lys Tyr Tyr Tyr Ala	
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Ser Glu Cys Ala Pro Val Asp Gly Phe Asn Glu Glu Val Glu Gly Met	
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Val His Gly His Cys Met Cys Arg His Asn Thr Lys Gly Leu Asn Cys	
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Glu Leu Cys Met Asp Phe Tyr His Asp Leu Pro Trp Arg Pro Ala Glu	
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Ser Gly Gly Val Cys Asp Asp Cys Gln His Asn Thr Met Gly Arg Asn	
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Cys Glu Gln Cys Lys Pro Phe Tyr Tyr Gln His Pro Glu Arg Asp Ile	
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Asp Val Cys Lys Glu Gly Phe Tyr Asp Leu Ser Ser Glu Asp Pro Phe	
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Gly Cys Lys Ser Cys Ala Cys Asn Pro Leu Gly Thr Ile Pro Gly Gly	
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Thr Gly Gln His Cys Asp Gln Cys Leu Pro Glu His Trp Gly Leu Ser	
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Leu Asn Asn Ser Cys Phe Ala Glu Ser Gly Gln Cys Ser Cys Arg Pro	
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His Met Ile Gly Arg Gln Cys Asn Glu Val Glu Pro Gly Tyr Tyr Phe	
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Glu Phe Phe Ile Asp Asn Ile Pro Tyr Ser Met Glu Tyr Asp Ile Leu	
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Tyr Thr Val Arg Leu Glu Leu Pro Gln Tyr Thr Ser Ser Asp Ser Asp	
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Cys Lys Ser Leu Asp Ile Phe Thr Val Gly Gly Ser Gly Asp Gly Val	
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Val Thr Asn Ser Ala Trp Glu Thr Phe Gln Arg Tyr Arg Cys Leu Glu	
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Cys Asn Tyr Leu Gly Thr Val Gln Glu His Cys Asn Gly Ser Asp Cys	
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 Lys Leu Ser Asp Thr Thr Ser Gln Ser Asn Ser Thr Ala Lys Glu Leu
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His Glu Thr Leu Asn Pro Asp Ser His Leu Ile Glu Asn Val Val Thr
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Phe Lys Ile Glu Asp Pro Tyr Ser Pro Arg Ile Gln Asn Leu Leu Lys
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Ile Thr Asn Leu Arg Ile Lys Phe Val Lys Leu His Thr Leu Gly Asp

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Val Tyr Asp Met Val Val Arg Gly Asn Cys Phe Cys Tyr Gly His Ala					
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Ser Glu Cys Ala Pro Val Asp Gly Phe Asn Glu Glu Val Glu Gly Met					
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Val His Gly His Cys Met Cys Arg His Asn Thr Lys Gly Leu Asn Cys					
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Glu Leu Cys Met Asp Phe Tyr His Asp Leu Pro Trp Arg Pro Ala Glu					
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Gly Arg Asn Ser Asn Ala Cys Lys Lys Cys Asn Cys Asn Glu His Ser					
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Ser Gly Gly Val Cys Asp Asp Cys Gln His Asn Thr Met Gly Arg Asn					
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Cys Glu Gln Cys Lys Pro Phe Tyr Tyr Gln His Pro Glu Arg Asp Ile					
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Gln Asn Glu Gly Ile Cys Asp Ser Tyr Thr Asp Phe Ser Thr Gly Leu					
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Asp Val Cys Lys Glu Gly Phe Tyr Asp Leu Ser Ser Glu Asp Pro Phe					
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Asn Pro Cys Asp Ser Glu Thr Gly His Cys Tyr Cys Lys Arg Leu Val					
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Cys Arg Lys Cys Val Cys Asn Tyr Leu Gly Thr Val Lys Glu His Cys	
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aat ggc tct gac tgc cac tgt gac aaa gcc act ggt cag tgc tcg tgc	3345
Asn Gly Ser Asp Cys His Cys Asp Lys Ala Thr Gly Gln Cys Ser Cys	
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ctt ccc aat gtg atc ggg cag aac tgt gac cgg tgt gcg ccc aac acc	3393
Leu Pro Asn Val Ile Gly Gln Asn Cys Asp Arg Cys Ala Pro Asn Thr	
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tgg cag ctg gct agc ggg act ggc tgc ggg ccc tgc aat tgc aat gct	3441
Trp Gln Leu Ala Ser Gly Thr Gly Cys Gly Pro Cys Asn Cys Asn Ala	
1075 1080 1085	
gcg cat tcc ttt ggg cca tcc tgc aac gag ttc aca ggg cag tgc cag	3489
Ala His Ser Phe Gly Pro Ser Cys Asn Glu Phe Thr Gly Gln Cys Gln	
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Cys Met Pro Gly Phe Gly Gly Arg Thr Cys Ser Glu Cys Gln Glu Leu	
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Phe Trp Gly Asp Pro Asp Val Glu Cys Arg Ala Cys Asp Cys Asp Pro	
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Arg Gly Ile Glu Thr Pro Gln Cys Asp Gln Ser Thr Gly Gln Cys Val	
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Cys Val Glu Gly Val Glu Gly Pro Arg Cys Asp Lys Cys Thr Arg Gly	
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Tyr Ser Gly Val Phe Pro Asp Cys Thr Pro Cys His Gln Cys Phe Ala	
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 Leu Glu Lys Ala Lys Ala Leu Lys Ile Ser Gly Val Ile Gly Pro Tyr
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cga gag acc gtg gac tct gta gag aag aaa gtc aat gag ata aaa gac 3873
 Arg Glu Thr Val Asp Ser Val Glu Lys Lys Val Asn Glu Ile Lys Asp
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atc ctg gcc cag agc cca gca gcg gaa cca ctg aaa aac att ggc att 3921
 Ile Leu Ala Gln Ser Pro Ala Ala Glu Pro Leu Lys Asn Ile Gly Ile
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ctc ttc gag gag gca gag aaa cta acc aaa gat gtc aca gaa aag atg 3969
 Leu Phe Glu Glu Ala Glu Lys Leu Thr Lys Asp Val Thr Glu Lys Met
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115

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Lys Tyr Lys Lys Val Glu Ser Leu Ile Ala Gln Lys Thr Glu Glu Ser				
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Ala Asp Ala Arg Arg Lys Ala Glu Leu Leu Gln Asn Glu Ala Lys Thr				
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Gly Ser Cys Tyr Pro Ala Thr Gly Asp Leu Leu Ile Gly Arg Ala Gln				
	35	40	45	
Lys Leu Ser Val Thr Ser Thr Cys Gly Leu His Lys Pro Glu Pro Tyr				
	50	55	60	
Cys Ile Val Ser His Leu Gln Glu Asp Lys Lys Cys Phe Ile Cys Asp				
	65	70	75	80
Ser Arg Asp Pro Tyr His Glu Thr Leu Asn Pro Asp Ser His Leu Ile				
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 Gln Ser Glu Asn Gly Val Glu Asn Val Thr Ile Gln Leu Asp Leu Glu
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 Ala Glu Phe His Phe Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg
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 Pro Ala Ala Met Leu Ile Glu Arg Ser Ser Asp Phe Gly Lys Thr Trp
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 Gly Val Tyr Arg Tyr Phe Ala Tyr Asp Cys Glu Ser Ser Phe Pro Gly
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 Ile Ser Thr Gly Pro Met Lys Lys Val Asp Asp Ile Ile Cys Asp Ser
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 Arg Tyr Ser Asp Ile Glu Pro Ser Thr Glu Gly Glu Val Ile Phe Arg
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 Ala Leu Asp Pro Ala Phe Lys Ile Glu Asp Pro Tyr Ser Pro Arg Ile
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 Gln Asn Leu Leu Lys Ile Thr Asn Leu Arg Ile Lys Phe Val Lys Leu
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 His Thr Leu Gly Asp Asn Leu Leu Asp Ser Arg Met Glu Ile Arg Glu
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 Lys Tyr Tyr Tyr Ala Val Tyr Asp Met Val Val Arg Gly Asn Cys Phe
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 Cys Tyr Gly His Ala Ser Glu Cys Ala Pro Val Asp Gly Val Asn Glu
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 Glu Val Glu Gly Met Val His Gly His Cys Met Cys Arg His Asn Thr
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 Lys Gly Leu Asn Cys Glu Leu Cys Met Asp Phe Tyr His Asp Leu Pro
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 Trp Arg Pro Ala Glu Gly Arg Asn Ser Asn Ala Cys Lys Lys Cys Asn
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 Phe Ser Val Gly Leu Ile Ala Gly Gln Cys Arg Cys Lys Leu His Val

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Leu Ser Pro Gly Ser Arg Tyr Val Val Leu Pro Arg Pro Val Cys Phe		
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 Asp Thr Gly Arg Cys Leu Lys Cys Leu Tyr His Thr Glu Gly Asp His
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Cys Gly Gly Pro Gly Cys Gly Gly Leu Val Thr Val Ala His Ser Ala 1425	1430	1435 1440
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Lys Gln Ile Arg Asn Phe Leu Thr Glu Asp Ser Ala Asp Leu Asp Ser 1505	1510	1515 1520
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 His Leu Ile Glu Asn Val Val Thr Thr Phe Ala Pro Asn Arg Leu Lys
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Gln Tyr Thr Ala Ser Gly Ser Asp Val Glu Ser Pro Tyr Thr Phe Ile				
625 630 635 640				

gac tgc ctt gtt ctc atg ccc tac tgt aaa tgc ctg gac atc ttc act	1968
Asp Ser Leu Val Leu Met Pro Tyr Cys Lys Ser Leu Asp Ile Phe Thr	
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gtt ggc ggc tca ggc gat ggg gag gtc acc aat agt gcc tgg gaa acc	2016
Val Gly Gly Ser Gly Asp Gly Glu Val Thr Asn Ser Ala Trp Glu Thr	
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ttc cag cgc tac agg tgt ctg gag aac agc agg agt gtg gta aaa aca	2064
Phe Gln Arg Tyr Arg Cys Leu Glu Asn Ser Arg Ser Val Val Lys Thr	
675 680 685	
ccc atg aca gat gtc tgc aga aac att atc ttc agc att tct gcc ttg	2112
Pro Met Thr Asp Val Cys Arg Asn Ile Ile Phe Ser Ile Ser Ala Leu	
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Ile His Gln Thr Gly Leu Ala Cys Glu Cys Asp Pro Gln Gly Ser Leu	
705 710 715 720	
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Ser Ser Val Cys Asp Pro Asn Gly Gly Gln Cys Gln Cys Arg Pro Asn	
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gtg gtt gga aga acc tgc aac agg tgt gcc ccg ggc acc ttt ggc ttt	2256
Val Val Gly Arg Thr Cys Asn Arg Cys Ala Pro Gly Thr Phe Gly Phe	
740 745 750	
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Gly Pro Asn Gly Cys Lys Pro Cys Asp Cys His Leu Gln Gly Ser Ala	
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Ser Ala Phe Cys Asp Ala Ile Thr Gly Gln Cys His Cys Phe Gln Gly	
770 775 780	
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Ile Tyr Ala Arg Gln Cys Asp Arg Cys Leu Pro Gly Tyr Trp Gly Phe	
785 790 795 800	
ccc agc tgc cag ccc tgc cag tgt aat ggt cat gct cta gac tgt gac	2448
Pro Ser Cys Gln Pro Cys Gln Cys Asn Gly His Ala Leu Asp Cys Asp	
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aac tgc gaa agg tgc ctg gct ggc tac tac ggt gat ccc atc att ggg	2544
Asn Cys Glu Arg Cys Leu Ala Gly Tyr Tyr Gly Asp Pro Ile Ile Gly	
835 840 845	
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Ser Gly Asp His Cys Arg Pro Cys Pro Cys Pro Asp Gly Pro Asp Ser	
850 855 860	
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Gly Arg Gln Phe Ala Arg Ser Cys Tyr Gln Asp Pro Val Thr Leu Gln	
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885 890 895	
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Cys Ala Ser Gly Phe Phe Gly Asn Pro Ser Asp Phe Gly Gly Ser Cys	
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Gln Pro Cys Gln Cys His His Asn Ile Asp Thr Thr Asp Pro Glu Ala	
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Cys Asp Lys Asp Thr Gly Arg Cys Leu Lys Cys Leu Tyr His Thr Glu	
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Gly Asp His Cys Gln Leu Cys Gln Tyr Gly Tyr Tyr Gly Asp Ala Leu	
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Arg Gln Asp Cys Arg Lys Cys Val Cys Asn Tyr Leu Gly Thr Val Lys	
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Glu His Cys Asn Gly Ser Asp Cys His Cys Asp Lys Ala Thr Gly Gln	
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Cys Ser Cys Leu Pro Asn Val Ile Gly Gln Asn Cys Asp Arg Cys Ala	
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Pro Asn Thr Trp Gln Leu Ala Ser Gly Thr Gly Cys Gly Pro Cys Asn	
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Cys Asn Ala Ala His Ser Phe Gly Pro Ser Cys Asn Glu Phe Thr Gly	
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Gln Cys Gln Cys Met Pro Gly Phe Gly Gly Arg Thr Cys Ser Glu Cys	
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Gln Glu Leu Phe Trp Gly Asp Pro Asp Val Glu Cys Arg Ala Cys Asp	
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Cys Asp Pro Arg Gly Ile Glu Thr Pro Gln Cys Asp Gln Ser Thr Gly	
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Gln Cys Val Cys Val Glu Gly Val Glu Gly Pro Arg Cys Asp Lys Cys	
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acc aga ggt tac tcg ggg gtc ttt cct gac tgc aca ccc tgc cac cag	3360
Thr Arg Gly Tyr Ser Gly Val Phe Pro Asp Cys Thr Pro Cys His Gln	
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Cys Phe Ala Leu Trp Asp Ala Ile Ile Gly Glu Leu Thr Asn Arg Thr	
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His Lys Phe Leu Glu Lys Ala Lys Ala Leu Lys Ile Ser Gly Val Ile	
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ggt ccc tac cga gag acc gtg gac tct gta gag aag aaa gtc aat gag	3504
Gly Pro Tyr Arg Glu Thr Val Asp Ser Val Glu Lys Lys Val Asn Glu	
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Ser Asn Ser Thr Ala Gly Glu Leu Gly Ala Leu Gln Ala Glu Ala Glu	
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Ser Leu Asp Lys Thr Val Lys Glu Leu Ala Glu Gln Leu Glu Phe Ile	
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Lys Asn Ser Asp Ile Gln Gly Ala Leu Asp Ser Ile Thr Lys Tyr Phe	
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Cys Ser Glu Ser Glu Cys Gly Gly Pro Asn Cys Arg Thr Asp Glu Gly	
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His Ser Ala Trp Gln Lys Ala Met Asp Phe Asp Arg Asp Val Leu Ser			
1380	1385	1390	
gcc ctg gct gaa gtc gaa cag ctc tcc aag atg gtc tct gaa gca aaa			4224
Ala Leu Ala Glu Val Glu Gln Leu Ser Lys Met Val Ser Glu Ala Lys			
1395	1400	1405	
gtg aga gca gat gag gcg aag cag aat gcg cag gat gtc ctg tta aaa			4272
Val Arg Ala Asp Glu Ala Lys Gln Asn Ala Gln Asp Val Leu Leu Lys			
1410	1415	1420	
aca aat gct acc aaa gaa aaa gtg gac aag agc aac gag gac ctg cgg			4320
Thr Asn Ala Thr Lys Glu Lys Val Asp Lys Ser Asn Glu Asp Leu Arg			
1425	1430	1435	1440
aac ctc atc aag cag atc aga aac ttc ctg act gag gat agt gct gat			4368
Asn Leu Ile Lys Gln Ile Arg Asn Phe Leu Thr Glu Asp Ser Ala Asp			
1445	1450	1455	
cta gac agt att gaa gca gtt gct aat gaa gta ctg aaa agt gga aat			4416
Leu Asp Ser Ile Glu Ala Val Ala Asn Glu Val Leu Lys Ser Gly Asn			
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gct agc acg cca cag cag tta cag aac cta aca gaa gac att cgg gag			4464
Ala Ser Thr Pro Gln Gln Leu Gln Asn Leu Thr Glu Asp Ile Arg Glu			
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Arg Val Glu Thr Leu Ser Gln Val Glu Val Ile Leu Gln Gln Ser Ala			
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Lys Gln Ala Asp Glu Asp Ile Gln Gly Thr Gln Asn Leu Leu Thr Ser			
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att gaa tct gaa acg gca gct tct gag gaa acc ctg acc aac gcc tcc			4752
Ile Glu Ser Glu Thr Ala Ala Ser Glu Glu Thr Leu Thr Asn Ala Ser			
1570	1575	1580	
cag cgc atc agc aag ctt gag agg aac gtg gaa gag ctt aag cgt aaa			4800
Gln Arg Ile Ser Lys Leu Glu Arg Asn Val Glu Glu Leu Lys Arg Lys			
1585	1590	1595	1600
gct gcc cag aac tct ggg gag gca gaa tat atc gaa aaa gta gta tat			4848
Ala Ala Gln Asn Ser Gly Glu Ala Glu Tyr Ile Glu Lys Val Val Tyr			
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tct gta aaa cag aat gca gac gat gtt aaa aag act cta gat ggc gaa 4896
 Ser Val Lys Gln Asn Ala Asp Asp Val Lys Lys Thr Leu Asp Gly Glu
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gaa gag tca gca gat gcc agg agg aaa gct gag ctg cta caa aat gaa 4992
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 1665 1670 1675 1680

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 1685 1690 1695

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His Leu Ile Glu Asn Val Val Thr Thr Phe Ala Pro Asn Arg Leu Lys
 35 40 45

Ile Trp Trp Gln Ser Glu Asn Gly Val Glu Asn Val Thr Ile Gln Leu
 50 55 60

Asp Leu Glu Ala Glu Phe His Phe Thr His Leu Ile Met Thr Phe Lys
 65 70 75 80

Thr Phe Arg Pro Ala Ala Met Leu Ile Glu Arg Ser Ser Asp Phe Gly
 85 90 95

Lys Thr Trp Gly Val Tyr Arg Tyr Phe Ala Tyr Asp Cys Glu Ser Ser

100					105					110					
Phe	Pro	Gly	Ile	Ser	Thr	Gly	Pro	Met	Lys	Lys	Val	Asp	Asp	Ile	Ile
		115					120					125			
Cys	Asp	Ser	Arg	Tyr	Ser	Asp	Ile	Glu	Pro	Ser	Thr	Glu	Gly	Glu	Val
	130					135					140				
Ile	Phe	Arg	Ala	Leu	Asp	Pro	Ala	Phe	Lys	Ile	Glu	Asp	Pro	Tyr	Ser
145					150					155					160
Pro	Arg	Ile	Gln	Asn	Leu	Leu	Lys	Ile	Thr	Asn	Leu	Arg	Ile	Lys	Phe
				165					170					175	
Val	Lys	Leu	His	Thr	Leu	Gly	Asp	Asn	Leu	Leu	Asp	Ser	Arg	Met	Glu
			180					185					190		
Ile	Arg	Glu	Lys	Tyr	Tyr	Tyr	Ala	Val	Tyr	Asp	Met	Val	Val	Arg	Gly
		195					200					205			
Asn	Cys	Phe	Cys	Tyr	Gly	His	Ala	Ser	Glu	Cys	Ala	Pro	Val	Asp	Gly
	210					215					220				
Val	Asn	Glu	Glu	Val	Glu	Gly	Met	Val	His	Gly	His	Cys	Met	Cys	Arg
225					230					235					240
His	Asn	Thr	Lys	Gly	Leu	Asn	Cys	Glu	Leu	Cys	Met	Asp	Phe	Tyr	His
				245					250					255	
Asp	Leu	Pro	Trp	Arg	Pro	Ala	Glu	Gly	Arg	Asn	Ser	Asn	Ala	Cys	Lys
			260					265					270		
Lys	Cys	Asn	Cys	Asn	Glu	His	Ser	Ser	Ser	Cys	His	Phe	Asp	Met	Ala
		275					280					285			
Val	Phe	Leu	Ala	Thr	Gly	Asn	Val	Ser	Gly	Gly	Val	Cys	Asp	Asn	Cys
	290					295					300				
Gln	His	Asn	Thr	Met	Gly	Arg	Asn	Cys	Glu	Gln	Cys	Lys	Pro	Phe	Tyr
305					310					315					320
Phe	Gln	His	Pro	Glu	Arg	Asp	Ile	Arg	Asp	Pro	Asn	Leu	Cys	Glu	Pro
				325					330					335	
Cys	Thr	Cys	Asp	Pro	Ala	Gly	Ser	Glu	Asn	Gly	Gly	Ile	Cys	Asp	Gly
			340					345					350		
Tyr	Thr	Asp	Phe	Ser	Val	Gly	Leu	Ile	Ala	Gly	Gln	Cys	Arg	Cys	Lys
		355					360					365			
Leu	His	Val	Glu	Gly	Glu	Arg	Cys	Asp	Val	Cys	Lys	Glu	Gly	Phe	Tyr
	370					375					380				
Asp	Leu	Ser	Ala	Glu	Asp	Pro	Tyr	Gly	Cys	Lys	Ser	Cys	Ala	Cys	Asn
385					390					395					400
Pro	Leu	Gly	Thr	Ile	Pro	Gly	Gly	Asn	Pro	Cys	Asp	Ser	Glu	Thr	Gly
				405					410					415	
Tyr	Cys	Tyr	Cys	Lys	Arg	Leu	Val	Thr	Gly	Gln	Arg	Cys	Asp	Gln	Cys
			420					425					430		

Leu Pro Gln His Trp Gly Leu Ser Asn Asp Leu Asp Gly Cys Arg Pro
 435 440 445
 Cys Asp Cys Asp Leu Gly Gly Ala Leu Asn Asn Ser Cys Ser Glu Asp
 450 455 460
 Ser Gly Gln Cys Ser Cys Leu Pro His Met Ile Gly Arg Gln Cys Asn
 465 470 475 480
 Glu Val Glu Ser Gly Tyr Tyr Phe Thr Thr Leu Asp His Tyr Ile Tyr
 485 490 495
 Glu Ala Glu Glu Ala Asn Leu Gly Pro Gly Val Val Val Val Glu Arg
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 Gln Tyr Ile Gln Asp Arg Ile Pro Ser Trp Thr Gly Pro Gly Phe Val
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 Tyr Ser Met Glu Tyr Glu Ile Leu Ile Arg Tyr Glu Pro Gln Leu Pro
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 Asp His Trp Glu Lys Ala Val Ile Thr Val Gln Arg Pro Gly Lys Ile
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 Pro Ala Ser Ser Arg Cys Gly Asn Thr Val Pro Asp Asp Asp Asn Gln
 580 585 590
 Val Val Ser Leu Ser Pro Gly Ser Arg Tyr Val Val Leu Pro Arg Pro
 595 600 605
 Val Cys Phe Glu Lys Gly Met Asn Tyr Thr Val Arg Leu Glu Leu Pro
 610 615 620
 Gln Tyr Thr Ala Ser Gly Ser Asp Val Glu Ser Pro Tyr Thr Phe Ile
 625 630 635 640
 Asp Ser Leu Val Leu Met Pro Tyr Cys Lys Ser Leu Asp Ile Phe Thr
 645 650 655
 Val Gly Gly Ser Gly Asp Gly Glu Val Thr Asn Ser Ala Trp Glu Thr
 660 665 670
 Phe Gln Arg Tyr Arg Cys Leu Glu Asn Ser Arg Ser Val Val Lys Thr
 675 680 685
 Pro Met Thr Asp Val Cys Arg Asn Ile Ile Phe Ser Ile Ser Ala Leu
 690 695 700
 Ile His Gln Thr Gly Leu Ala Cys Glu Cys Asp Pro Gln Gly Ser Leu
 705 710 715 720
 Ser Ser Val Cys Asp Pro Asn Gly Gly Gln Cys Gln Cys Arg Pro Asn
 725 730 735
 Val Val Gly Arg Thr Cys Asn Arg Cys Ala Pro Gly Thr Phe Gly Phe
 740 745 750

Gly	Pro	Asn	Gly	Cys	Lys	Pro	Cys	Asp	Cys	His	Leu	Gln	Gly	Ser	Ala	755	760	765
Ser	Ala	Phe	Cys	Asp	Ala	Ile	Thr	Gly	Gln	Cys	His	Cys	Phe	Gln	Gly	770	775	780
Ile	Tyr	Ala	Arg	Gln	Cys	Asp	Arg	Cys	Leu	Pro	Gly	Tyr	Trp	Gly	Phe	785	790	795
Pro	Ser	Cys	Gln	Pro	Cys	Gln	Cys	Asn	Gly	His	Ala	Leu	Asp	Cys	Asp	805	810	815
Thr	Val	Thr	Gly	Glu	Cys	Leu	Ser	Cys	Gln	Asp	Tyr	Thr	Thr	Gly	His	820	825	830
Asn	Cys	Glu	Arg	Cys	Leu	Ala	Gly	Tyr	Tyr	Gly	Asp	Pro	Ile	Ile	Gly	835	840	845
Ser	Gly	Asp	His	Cys	Arg	Pro	Cys	Pro	Cys	Pro	Asp	Gly	Pro	Asp	Ser	850	855	860
Gly	Arg	Gln	Phe	Ala	Arg	Ser	Cys	Tyr	Gln	Asp	Pro	Val	Thr	Leu	Gln	865	870	875
Leu	Ala	Cys	Val	Cys	Asp	Pro	Gly	Tyr	Ile	Gly	Ser	Arg	Cys	Asp	Asp	885	890	895
Cys	Ala	Ser	Gly	Phe	Phe	Gly	Asn	Pro	Ser	Asp	Phe	Gly	Gly	Ser	Cys	900	905	910
Gln	Pro	Cys	Gln	Cys	His	His	Asn	Ile	Asp	Thr	Thr	Asp	Pro	Glu	Ala	915	920	925
Cys	Asp	Lys	Asp	Thr	Gly	Arg	Cys	Leu	Lys	Cys	Leu	Tyr	His	Thr	Glu	930	935	940
Gly	Asp	His	Cys	Gln	Leu	Cys	Gln	Tyr	Gly	Tyr	Tyr	Gly	Asp	Ala	Leu	945	950	955
Arg	Gln	Asp	Cys	Arg	Lys	Cys	Val	Cys	Asn	Tyr	Leu	Gly	Thr	Val	Lys	965	970	975
Glu	His	Cys	Asn	Gly	Ser	Asp	Cys	His	Cys	Asp	Lys	Ala	Thr	Gly	Gln	980	985	990
Cys	Ser	Cys	Leu	Pro	Asn	Val	Ile	Gly	Gln	Asn	Cys	Asp	Arg	Cys	Ala	995	1000	1005
Pro	Asn	Thr	Trp	Gln	Leu	Ala	Ser	Gly	Thr	Gly	Cys	Gly	Pro	Cys	Asn	1010	1015	1020
Cys	Asn	Ala	Ala	His	Ser	Phe	Gly	Pro	Ser	Cys	Asn	Glu	Phe	Thr	Gly	1025	1030	1035
Gln	Cys	Gln	Cys	Met	Pro	Gly	Phe	Gly	Gly	Arg	Thr	Cys	Ser	Glu	Cys	1045	1050	1055
Gln	Glu	Leu	Phe	Trp	Gly	Asp	Pro	Asp	Val	Glu	Cys	Arg	Ala	Cys	Asp	1060	1065	1070
Cys	Asp	Pro	Arg	Gly	Ile	Glu	Thr	Pro	Gln	Cys	Asp	Gln	Ser	Thr	Gly			

1075					1080					1085				
Gln Cys Val Cys Val	Glu Gly Val Glu Gly	Pro Arg Cys Asp Lys Cys												
1090	1095	1100												
Thr Arg Gly Tyr Ser Gly	Val Phe Pro Asp Cys Thr	Pro Cys His Gln												
1105	1110	1115										1120		
Cys Phe Ala Leu Trp Asp	Ala Ile Ile Gly Glu Leu	Thr Asn Arg Thr												
	1125	1130										1135		
His Lys Phe Leu Glu Lys	Ala Lys Ala Leu Lys	Ile Ser Gly Val Ile												
	1140	1145										1150		
Gly Pro Tyr Arg Glu Thr	Val Asp Ser Val Glu Lys	Lys Val Asn Glu												
	1155	1160										1165		
Ile Lys Asp Ile Leu Ala	Gln Ser Pro Ala Ala	Glu Pro Leu Lys Asn												
	1170	1175										1180		
Ile Gly Ile Leu Phe Glu	Glu Ala Glu Lys Leu Thr	Lys Asp Val Thr												
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Glu Lys Met Ala Gln Val	Glu Val Lys Leu Thr Asp	Thr Ala Ser Gln												
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Ser Asn Ser Thr Ala Gly	Glu Leu Gly Ala Leu Gln	Ala Glu Ala Glu												
	1220	1225										1230		
Ser Leu Asp Lys Thr Val	Lys Glu Leu Ala Glu Gln	Leu Glu Phe Ile												
	1235	1240										1245		
Lys Asn Ser Asp Ile Gln	Gly Ala Leu Asp Ser Ile	Thr Lys Tyr Phe												
	1250	1255										1260		
Gln Met Ser Leu Glu Ala	Glu Lys Arg Val Asn Ala	Ser Thr Thr Asp												
1265	1270	1275										1280		
Pro Asn Ser Thr Val Glu	Gln Ser Ala Leu Thr Arg	Asp Arg Val Glu												
	1285	1290										1295		
Asp Leu Met Leu Glu Arg	Glu Ser Pro Phe Lys Glu	Gln Gln Glu Glu												
	1300	1305										1310		
Gln Ala Arg Leu Leu Asp	Glu Leu Ala Gly Lys Leu	Gln Ser Leu Asp												
	1315	1320										1325		
Leu Ser Ala Ala Ala Gln	Met Thr Cys Gly Thr Pro	Pro Gly Ala Asp												
	1330	1335										1340		
Cys Ser Glu Ser Glu Cys	Gly Gly Pro Asn Cys Arg	Thr Asp Glu Gly												
1345	1350	1355										1360		
Glu Lys Lys Cys Gly Gly	Pro Gly Cys Gly Gly Leu	Val Thr Val Ala												
	1365	1370										1375		
His Ser Ala Trp Gln Lys	Ala Met Asp Phe Asp Arg	Asp Val Leu Ser												
	1380	1385										1390		
Ala Leu Ala Glu Val Glu	Gln Leu Ser Lys Met Val	Ser Glu Ala Lys												
	1395	1400										1405		

Val Arg Ala Asp Glu Ala Lys Gln Asn Ala Gln Asp Val Leu Leu Lys
 1410 1415 1420
 Thr Asn Ala Thr Lys Glu Lys Val Asp Lys Ser Asn Glu Asp Leu Arg
 1425 1430 1435 1440
 Asn Leu Ile Lys Gln Ile Arg Asn Phe Leu Thr Glu Asp Ser Ala Asp
 1445 1450 1455
 Leu Asp Ser Ile Glu Ala Val Ala Asn Glu Val Leu Lys Ser Gly Asn
 1460 1465 1470
 Ala Ser Thr Pro Gln Gln Leu Gln Asn Leu Thr Glu Asp Ile Arg Glu
 1475 1480 1485
 Arg Val Glu Thr Leu Ser Gln Val Glu Val Ile Leu Gln Gln Ser Ala
 1490 1495 1500
 Ala Asp Ile Ala Arg Ala Glu Leu Leu Leu Glu Glu Ala Lys Arg Ala
 1505 1510 1515 1520
 Ser Lys Ser Ala Thr Asp Val Lys Val Thr Ala Asp Met Val Lys Glu
 1525 1530 1535
 Ala Leu Glu Glu Ala Glu Lys Ala Gln Val Ala Ala Glu Lys Ala Ile
 1540 1545 1550
 Lys Gln Ala Asp Glu Asp Ile Gln Gly Thr Gln Asn Leu Leu Thr Ser
 1555 1560 1565
 Ile Glu Ser Glu Thr Ala Ala Ser Glu Glu Thr Leu Thr Asn Ala Ser
 1570 1575 1580
 Gln Arg Ile Ser Lys Leu Glu Arg Asn Val Glu Glu Leu Lys Arg Lys
 1585 1590 1595 1600
 Ala Ala Gln Asn Ser Gly Glu Ala Glu Tyr Ile Glu Lys Val Val Tyr
 1605 1610 1615
 Ser Val Lys Gln Asn Ala Asp Asp Val Lys Lys Thr Leu Asp Gly Glu
 1620 1625 1630
 Leu Asp Glu Lys Tyr Lys Lys Val Glu Ser Leu Ile Ala Gln Lys Thr
 1635 1640 1645
 Glu Glu Ser Ala Asp Ala Arg Arg Lys Ala Glu Leu Leu Gln Asn Glu
 1650 1655 1660
 Ala Lys Thr Leu Leu Ala Gln Ala Asn Ser Lys Leu Gln Leu Leu Glu
 1665 1670 1675 1680
 Asp Leu Glu Arg Lys Tyr Glu Asp Asn Gln Lys Tyr Leu Glu Asp Lys
 1685 1690 1695
 Ala Gln Glu Leu Val Arg Leu Glu Gly Glu Val Arg Ser Leu Leu Lys
 1700 1705 1710
 Asp Ile Ser Glu Lys Val Ala Val Tyr Ser Thr Cys Leu
 1715 1720 1725

<400> 21																	
cggggcaggc	tgctcccggg	gtaggtgagg	gaagcgcgga	ggcggcgcg	gggggcagtg												60
gtcggcgagc	agcgcggtcc	tcgctagggg	cgcccacccg	tcagtctctc	cggcgcgagc												120
cgccgccacc	gcccgcgccg	gagtcaggcc	cctggggcccc	caggctcaag	cagcgaagcg												180
gcctccgggg	gacgccgcta	ggcgagagga	acgcgccggg	gcccttgcc	tcgccgtgac												240
ccagcgtgcg	ggcggcggg	atg	aga	ggg	agc	cat	cgg	gcc	gcg	ccg	gcc	ctg					292
		Met	Arg	Gly	Ser	His	Arg	Ala	Ala	Pro	Ala	Leu					
		1					5					10					
cgg	ccc	cgg	ggg	cgg	ctc	tgg	ccc	gtg	ctg	gcc	gtg	ctg	gcg	gcg	gcc	340	
Arg	Pro	Arg	Gly	Arg	Leu	Trp	Pro	Val	Leu	Ala	Val	Leu	Ala	Ala	Ala		
			15					20					25				
gcc	gcg	gcg	ggc	tgt	gcc	cag	gca	gcc	atg	gac	gag	tgc	acg	gac	gag	388	
Ala	Ala	Ala	Gly	Cys	Ala	Gln	Ala	Ala	Met	Asp	Glu	Cys	Thr	Asp	Glu		
			30				35					40					
ggc	ggg	cgg	ccg	cag	cgc	tgc	atg	ccc	gag	ttc	gtc	aac	gcc	gct	ttc	436	
Gly	Gly	Arg	Pro	Gln	Arg	Cys	Met	Pro	Glu	Phe	Val	Asn	Ala	Ala	Phe		
		45				50					55						
aac	gtg	act	gtg	gtg	gcc	acc	aac	acg	tgt	ggg	act	ccg	ccc	gag	gaa	484	
Asn	Val	Thr	Val	Val	Ala	Thr	Asn	Thr	Cys	Gly	Thr	Pro	Pro	Glu	Glu		
	60				65				70						75		
tac	tgt	gtg	cag	acc	ggg	gtg	acc	ggg	gtc	acc	aag	tcc	tgt	cac	ctg	532	
Tyr	Cys	Val	Gln	Thr	Gly	Val	Thr	Gly	Val	Thr	Lys	Ser	Cys	His	Leu		
			80					85						90			
tgc	gac	gcc	ggg	cag	ccc	cac	ctg	cag	cac	ggg	gca	gcc	ttc	ctg	acc	580	
Cys	Asp	Ala	Gly	Gln	Pro	His	Leu	Gln	His	Gly	Ala	Ala	Phe	Leu	Thr		
			95				100					105					
gac	tac	aac	aac	cag	gcc	gac	acc	acc	tgg	tgg	caa	agc	cag	acc	atg	628	
Asp	Tyr	Asn	Asn	Gln	Ala	Asp	Thr	Thr	Trp	Trp	Gln	Ser	Gln	Thr	Met		
		110					115					120					
ctg	gcc	ggg	gtg	cag	tac	ccc	agc	tcc	atc	aac	ctc	acg	ctg	cac	ctg	676	
Leu	Ala	Gly	Val	Gln	Tyr	Pro	Ser	Ser	Ile	Asn	Leu	Thr	Leu	His	Leu		
	125					130					135						
gga	aaa	gct	ttt	gac	atc	acc	tat	gtg	cgt	ctc	aag	ttc	cac	acc	agc	724	
Gly	Lys	Ala	Phe	Asp	Ile	Thr	Tyr	Val	Arg	Leu	Lys	Phe	His	Thr	Ser		

140	145	150	155	
cgc ccg gag agc ttt gcc att tac aag cgc aca cgg gaa gac ggg ccc	772			
Arg Pro Glu Ser Phe Ala Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro				
160	165	170		
tgg att cct tac cag tac tac agt ggt tcc tgc gag aac acc tac tcc	820			
Trp Ile Pro Tyr Gln Tyr Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser				
175	180	185		
aag gca aac cgc ggc ttc atc agg aca gga ggg gac gag cag cag gcc	868			
Lys Ala Asn Arg Gly Phe Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala				
190	195	200		
ttg tgt act gat gaa ttc agt gac att tct ccc ctc act ggg ggc aac	916			
Leu Cys Thr Asp Glu Phe Ser Asp Ile Ser Pro Leu Thr Gly Gly Asn				
205	210	215		
gtg gcc ttt tct acc ctg gaa gga agg ccc agc gcc tat aac ttt gac	964			
Val Ala Phe Ser Thr Leu Glu Gly Arg Pro Ser Ala Tyr Asn Phe Asp				
220	225	230	235	
aat agc cct gtg ctg cag gaa tgg gta act gcc act gac atc aga gta	1012			
Asn Ser Pro Val Leu Gln Glu Trp Val Thr Ala Thr Asp Ile Arg Val				
240	245	250		
act ctt aat cgc ctg aac act ttt gga gat gaa gtg ttt aac gat ccc	1060			
Thr Leu Asn Arg Leu Asn Thr Phe Gly Asp Glu Val Phe Asn Asp Pro				
255	260	265		
aaa gtt ctc aag tcc tat tat tat gcc atc tct gat ttt gct gta ggt	1108			
Lys Val Leu Lys Ser Tyr Tyr Tyr Ala Ile Ser Asp Phe Ala Val Gly				
270	275	280		
ggc aga tgt aaa tgt aat gga cac gca agc gag tgt atg aag aac gaa	1156			
Gly Arg Cys Lys Cys Asn Gly His Ala Ser Glu Cys Met Lys Asn Glu				
285	290	295		
ttt gat aag ctg gtg tgt aat tgc aaa cat aac aca tat gga gta gac	1204			
Phe Asp Lys Leu Val Cys Asn Cys Lys His Asn Thr Tyr Gly Val Asp				
300	305	310	315	
tgt gaa aag tgt ctt cct ttc ttc aat gac cgg ccg tgg agg agg gca	1252			
Cys Glu Lys Cys Leu Pro Phe Phe Asn Asp Arg Pro Trp Arg Arg Ala				
320	325	330		
act gcg gaa agt gcc agt gaa tgc ctg ccc tgt gat tgc aat ggt cga	1300			
Thr Ala Glu Ser Ala Ser Glu Cys Leu Pro Cys Asp Cys Asn Gly Arg				
335	340	345		
tcc cag gaa tgc tac ttc gac cct gaa ctc tat cgt tcc act ggc cat	1348			
Ser Gln Glu Cys Tyr Phe Asp Pro Glu Leu Tyr Arg Ser Thr Gly His				
350	355	360		
ggg ggc cac tgt acc aac tgc cag gat aac aca gat ggc gcc cac tgt	1396			
Gly Gly His Cys Thr Asn Cys Gln Asp Asn Thr Asp Gly Ala His Cys				
365	370	375		
gag agg tgc cga gag aac ttc ttc cgc ctt ggc aac aat gaa gcc tgc	1444			
Glu Arg Cys Arg Glu Asn Phe Phe Arg Leu Gly Asn Asn Glu Ala Cys				
380	385	390	395	

tct tca tgc cac tgt agt cct gtg ggc tct cta agc aca cag tgt gat	1492
Ser Ser Cys His Cys Ser Pro Val Gly Ser Leu Ser Thr Gln Cys Asp	
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agt tac ggc aga tgc agc tgt aag cca gga gtg atg ggg gac aaa tgt	1540
Ser Tyr Gly Arg Cys Ser Cys Lys Pro Gly Val Met Gly Asp Lys Cys	
415 420 425	
gac cgt tgc cag cct gga ttc cat tct ctc act gaa gca gga tgc agg	1588
Asp Arg Cys Gln Pro Gly Phe His Ser Leu Thr Glu Ala Gly Cys Arg	
430 435 440	
cca tgc tct tgt gat ccc tct ggc agc ata gat gaa tgt aat gtt gaa	1636
Pro Cys Ser Cys Asp Pro Ser Gly Ser Ile Asp Glu Cys Asn Val Glu	
445 450 455	
aca gga aga tgt gtt tgc aaa gac aat gtc gaa ggc ttc aat tgt gaa	1684
Thr Gly Arg Cys Val Cys Lys Asp Asn Val Glu Gly Phe Asn Cys Glu	
460 465 470 475	
aga tgc aaa cct gga ttt ttt aat ctg gaa tca tct aat cct cgg ggt	1732
Arg Cys Lys Pro Gly Phe Phe Asn Leu Glu Ser Ser Asn Pro Arg Gly	
480 485 490	
tgc aca ccc tgc ttc tgc ttt ggg cat tct tct gtc tgt aca aac gct	1780
Cys Thr Pro Cys Phe Cys Phe Gly His Ser Ser Val Cys Thr Asn Ala	
495 500 505	
gtt ggc tac agt gtt tat tct atc tcc tct acc ttt cag att gat gag	1828
Val Gly Tyr Ser Val Tyr Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu	
510 515 520	
gat ggg tgg cgt gcg gaa cag aga gat ggc tct gaa gca tct ctc gag	1876
Asp Gly Trp Arg Ala Glu Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu	
525 530 535	
tgg tcc tct gag agg caa gat atc gcc gtg atc tca gac agc tac ttt	1924
Trp Ser Ser Glu Arg Gln Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe	
540 545 550 555	
cct cgg tac ttc att gct cct gca aag ttc ttg ggc aag cag gtg ttg	1972
Pro Arg Tyr Phe Ile Ala Pro Ala Lys Phe Leu Gly Lys Gln Val Leu	
560 565 570	
agt tat ggt cag aac ctc tcc ttc tcc ttt cga gtg gac agg cga gat	2020
Ser Tyr Gly Gln Asn Leu Ser Phe Ser Phe Arg Val Asp Arg Arg Asp	
575 580 585	
act cgc ctc tct gcc gaa gac ctt gtg ctt gag gga gct ggc tta aga	2068
Thr Arg Leu Ser Ala Glu Asp Leu Val Leu Glu Gly Ala Gly Leu Arg	
590 595 600	
gta tct gta ccc ttg atc gct cag ggc aat tcc tat cca agt gag acc	2116
Val Ser Val Pro Leu Ile Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr	
605 610 615	
act gtg aag tat gtc ttc agg ctc cat gaa gca aca gat tac cct tgg	2164
Thr Val Lys Tyr Val Phe Arg Leu His Glu Ala Thr Asp Tyr Pro Trp	
620 625 630 635	

agg cct gct ctt acc cct ttt gaa ttt cag aag ctc cta aac aac ttg	2212
Arg Pro Ala Leu Thr Pro Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu	
640 645 650	
acc tct atc aag ata cgt ggg aca tac agt gag aga agt gct gga tat	2260
Thr Ser Ile Lys Ile Arg Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr	
655 660 665	
ttg gat gat gtc acc ctg gca agt gct cgt cct ggg cct gga gtc cct	2308
Leu Asp Asp Val Thr Leu Ala Ser Ala Arg Pro Gly Pro Gly Val Pro	
670 675 680	
gca act tgg gtg gag tcc tgc acc tgt cct gtg gga tat gga ggg cag	2356
Ala Thr Trp Val Glu Ser Cys Thr Cys Pro Val Gly Tyr Gly Gly Gln	
685 690 695	
ttt tgt gag atg tgc ctc tca ggt tac aga aga gaa act cct aat ctt	2404
Phe Cys Glu Met Cys Leu Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu	
700 705 710 715	
gga cca tac agt cca tgt gtg ctt tgc gcc tgc aat gga cac agc gag	2452
Gly Pro Tyr Ser Pro Cys Val Leu Cys Ala Cys Asn Gly His Ser Glu	
720 725 730	
acc tgt gat cct gag aca ggt gtt tgt aac tgc aga gac aat acg gct	2500
Thr Cys Asp Pro Glu Thr Gly Val Cys Asn Cys Arg Asp Asn Thr Ala	
735 740 745	
ggc ccg cac tgt gag aag tgc agt gat ggg tac tat gga gat tca act	2548
Gly Pro His Cys Glu Lys Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr	
750 755 760	
gca ggc acc tcc tcc gat tgc caa ccc tgt ccg tgt cct gga ggt tca	2596
Ala Gly Thr Ser Ser Asp Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser	
765 770 775	
agt tgt gct gtt gtt ccc aag aca aag gag gtg gtg tgc acc aac tgt	2644
Ser Cys Ala Val Val Pro Lys Thr Lys Glu Val Val Cys Thr Asn Cys	
780 785 790 795	
cct act ggc acc act ggt aag aga tgt gag ctc tgt gat gat ggc tac	2692
Pro Thr Gly Thr Thr Gly Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr	
800 805 810	
ttt gga gac ccc ctg ggt aga aac ggc cct gtg aga ctt tgc cgc ctg	2740
Phe Gly Asp Pro Leu Gly Arg Asn Gly Pro Val Arg Leu Cys Arg Leu	
815 820 825	
tgc cag tgc agt gac aac atc gat ccc aac gca gtt gga aat tgc aat	2788
Cys Gln Cys Ser Asp Asn Ile Asp Pro Asn Ala Val Gly Asn Cys Asn	
830 835 840	
cgc ttg acg gga gaa tgc ctg aag tgc atc tat aac act gct ggc ttc	2836
Arg Leu Thr Gly Glu Cys Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe	
845 850 855	
tat tgt gac cgg tgc aaa gac gga ttt ttt gga aat ccc ctg gct ccc	2884
Tyr Cys Asp Arg Cys Lys Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro	
860 865 870 875	
aat cca gca gac aaa tgc aaa gcc tgc aat tgc aat ccg tat ggg acc	2932

Asn	Pro	Ala	Asp	Lys	Cys	Lys	Ala	Cys	Asn	Cys	Asn	Pro	Tyr	Gly	Thr	
				880					885					890		
atg	aag	cag	cag	agc	agc	tgt	aac	ccc	gtg	acg	ggg	cag	tgt	gaa	tgt	2980
Met	Lys	Gln	Gln	Ser	Ser	Cys	Asn	Pro	Val	Thr	Gly	Gln	Cys	Glu	Cys	
				895				900					905			
ttg	cct	cac	gtg	act	ggc	cag	gac	tgt	ggg	gct	tgt	gac	cct	gga	ttc	3028
Leu	Pro	His	Val	Thr	Gly	Gln	Asp	Cys	Gly	Ala	Cys	Asp	Pro	Gly	Phe	
		910					915					920				
tac	aat	ctg	cag	agt	ggg	caa	ggc	tgt	gag	agg	tgt	gac	tgc	cat	gcc	3076
Tyr	Asn	Leu	Gln	Ser	Gly	Gln	Gly	Cys	Glu	Arg	Cys	Asp	Cys	His	Ala	
	925					930					935					
ttg	ggc	tcc	acc	aat	ggg	cag	tgt	gac	atc	cgc	acc	ggc	cag	tgt	gag	3124
Leu	Gly	Ser	Thr	Asn	Gly	Gln	Cys	Asp	Ile	Arg	Thr	Gly	Gln	Cys	Glu	
940					945				950					955		
tgc	cag	ccc	ggc	atc	act	ggg	cag	cac	tgt	gag	cgc	tgt	gag	gtc	aac	3172
Cys	Gln	Pro	Gly	Ile	Thr	Gly	Gln	His	Cys	Glu	Arg	Cys	Glu	Val	Asn	
				960					965					970		
cac	ttt	ggg	ttt	gga	cct	gaa	ggc	tgc	aaa	ccc	tgt	gac	tgt	cat	cct	3220
His	Phe	Gly	Phe	Gly	Pro	Glu	Gly	Cys	Lys	Pro	Cys	Asp	Cys	His	Pro	
			975					980					985			
gag	gga	tct	ctt	tca	ctt	cag	tgc	aaa	gat	gat	ggg	cgc	tgt	gaa	tgc	3268
Glu	Gly	Ser	Leu	Ser	Leu	Gln	Cys	Lys	Asp	Asp	Gly	Arg	Cys	Glu	Cys	
		990					995					1000				
aga	gaa	ggc	ttt	gtg	gga	aat	cgc	tgt	gac	cag	tgt	gaa	gaa	aac	tat	3316
Arg	Glu	Gly	Phe	Val	Gly	Asn	Arg	Cys	Asp	Gln	Cys	Glu	Glu	Asn	Tyr	
	1005					1010					1015					
ttc	tac	aat	cgg	tct	tgg	cct	ggc	tgc	cag	gaa	tgt	cca	gct	tgt	tac	3364
Phe	Tyr	Asn	Arg	Ser	Trp	Pro	Gly	Cys	Gln	Glu	Cys	Pro	Ala	Cys	Tyr	
1020				1025					1030					1035		
cgg	ctg	gta	aag	gat	aag	gtt	gct	gat	cat	aga	gtg	aag	ctc	cag	gaa	3412
Arg	Leu	Val	Lys	Asp	Lys	Val	Ala	Asp	His	Arg	Val	Lys	Leu	Gln	Glu	
			1040					1045					1050			
tta	gag	agt	ctc	ata	gca	aac	ctt	gga	act	ggg	gat	gag	atg	gtg	aca	3460
Leu	Glu	Ser	Leu	Ile	Ala	Asn	Leu	Gly	Thr	Gly	Asp	Glu	Met	Val	Thr	
		1055					1060					1065				
gat	caa	gcc	ttc	gag	gat	aga	cta	aag	gaa	gca	gag	agg	gaa	gtt	atg	3508
Asp	Gln	Ala	Phe	Glu	Asp	Arg	Leu	Lys	Glu	Ala	Glu	Arg	Glu	Val	Met	
		1070					1075					1080				
gac	ctc	ctt	cgt	gag	gcc	cag	gat	gtc	aaa	gat	gtt	gac	cag	aat	ttg	3556
Asp	Leu	Leu	Arg	Glu	Ala	Gln	Asp	Val	Lys	Asp	Val	Asp	Gln	Asn	Leu	
	1085					1090					1095					
atg	gat	cgc	cta	cag	aga	gtg	aat	aac	act	ctg	tcc	agc	caa	att	agc	3604
Met	Asp	Arg	Leu	Gln	Arg	Val	Asn	Asn	Thr	Leu	Ser	Ser	Gln	Ile	Ser	
1100				1105					1110					1115		
cgt	tta	cag	aat	atc	cgg	aat	acc	att	gaa	gag	act	gga	aac	ttg	gct	3652
Arg	Leu	Gln	Asn	Ile	Arg	Asn	Thr	Ile	Glu	Glu	Thr	Gly	Asn	Leu	Ala	

1120	1125	1130	
gaa caa gcg cgt gcc cat gta gag aac aca gag cgg ttg att gaa atc			3700
Glu Gln Ala Arg Ala His Val Glu Asn Thr Glu Arg Leu Ile Glu Ile			
1135	1140	1145	
gca tcc aga gaa ctt gag aaa gca aaa gtc gct gct gcc aat gtg tca			3748
Ala Ser Arg Glu Leu Glu Lys Ala Lys Val Ala Ala Ala Asn Val Ser			
1150	1155	1160	
gtc act cag cca gaa tct aca ggg gac cca aac aac atg act ctt ttg			3796
Val Thr Gln Pro Glu Ser Thr Gly Asp Pro Asn Asn Met Thr Leu Leu			
1165	1170	1175	
gca gaa gag gct cga aag ctt gct gaa cgt cat aaa cag gaa gct gat			3844
Ala Glu Glu Ala Arg Lys Leu Ala Glu Arg His Lys Gln Glu Ala Asp			
1180	1185	1190	1195
gac att gtt cga gtg gca aag aca gcc aat gat acg tca act gag gca			3892
Asp Ile Val Arg Val Ala Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala			
1200	1205	1210	
tac aac ctg ctt ctg agg aca ctg gca gga gaa aat caa aca gca ttt			3940
Tyr Asn Leu Leu Leu Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe			
1215	1220	1225	
gag att gaa gag ctt aat agg aag tat gaa caa gcg aag aac atc tca			3988
Glu Ile Glu Glu Leu Asn Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser			
1230	1235	1240	
cag gat ctg gaa aaa caa gct gcc cga gta cat gag gag gcc aaa agg			4036
Gln Asp Leu Glu Lys Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg			
1245	1250	1255	
gcc ggt gac aaa gct gtg gag atc tat gcc agc gtg gct cag ctg agc			4084
Ala Gly Asp Lys Ala Val Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser			
1260	1265	1270	1275
cct ttg gac tct gag aca ctg gag aat gaa gca aat aac ata aag atg			4132
Pro Leu Asp Ser Glu Thr Leu Glu Asn Glu Ala Asn Asn Ile Lys Met			
1280	1285	1290	
gaa gct gag aat ctg gaa caa ctg att gac cag aaa tta aaa gat tat			4180
Glu Ala Glu Asn Leu Glu Gln Leu Ile Asp Gln Lys Leu Lys Asp Tyr			
1295	1300	1305	
gag gac ctc aga gaa gat atg aga ggg aag gaa ctt gaa gtc aag aac			4228
Glu Asp Leu Arg Glu Asp Met Arg Gly Lys Glu Leu Glu Val Lys Asn			
1310	1315	1320	
ctt ctg gag aaa ggc aag act gaa cag cag acc gca gac caa ctc cta			4276
Leu Leu Glu Lys Gly Lys Thr Glu Gln Gln Thr Ala Asp Gln Leu Leu			
1325	1330	1335	
gcc cga gct gat gct gcc aag gcc ctc gct gaa gaa gct gca aag aag			4324
Ala Arg Ala Asp Ala Ala Lys Ala Leu Ala Glu Glu Ala Ala Lys Lys			
1340	1345	1350	1355
gga cgg gat acc tta caa gaa gct aat gac att ctc aac aac ctg aaa			4372
Gly Arg Asp Thr Leu Gln Glu Ala Asn Asp Ile Leu Asn Asn Leu Lys			
1360	1365	1370	

gat ttt gat agg cgc gtg aac gat aac aag acg gcc gca gag gag gca	4420
Asp Phe Asp Arg Arg Val Asn Asp Asn Lys Thr Ala Ala Glu Glu Ala	
1375 1380 1385	
cta agg aag att cct gcc atc aac cag acc atc act gaa gcc aat gaa	4468
Leu Arg Lys Ile Pro Ala Ile Asn Gln Thr Ile Thr Glu Ala Asn Glu	
1390 1395 1400	
aag acc aga gaa gcc cag cag gcc ctg ggc agt gct gcg gcg gat gcc	4516
Lys Thr Arg Glu Ala Gln Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala	
1405 1410 1415	
aca gag gcc aag aac aag gcc cat gag gcg gag agg atc gca agc gct	4564
Thr Glu Ala Lys Asn Lys Ala His Glu Ala Glu Arg Ile Ala Ser Ala	
1420 1425 1430 1435	
gtc caa aag aat gcc acc agc acc aag gca gaa gct gaa aga act ttt	4612
Val Gln Lys Asn Ala Thr Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe	
1440 1445 1450	
gca gaa gtt aca gat ctg gat aat gag gtg aac aat atg ttg aag caa	4660
Ala Glu Val Thr Asp Leu Asp Asn Glu Val Asn Asn Met Leu Lys Gln	
1455 1460 1465	
ctg cag gaa gca gaa aaa gag cta aag aga aaa caa gat gac gct gac	4708
Leu Gln Glu Ala Glu Lys Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp	
1470 1475 1480	
cag gac atg atg atg gca ggg atg gct tca cag gct gct caa gaa gcc	4756
Gln Asp Met Met Met Ala Gly Met Ala Ser Gln Ala Ala Gln Glu Ala	
1485 1490 1495	
gag atc aat gcc aga aaa gcc aaa aac tct gtt act agc ctc ctc agc	4804
Glu Ile Asn Ala Arg Lys Ala Lys Asn Ser Val Thr Ser Leu Leu Ser	
1500 1505 1510 1515	
att att aat gac ctc ttg gag cag ctg ggg cag ctg gat aca gtg gac	4852
Ile Ile Asn Asp Leu Leu Glu Gln Leu Gly Gln Leu Asp Thr Val Asp	
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ctg aat aag cta aac gag att gaa ggc acc cta aac aaa gcc aaa gat	4900
Leu Asn Lys Leu Asn Glu Ile Glu Gly Thr Leu Asn Lys Ala Lys Asp	
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gaa atg aag gtc agc gat ctt gat agg aaa gtg tct gac ctg gag aat	4948
Glu Met Lys Val Ser Asp Leu Asp Arg Lys Val Ser Asp Leu Glu Asn	
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gaa gcc aag aag cag gag gct gcc atc atg gac tat aac cga gat atc	4996
Glu Ala Lys Lys Gln Glu Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile	
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gag gag atc atg aag gac att cgc aat ctg gag gac atc agg aag acc	5044
Glu Glu Ile Met Lys Asp Ile Arg Asn Leu Glu Asp Ile Arg Lys Thr	
1580 1585 1590 1595	
tta cca tct ggc tgc ttc aac acc ccg tcc att gaa aag ccc	5086
Leu Pro Ser Gly Cys Phe Asn Thr Pro Ser Ile Glu Lys Pro	
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 ctgtcctttt gaaccaggaa aagtcacaga gtttaaagag aagcaaatta aacatcctga 5266
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 Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val
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 Ala Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr
 65 70 75 80
 Gly Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln
 85 90 95
 Pro His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln
 100 105 110
 Ala Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln
 115 120 125
 Tyr Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp
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 Ile Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe
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 Ala Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln
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 Tyr Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly
 180 185 190
 Phe Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu
 195 200 205
 Phe Ser Asp Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser Thr
 210 215 220
 Leu Glu Gly Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val Leu
 225 230 235 240
 Gln Glu Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg Leu

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Tyr	Tyr	Tyr	Ala	Ile	Ser	Asp	Phe	Ala	Val	Gly	Gly	Arg	Cys	Lys	Cys				
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Asn	Gly	His	Ala	Ser	Glu	Cys	Met	Lys	Asn	Glu	Phe	Asp	Lys	Leu	Val				
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Cys	Asn	Cys	Lys	His	Asn	Thr	Tyr	Gly	Val	Asp	Cys	Glu	Lys	Cys	Leu				
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Pro	Phe	Phe	Asn	Asp	Arg	Pro	Trp	Arg	Arg	Ala	Thr	Ala	Glu	Ser	Ala				
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Cys	Phe	Gly	His	Ser	Ser	Val	Cys	Thr	Asn	Ala	Val	Gly	Tyr	Ser	Val				
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Gln	Asp	Ile	Ala	Val	Ile	Ser	Asp	Ser	Tyr	Phe	Pro	Arg	Tyr	Phe	Ile				
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 Ile Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Val
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 Phe Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr
 625 630 635 640
 Pro Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile
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 675 680 685
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 690 695 700
 Leu Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu Gly Pro Tyr Ser Pro
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 Cys Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu
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 Thr Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu
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 Asp Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val
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 Pro Lys Thr Lys Glu Val Val Cys Thr Asn Cys Pro Thr Gly Thr Thr
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 Gly Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu
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 Asn Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu
 835 840 845
 Cys Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys
 850 855 860
 Lys Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys
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 Cys Lys Ala Cys Asn Cys Asn Pro Tyr Gly Thr Met Lys Gln Gln Ser
 885 890 895

Ser Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr
 900 905 910
 Gly Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser
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 Gly Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn
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 Gly Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile
 945 950 955 960
 Thr Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly
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 Pro Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser
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 Leu Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val
 995 1000 1005
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 1075 1080 1085
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 Ser Thr Gly Asp Pro Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg
 1170 1175 1180
 Lys Leu Ala Glu Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val
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 Ala Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu Leu
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 Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe Glu Ile Glu Glu Leu

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Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala 1250	1255	1260
Val Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu 265	1270	1275 1280
Thr Leu Glu Asn Glu Ala Asn Asn Ile Lys Met Glu Ala Glu Asn Leu 1285	1290	1295
Glu Gln Leu Ile Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu 1300	1305	1310
Asp Met Arg Gly Lys Glu Leu Glu Val Lys Asn Leu Leu Glu Lys Gly 1315	1320	1325
Lys Thr Glu Gln Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala 1330	1335	1340
Ala Lys Ala Leu Ala Glu Glu Ala Ala Lys Lys Gly Arg Asp Thr Leu 345	1350	1355 1360
Gln Glu Ala Asn Asp Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg 1365	1370	1375
Val Asn Asp Asn Lys Thr Ala Ala Glu Glu Ala Leu Arg Lys Ile Pro 1380	1385	1390
Ala Ile Asn Gln Thr Ile Thr Glu Ala Asn Glu Lys Thr Arg Glu Ala 1395	1400	1405
Gln Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn 1410	1415	1420
Lys Ala His Glu Ala Glu Arg Ile Ala Ser Ala Val Gln Lys Asn Ala 425	1430	1435 1440
Thr Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp 1445	1450	1455
Leu Asp Asn Glu Val Asn Asn Met Leu Lys Gln Leu Gln Glu Ala Glu 1460	1465	1470
Lys Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Met 1475	1480	1485
Ala Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala Arg 1490	1495	1500
Lys Ala Lys Asn Ser Val Thr Ser Leu Leu Ser Ile Ile Asn Asp Leu 505	1510	1515 1520
Leu Glu Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn 1525	1530	1535
Glu Ile Glu Gly Thr Leu Asn Lys Ala Lys Asp Glu Met Lys Val Ser 1540	1545	1550

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Glu Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile Glu Glu Ile Met Lys
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 Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val Ala
 20 25 30

acc aac acg tgt ggg act ccg ccc gag gaa tac tgt gtg cag acc ggg 144
 Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly
 35 40 45

gtg acc ggg gtc acc aag tcc tgt cac ctg tgc gac gcc ggg cag ccc 192
 Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro
 50 55 60

cac ctg cag cac ggg gca gcc ttc ctg acc gac tac aac aac cag gcc 240
 His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala
 65 70 75 80

gac acc acc tgg tgg caa agc cag acc atg ctg gcc ggg gtg cag tac 288
 Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr
 85 90 95

ccc agc tcc atc aac ctc acg ctg cac ctg gga aaa gct ttt gac atc 336
 Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile
 100 105 110

acc tat gtg cgt ctc aag ttc cac acc agc cgc ccg gag agc ttt gcc 384
 Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala
 115 120 125

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 Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln Tyr
 130 135 140

tac agt ggt tcc tgc gag aac acc tac tcc aag gca aac cgc ggc ttc 480

Tyr 145	Ser	Gly	Ser	Cys	Glu 150	Asn	Thr	Tyr	Ser	Lys 155	Ala	Asn	Arg	Gly	Phe 160	
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Ser	Asp	Ile	Ser	Pro	Leu	Thr	Gly	Gly	Asn 185	Val	Ala	Phe	Ser	Thr 190	Leu	
gaa	gga	agg	ccc	agc	gcc	tat	aac	ttt	gac	aat	agc	cct	gtg	ctg	cag	624
Glu	Gly	Arg	Pro	Ser	Ala	Tyr	Asn 200	Phe	Asp	Asn	Ser	Pro 205	Val	Leu	Gln	
gaa	tgg	gta	act	gcc	act	gac	atc	aga	gta	act	ctt	aat	cgc	ctg	aac	672
Glu	Trp	Val	Thr	Ala	Thr	Asp	Ile 215	Arg	Val	Thr	Leu 220	Asn	Arg	Leu	Asn	
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Gly	His	Ala	Ser	Glu	Cys	Met	Lys 265	Asn	Glu	Phe	Asp	Lys	Leu	Val	Cys 270	
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Phe	Phe	Asn	Asp	Arg	Pro	Trp	Arg 295	Arg	Ala	Thr	Ala 300	Glu	Ser	Ala	Ser	
gaa	tgc	ctg	ccc	tgt	gat	tgc	aat	ggg	cga	tcc	cag	gaa	tgc	tac	ttc	960
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Asp	Pro	Glu	Leu	Tyr	Arg	Ser	Thr 325	Gly	His	Gly	Gly	His	Cys	Thr 335	Asn	
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Cys	Gln	Asp	Asn	Thr	Asp	Gly	Ala 345	His	Cys	Glu	Arg	Cys	Arg	Glu	Asn 350	
ttc	ttc	cgc	ctt	ggc	aac	aat	gaa	gcc	tgc	tct	tca	tgc	cac	tgt	agt	1104
Phe	Phe	Arg	Leu	Gly	Asn	Asn	Glu 360	Ala	Cys	Ser	Ser	Cys 365	His	Cys	Ser	
cct	gtg	ggc	tct	cta	agc	aca	cag	tgt	gat	agt	tac	ggc	aga	tgc	agc	1152
Pro	Val	Gly	Ser	Leu	Ser	Thr	Gln 375	Cys	Asp	Ser	Tyr	Gly	Arg	Cys	Ser 380	
tgt	aag	cca	gga	gtg	atg	ggg	gac	aaa	tgt	gac	cgt	tgc	cag	cct	gga	1200
Cys	Lys	Pro	Gly	Val	Met	Gly	Asp	Lys	Cys	Asp	Arg	Cys	Gln	Pro	Gly	

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Phe His Ser Leu Thr 405	Glu Ala Gly Cys Arg 410	Pro Cys Ser Cys Asp 415	Pro	
tct ggc agc ata gat gaa tgt aat gtt gaa aca gga aga tgt gtt tgc				1296
Ser Gly Ser Ile Asp 420	Glu Cys Asn Val 425	Glu Thr Gly Arg Cys 430	Val Cys	
aaa gac aat gtc gaa ggc ttc aat tgt gaa aga tgc aaa cct gga ttt				1344
Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly Phe	435	440	445	
ttt aat ctg gaa tca tct aat cct cgg ggt tgc aca ccc tgc ttc tgc				1392
Phe Asn Leu Glu Ser Ser Asn Pro Arg Gly Cys Thr Pro Cys Phe Cys	450	455	460	
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Phe Gly His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val Tyr	465	470	475	480
tct atc tcc tct acc ttt cag att gat gag gat ggg tgg cgt gcg gaa				1488
Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Ala Glu	485	490	495	
cag aga gat ggc tct gaa gca tct ctc gag tgg tcc tct gag agg caa				1536
Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg Gln	500	505	510	
gat atc gcc gtg atc tca gac agc tac ttt cct cgg tac ttc att gct				1584
Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile Ala	515	520	525	
cct gca aag ttc ttg ggc aag cag gtg ttg agt tat ggt cag aac ctc				1632
Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn Leu	530	535	540	
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Ser Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala Glu	545	550	555	560
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Asp Leu Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu Ile	565	570	575	
gct cag ggc aat tcc tat cca agt gag acc act gtg aag tat gtc ttc				1776
Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Val Phe	580	585	590	
agg ctc cat gaa gca aca gat tac cct tgg agg cct gct ctt acc cct				1824
Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr Pro	595	600	605	
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Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile Arg	610	615	620	
ggg aca tac agt gag aga agt gct gga tat ttg gat gat gtc acc ctg				1920
Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr Leu	625	630	635	640

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Ala Ser Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val Glu Ser	
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Cys Thr Cys Pro Val Gly Tyr Gly Gly Gln Phe Cys Glu Met Cys Leu	
660 665 670	
tca ggt tac aga aga gaa act cct aat ctt gga cca tac agt cca tgt	2064
Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu Gly Pro Tyr Ser Pro Cys	
675 680 685	
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Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu Thr	
690 695 700	
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Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu Lys	
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Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr Ala Gly Thr Ser Ser Asp	
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Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val Pro	
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Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu Gly	
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Arg Asn Gly Pro Val Arg Leu Cys Arg Leu Cys Gln Cys Ser Asp Asn	
785 790 795 800	
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Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu Cys	
805 810 815	
ctg aag tgc atc tat aac act gct ggc ttc tat tgt gac cgg tgc aaa	2496
Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys Lys	
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gac gga ttt ttt gga aat ccc ctg gct ccc aat cca gca gac aaa tgc	2544
Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys Cys	
835 840 845	
aaa gcc tgc aat tgc aat ccg tat ggg acc atg aag cag cag agc agc	2592
Lys Ala Cys Asn Cys Asn Pro Tyr Gly Thr Met Lys Gln Gln Ser Ser	
850 855 860	
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Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr Gly	
865 870 875 880	

cag gac tgt ggt gct tgt gac cct gga ttc tac aat ctg cag agt ggg	2688
Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser Gly	
885 890 895	
caa ggc tgt gag agg tgt gac tgc cat gcc ttg ggc tcc acc aat ggg	2736
Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn Gly	
900 905 910	
cag tgt gac atc cgc acc ggc cag tgt gag tgc cag ccc ggc atc act	2784
Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile Thr	
915 920 925	
ggt cag cac tgt gag cgc tgt gag gtc aac cac ttt ggg ttt gga cct	2832
Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly Pro	
930 935 940	
gaa ggc tgc aaa ccc tgt gac tgt cat cct gag gga tct ctt tca ctt	2880
Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser Leu	
945 950 955 960	
cag tgc aaa gat gat ggt cgc tgt gaa tgc aga gaa ggc ttt gtg gga	2928
Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val Gly	
965 970 975	
aat cgc tgt gac cag tgt gaa gaa aac tat ttc tac aat cgg tct tgg	2976
Asn Arg Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser Trp	
980 985 990	
cct ggc tgc cag gaa tgt cca gct tgt tac cgg ctg gta aag gat aag	3024
Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp Lys	
995 1000 1005	
gtt gct gat cat aga gtg aag ctc cag gaa tta gag agt ctc ata gca	3072
Val Ala Asp His Arg Val Lys Leu Gln Glu Leu Glu Ser Leu Ile Ala	
1010 1015 1020	
aac ctt gga act ggg gat gag atg gtg aca gat caa gcc ttc gag gat	3120
Asn Leu Gly Thr Gly Asp Glu Met Val Thr Asp Gln Ala Phe Glu Asp	
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aga cta aag gaa gca gag agg gaa gtt atg gac ctc ctt cgt gag gcc	3168
Arg Leu Lys Glu Ala Glu Arg Glu Val Met Asp Leu Leu Arg Glu Ala	
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cag gat gtc aaa gat gtt gac cag aat ttg atg gat cgc cta cag aga	3216
Gln Asp Val Lys Asp Val Asp Gln Asn Leu Met Asp Arg Leu Gln Arg	
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gtg aat aac act ctg tcc agc caa att agc cgt tta cag aat atc cgg	3264
Val Asn Asn Thr Leu Ser Ser Gln Ile Ser Arg Leu Gln Asn Ile Arg	
1075 1080 1085	
aat acc att gaa gag act gga aac ttg gct gaa caa gcg cgt gcc cat	3312
Asn Thr Ile Glu Glu Thr Gly Asn Leu Ala Glu Gln Ala Arg Ala His	
1090 1095 1100	
gta gag aac aca gag cgg ttg att gaa atc gca tcc aga gaa ctt gag	3360
Val Glu Asn Thr Glu Arg Leu Ile Glu Ile Ala Ser Arg Glu Leu Glu	
1105 1110 1115 1120	
aaa gca aaa gtc gct gct gcc aat gtg tca gtc act cag cca gaa tct	3408

Lys	Ala	Lys	Val	Ala	Ala	Ala	Asn	Val	Ser	Val	Thr	Gln	Pro	Glu	Ser	
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aca	ggg	gac	cca	aac	aac	atg	act	ctt	ttg	gca	gaa	gag	gct	cga	aag	3456
Thr	Gly	Asp	Pro	Asn	Asn	Met	Thr	Leu	Leu	Ala	Glu	Glu	Ala	Arg	Lys	
			1140					1145					1150			
ctt	gct	gaa	cgt	cat	aaa	cag	gaa	gct	gat	gac	att	gtt	cga	gtg	gca	3504
Leu	Ala	Glu	Arg	His	Lys	Gln	Glu	Ala	Asp	Asp	Ile	Val	Arg	Val	Ala	
		1155					1160					1165				
aag	aca	gcc	aat	gat	acg	tca	act	gag	gca	tac	aac	ctg	ctt	ctg	agg	3552
Lys	Thr	Ala	Asn	Asp	Thr	Ser	Thr	Glu	Ala	Tyr	Asn	Leu	Leu	Leu	Arg	
	1170					1175				1180						
aca	ctg	gca	gga	gaa	aat	caa	aca	gca	ttt	gag	att	gaa	gag	ctt	aat	3600
Thr	Leu	Ala	Gly	Glu	Asn	Gln	Thr	Ala	Phe	Glu	Ile	Glu	Glu	Leu	Asn	
1185					1190				1195						1200	
agg	aag	tat	gaa	caa	gcg	aag	aac	atc	tca	cag	gat	ctg	gaa	aaa	caa	3648
Arg	Lys	Tyr	Glu	Gln	Ala	Lys	Asn	Ile	Ser	Gln	Asp	Leu	Glu	Lys	Gln	
			1205					1210						1215		
gct	gcc	cga	gta	cat	gag	gag	gcc	aaa	agg	gcc	ggg	gac	aaa	gct	gtg	3696
Ala	Ala	Arg	Val	His	Glu	Glu	Ala	Lys	Arg	Ala	Gly	Asp	Lys	Ala	Val	
		1220					1225					1230				
gag	atc	tat	gcc	agc	gtg	gct	cag	ctg	agc	cct	ttg	gac	tct	gag	aca	3744
Glu	Ile	Tyr	Ala	Ser	Val	Ala	Gln	Leu	Ser	Pro	Leu	Asp	Ser	Glu	Thr	
	1235					1240					1245					
ctg	gag	aat	gaa	gca	aat	aac	ata	aag	atg	gaa	gct	gag	aat	ctg	gaa	3792
Leu	Glu	Asn	Glu	Ala	Asn	Asn	Ile	Lys	Met	Glu	Ala	Glu	Asn	Leu	Glu	
	1250				1255				1260							
caa	ctg	att	gac	cag	aaa	tta	aaa	gat	tat	gag	gac	ctc	aga	gaa	gat	3840
Gln	Leu	Ile	Asp	Gln	Lys	Leu	Lys	Asp	Tyr	Glu	Asp	Leu	Arg	Glu	Asp	
1265				1270				1275						1280		
atg	aga	ggg	aag	gaa	ctt	gaa	gtc	aag	aac	ctt	ctg	gag	aaa	ggc	aag	3888
Met	Arg	Gly	Lys	Glu	Leu	Glu	Val	Lys	Asn	Leu	Leu	Glu	Lys	Gly	Lys	
			1285				1290						1295			
act	gaa	cag	cag	acc	gca	gac	caa	ctc	cta	gcc	cga	gct	gat	gct	gcc	3936
Thr	Glu	Gln	Gln	Thr	Ala	Asp	Gln	Leu	Leu	Ala	Arg	Ala	Asp	Ala	Ala	
		1300					1305					1310				
aag	gcc	ctc	gct	gaa	gaa	gct	gca	aag	aag	gga	cgg	gat	acc	tta	caa	3984
Lys	Ala	Leu	Ala	Glu	Glu	Ala	Ala	Lys	Lys	Gly	Arg	Asp	Thr	Leu	Gln	
	1315					1320					1325					
gaa	gct	aat	gac	att	ctc	aac	aac	ctg	aaa	gat	ttt	gat	agg	cgc	gtg	4032
Glu	Ala	Asn	Asp	Ile	Leu	Asn	Asn	Leu	Lys	Asp	Phe	Asp	Arg	Arg	Val	
	1330				1335				1340							
aac	gat	aac	aag	acg	gcc	gca	gag	gag	gca	cta	agg	aag	att	cct	gcc	4080
Asn	Asp	Asn	Lys	Thr	Ala	Ala	Glu	Glu	Ala	Leu	Arg	Lys	Ile	Pro	Ala	
1345				1350				1355					1360			
atc	aac	cag	acc	atc	act	gaa	gcc	aat	gaa	aag	acc	aga	gaa	gcc	cag	4128
Ile	Asn	Gln	Thr	Ile	Thr	Glu	Ala	Asn	Glu	Lys	Thr	Arg	Glu	Ala	Gln	

1365	1370	1375	
cag gcc ctg ggc agt gct gcg gcg gat gcc aca gag gcc aag aac aag			4176
Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys			
1380	1385	1390	
gcc cat gag gcg gag agg atc gca agc gct gtc caa aag aat gcc acc			4224
Ala His Glu Ala Glu Arg Ile Ala Ser Ala Val Gln Lys Asn Ala Thr			
1395	1400	1405	
agc acc aag gca gaa gct gaa aga act ttt gca gaa gtt aca gat ctg			4272
Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp Leu			
1410	1415	1420	
gat aat gag gtg aac aat atg ttg aag caa ctg cag gaa gca gaa aaa			4320
Asp Asn Glu Val Asn Asn Met Leu Lys Gln Leu Gln Glu Ala Glu Lys			
1425	1430	1435	1440
gag cta aag aga aaa caa gat gac gct gac cag gac atg atg atg gca			4368
Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Met Ala			
1445	1450	1455	
ggg atg gct tca cag gct gct caa gaa gcc gag atc aat gcc aga aaa			4416
Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala Arg Lys			
1460	1465	1470	
gcc aaa aac tct gtt act agc ctc ctc agc att att aat gac ctc ttg			4464
Ala Lys Asn Ser Val Thr Ser Leu Leu Ser Ile Ile Asn Asp Leu Leu			
1475	1480	1485	
gag cag ctg ggg cag ctg gat aca gtg gac ctg aat aag cta aac gag			4512
Glu Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu			
1490	1495	1500	
att gaa ggc acc cta aac aaa gcc aaa gat gaa atg aag gtc agc gat			4560
Ile Glu Gly Thr Leu Asn Lys Ala Lys Asp Glu Met Lys Val Ser Asp			
1505	1510	1515	1520
ctt gat agg aaa gtg tct gac ctg gag aat gaa gcc aag aag cag gag			4608
Leu Asp Arg Lys Val Ser Asp Leu Glu Asn Glu Ala Lys Lys Gln Glu			
1525	1530	1535	
gct gcc atc atg gac tat aac cga gat atc gag gag atc atg aag gac			4656
Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile Glu Glu Ile Met Lys Asp			
1540	1545	1550	
att cgc aat ctg gag gac atc agg aag acc tta cca tct ggc tgc ttc			4704
Ile Arg Asn Leu Glu Asp Ile Arg Lys Thr Leu Pro Ser Gly Cys Phe			
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aac acc ccg tcc att gaa aag ccc tagtgtcttt agggctggaa ggcagcatcc			4758
Asn Thr Pro Ser Ile Glu Lys Pro			
1570	1575		
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agacccccac tctctgctg ctgtccatca ctgtcctttt gaaccaggaa aagtcacaga			4878
gtttaaagag aagcaaatta aacatcctga atcggaaca aagggtttta tctaataaag			4938
tgtctcttcc			4948

<210> 24

<211> 1576

<212> PRT

<213> Homo sapiens

<400> 24

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Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val Ala
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Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly
 35 40 45

Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro
 50 55 60

His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala
 65 70 75 80

Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr
 85 90 95

Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile
 100 105 110

Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala
 115 120 125

Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln Tyr
 130 135 140

Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly Phe
 145 150 155 160

Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu Phe
 165 170 175

Ser Asp Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser Thr Leu
 180 185 190

Glu Gly Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val Leu Gln
 195 200 205

Glu Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg Leu Asn
 210 215 220

Thr Phe Gly Asp Glu Val Phe Asn Asp Pro Lys Val Leu Lys Ser Tyr
 225 230 235 240

Tyr Tyr Ala Ile Ser Asp Phe Ala Val Gly Gly Arg Cys Lys Cys Asn
 245 250 255

Gly His Ala Ser Glu Cys Met Lys Asn Glu Phe Asp Lys Leu Val Cys
 260 265 270

Asn Cys Lys His Asn Thr Tyr Gly Val Asp Cys Glu Lys Cys Leu Pro
 275 280 285

Phe Phe Asn Asp Arg Pro Trp Arg Arg Ala Thr Ala Glu Ser Ala Ser
 290 295 300
 Glu Cys Leu Pro Cys Asp Cys Asn Gly Arg Ser Gln Glu Cys Tyr Phe
 305 310 315 320
 Asp Pro Glu Leu Tyr Arg Ser Thr Gly His Gly Gly His Cys Thr Asn
 325 330 335
 Cys Gln Asp Asn Thr Asp Gly Ala His Cys Glu Arg Cys Arg Glu Asn
 340 345 350
 Phe Phe Arg Leu Gly Asn Asn Glu Ala Cys Ser Ser Cys His Cys Ser
 355 360 365
 Pro Val Gly Ser Leu Ser Thr Gln Cys Asp Ser Tyr Gly Arg Cys Ser
 370 375 380
 Cys Lys Pro Gly Val Met Gly Asp Lys Cys Asp Arg Cys Gln Pro Gly
 385 390 395 400
 Phe His Ser Leu Thr Glu Ala Gly Cys Arg Pro Cys Ser Cys Asp Pro
 405 410 415
 Ser Gly Ser Ile Asp Glu Cys Asn Val Glu Thr Gly Arg Cys Val Cys
 420 425 430
 Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly Phe
 435 440 445
 Phe Asn Leu Glu Ser Ser Asn Pro Arg Gly Cys Thr Pro Cys Phe Cys
 450 455 460
 Phe Gly His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val Tyr
 465 470 475 480
 Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Ala Glu
 485 490 495
 Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg Gln
 500 505 510
 Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile Ala
 515 520 525
 Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn Leu
 530 535 540
 Ser Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala Glu
 545 550 555 560
 Asp Leu Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu Ile
 565 570 575
 Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Val Phe
 580 585 590
 Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr Pro
 595 600 605

Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile Arg
 610 615 620
 Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr Leu
 625 630 635 640
 Ala Ser Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val Glu Ser
 645 650 655
 Cys Thr Cys Pro Val Gly Tyr Gly Gly Gln Phe Cys Glu Met Cys Leu
 660 665 670
 Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu Gly Pro Tyr Ser Pro Cys
 675 680 685
 Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu Thr
 690 695 700
 Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu Lys
 705 710 715 720
 Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr Ala Gly Thr Ser Ser Asp
 725 730 735
 Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val Pro
 740 745 750
 Lys Thr Lys Glu Val Val Cys Thr Asn Cys Pro Thr Gly Thr Thr Gly
 755 760 765
 Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu Gly
 770 775 780
 Arg Asn Gly Pro Val Arg Leu Cys Arg Leu Cys Gln Cys Ser Asp Asn
 785 790 795 800
 Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu Cys
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 Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys Lys
 820 825 830
 Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys Cys
 835 840 845
 Lys Ala Cys Asn Cys Asn Pro Tyr Gly Thr Met Lys Gln Gln Ser Ser
 850 855 860
 Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr Gly
 865 870 875 880
 Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser Gly
 885 890 895
 Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn Gly
 900 905 910
 Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile Thr
 915 920 925
 Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly Pro

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Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser Leu		
945	950	955 960
Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val Gly		
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Asn Arg Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser Trp		
	980	985 990
Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp Lys		
	995	1000 1005
Val Ala Asp His Arg Val Lys Leu Gln Glu Leu Glu Ser Leu Ile Ala		
1010	1015	1020
Asn Leu Gly Thr Gly Asp Glu Met Val Thr Asp Gln Ala Phe Glu Asp		
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Arg Leu Lys Glu Ala Glu Arg Glu Val Met Asp Leu Leu Arg Glu Ala		
	1045	1050 1055
Gln Asp Val Lys Asp Val Asp Gln Asn Leu Met Asp Arg Leu Gln Arg		
	1060	1065 1070
Val Asn Asn Thr Leu Ser Ser Gln Ile Ser Arg Leu Gln Asn Ile Arg		
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Asn Thr Ile Glu Glu Thr Gly Asn Leu Ala Glu Gln Ala Arg Ala His		
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Val Glu Asn Thr Glu Arg Leu Ile Glu Ile Ala Ser Arg Glu Leu Glu		
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Lys Ala Lys Val Ala Ala Ala Asn Val Ser Val Thr Gln Pro Glu Ser		
	1125	1130 1135
Thr Gly Asp Pro Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg Lys		
1140	1145	1150
Leu Ala Glu Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val Ala		
1155	1160	1165
Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu Leu Arg		
1170	1175	1180
Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe Glu Ile Glu Glu Leu Asn		
1185	1190	1195 1200
Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys Gln		
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Ala Ala Arg Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala Val		
1220	1225	1230
Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu Thr		
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Leu Glu Asn Glu Ala Asn Asn Ile Lys Met Glu Ala Glu Asn Leu Glu		
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Gln Leu Ile Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp
 1265 1270 1275 1280
 Met Arg Gly Lys Glu Leu Glu Val Lys Asn Leu Leu Glu Lys Gly Lys
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 Thr Glu Gln Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala
 1300 1305 1310
 Lys Ala Leu Ala Glu Glu Ala Ala Lys Lys Gly Arg Asp Thr Leu Gln
 1315 1320 1325
 Glu Ala Asn Asp Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg Val
 1330 1335 1340
 Asn Asp Asn Lys Thr Ala Ala Glu Glu Ala Leu Arg Lys Ile Pro Ala
 1345 1350 1355 1360
 Ile Asn Gln Thr Ile Thr Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln
 1365 1370 1375
 Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys
 1380 1385 1390
 Ala His Glu Ala Glu Arg Ile Ala Ser Ala Val Gln Lys Asn Ala Thr
 1395 1400 1405
 Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp Leu
 1410 1415 1420
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 1425 1430 1435 1440
 Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Met Ala
 1445 1450 1455
 Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala Arg Lys
 1460 1465 1470
 Ala Lys Asn Ser Val Thr Ser Leu Leu Ser Ile Ile Asn Asp Leu Leu
 1475 1480 1485
 Glu Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu
 1490 1495 1500
 Ile Glu Gly Thr Leu Asn Lys Ala Lys Asp Glu Met Lys Val Ser Asp
 1505 1510 1515 1520
 Leu Asp Arg Lys Val Ser Asp Leu Glu Asn Glu Ala Lys Lys Gln Glu
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 Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile Glu Glu Ile Met Lys Asp
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 Ile Arg Asn Leu Glu Asp Ile Arg Lys Thr Leu Pro Ser Gly Cys Phe
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<213> Mus musculus

$\langle 222 \rangle \quad (193) \dots (5010)$

<222> (193) .. (291)

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ggcctcggga tacgccgcta ggcgagtgca gcgcggcacc ccagcctttg ccgagggggcc 180

cgccgcagcg qq atg acg qgc qgc qgg cgg gcc gcg ctg gcc ctg cag ccc 231

Met Thr Gly Gly Gly Arg Ala Ala Leu Ala Leu Gln Pro
1 5 10

cgq ggg cgg ctg tgg ccg ctg ttg gct gtg ctg gcg gct gtg gcg ggc 279

Arg Gly Arg Leu Trp Pro Leu Leu Ala Val Leu Ala Ala Val Ala Gly
15 20 25

tgt gtc cgg gcg gcc atg gac gag tgc gcg gat gag ggc ggg cgg ccg 327

Cys Val Arg Ala Ala Met Asp Glu Cys Ala Asp Glu Gly Gly Arg Pro
30 35 40 45

cag cgc tgc atg ccg gag ttt gtt aat gcc gcc ttc aat gtg acc gtg 375

Gln Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val
50 55 60

gtg gct acc aac acg tgt ggg act ccg ccc gag gag tac tgc gtg cag 423

Val Ala Thr Asn Thr Cys Gly Thr Pro Glu Glu Tyr Cys Val Gln
65 70 75

act ggg qtg acc qga qtc act aaq tcc tgt cac ctg tgc qac qcc qgc 471

Thr	Gly	Val	Thr	Gly	Val	Thr	Lys	Ser	Cys	His	Leu	Cys	Asp	Ala	Gly
		80					85					90			

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Gln Gln His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn
95 100 105

caq gcc gac acc acc tgg tgg caa agc caq act atg ctg gcc ggg gtg 567

Gln Ala Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val
110 115 120 125

caq tac ccc aac tcc atc aac ctc acg ctg cac ctg gga aaq gct ttt 615

Gln Tyr Pro Asn Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe
130 135 140

gac atc act tac gtg cgc ctc aaq ttc cac acc agc cgt cca gaa agc 663

Asp	Ile	Thr	Tyr	Val	Arg	Leu	Lys	Phe	His	Thr	Ser	Arg	Pro	Glu	Ser
			145					150					155		

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Phe Ala Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr	
160 165 170	
cag tac tac agt ggg tcc tgt gag aac acg tac tca aag gct aac cgt	759
Gln Tyr Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg	
175 180 185	
ggc ttc atc agg acc gga ggg gac gag cag cag gcc ttg tgt act gat	807
Gly Phe Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp	
190 195 200 205	
gaa ttc agt gac att tcc ccc ctc acc ggt ggc aac gtg gcc ttt tca	855
Glu Phe Ser Asp Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser	
210 215 220	
acc ctg gaa gga cgg ccg agt gcc tac aac ttt gac aac agc cct gtg	903
Thr Leu Glu Gly Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val	
225 230 235	
ctc cag gaa tgg gta act gcc act gac atc aga gtg acg ctc aat cgc	951
Leu Gln Glu Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg	
240 245 250	
ctg aac acc ttt gga gat gaa gtg ttt aac gac ccc aaa gtt ctc aag	999
Leu Asn Thr Phe Gly Asp Glu Val Phe Asn Asp Pro Lys Val Leu Lys	
255 260 265	
tct tac tat tac gca atc tca gac ttt gct gtg ggc ggc agg tgt aaa	1047
Ser Tyr Tyr Tyr Ala Ile Ser Asp Phe Ala Val Gly Gly Arg Cys Lys	
270 275 280 285	
tgt aac gga cat gcc agc gag tgt gta aag aac gag ttt gac aaa ctc	1095
Cys Asn Gly His Ala Ser Glu Cys Val Lys Asn Glu Phe Asp Lys Leu	
290 295 300	
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Met Cys Asn Cys Lys His Asn Thr Tyr Gly Val Asp Cys Glu Lys Cys	
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ctg cct ttc ttc aat gac cgg ccg tgg agg agg gcg act gct gag agc	1191
Leu Pro Phe Phe Asn Asp Arg Pro Trp Arg Arg Ala Thr Ala Glu Ser	
320 325 330	
gcc agc gag tgc ctt cct tgt gac tgc aat ggc cga tcc caa gag tgc	1239
Ala Ser Glu Cys Leu Pro Cys Asp Cys Asn Gly Arg Ser Gln Glu Cys	
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Tyr Phe Asp Pro Glu Leu Tyr Arg Ser Thr Gly His Gly Gly His Cys	
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Thr Asn Cys Arg Asp Asn Thr Asp Gly Ala Lys Cys Glu Arg Cys Arg	
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<213> Mus musculus

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Tyr	Val	Arg	Leu	Lys	Phe	His	Thr	Ser	Arg	Pro	Glu	Ser	Phe	Ala	Ile	145	150	155	160
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Lys	Pro	Gly	Val	Met	Gly	Asp	Lys	Cys	Asp	Arg	Cys	Gln	Pro	Gly	Phe
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 Val Lys Phe Leu Gly Asn Gln Val Leu Ser Tyr Gly Gln Asn Leu Ser
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 Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala Glu Asp
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 Val Cys Asp Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu Lys Cys
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 Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys Lys Glu
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Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp Met Arg Gly		
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Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala Lys Ala Leu		
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1360		
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Lys Thr Ala Ala Glu Glu Ala Leu Arg Arg Ile Pro Ala Ile Asn Arg		
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Thr Ile Ala Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln Leu Ala Leu		
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Val Asn Gly Met Leu Arg Gln Leu Glu Glu Ala Glu Asn Glu Leu Lys		
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ccg gag ttt gtt aat gcc gcc ttc aat gtg acc gtg gtg gct acc aac	96
Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val Ala Thr Asn	
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Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly Val Thr	
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gga gtc act aag tcc tgt cac ctg tgc gac gcc ggc cag cag cac ctg	192
Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Gln His Leu	
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caa cac ggg gca gcc ttc ctg acc gac tac aac aac cag gcc gac acc	240
Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala Asp Thr	
65 70 75 80	
acc tgg tgg caa agc cag act atg ctg gcc ggg gtg cag tac ccc aac	288
Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr Pro Asn	

173

gat aac aca gat ggt gcc aag tgc gag agg tgc cgg gag aat ttc ttc	1056
Asp Asn Thr Asp Gly Ala Lys Cys Glu Arg Cys Arg Glu Asn Phe Phe	
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Arg Leu Gly Asn Thr Glu Ala Cys Ser Pro Cys His Cys Ser Pro Val	
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Gly Ser Leu Ser Thr Gln Cys Asp Ser Tyr Gly Arg Cys Ser Cys Lys	
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Pro Gly Val Met Gly Asp Lys Cys Asp Arg Cys Gln Pro Gly Phe His	
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Ser Leu Thr Glu Ala Gly Cys Arg Pro Cys Ser Cys Asp Pro Ser Gly	
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Leu Glu Ser Ser Asn Pro Lys Gly Cys Thr Pro Cys Phe Cys Phe Gly	
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His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val Tyr Asp Ile	
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Lys Phe Leu Gly Asn Gln Val Leu Ser Tyr Gly Gln Asn Leu Ser Phe	
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His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Ser Pro Phe Glu	
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Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile Arg Gly Thr	
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Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr Leu Gln Ser	
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Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val Glu Ser Cys Thr	
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tgt cca gtg gga tac ggg gga cag ttc tgt gag acg tgc ctc cca ggg	2016
Cys Pro Val Gly Tyr Gly Gly Gln Phe Cys Glu Thr Cys Leu Pro Gly	
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Tyr Arg Arg Glu Thr Pro Ser Leu Gly Pro Tyr Ser Pro Cys Val Leu	
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tgt acc tgt aat ggg cac agt gag acc tgt gac ccg gag aca ggt gtc	2112
Cys Thr Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu Thr Gly Val	
690 695 700	
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Cys Asp Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu Lys Cys Ser	
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gat ggg tac tat ggg gac tca acc ctg ggc acc tcc tct gac tgc cag	2208
Asp Gly Tyr Tyr Gly Asp Ser Thr Leu Gly Thr Ser Ser Asp Cys Gln	
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Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Ile Val Pro Lys Thr	
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Lys Glu Val Val Cys Thr His Cys Pro Thr Gly Thr Ala Gly Lys Arg	
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Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu Gly Ser Asn	
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785 790 795 800	
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Phe	Phe	Gly	Asn	Pro	Leu	Ala	Pro	Asn	Pro	Ala	Asp	Lys	Cys	Lys	Ala	
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Cys	Ala	Cys	Asn	Tyr	Gly	Thr	Val	Gln	Gln	Gln	Ser	Ser	Cys	Asn	Pro	
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Val	Thr	Gly	Gln	Cys	Gln	Cys	Leu	Pro	His	Val	Ser	Gly	Arg	Asp	Cys	
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ggt	act	tgt	gac	cct	ggc	tac	tac	aac	ctg	cag	agc	ggg	caa	ggc	tgc	2688
Gly	Thr	Cys	Asp	Pro	Gly	Tyr	Tyr	Asn	Leu	Gln	Ser	Gly	Gln	Gly	Cys	
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gag	agg	tgt	gac	tgc	cat	gct	ttg	ggt	tcc	acc	aat	ggg	cag	tgt	gac	2736
Glu	Arg	Cys	Asp	Cys	His	Ala	Leu	Gly	Ser	Thr	Asn	Gly	Gln	Cys	Asp	
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atc	cgc	acc	ggg	cag	tgt	gag	tgc	cag	cct	ggc	atc	acc	ggt	cag	cac	2784
Ile	Arg	Thr	Gly	Gln	Cys	Glu	Cys	Gln	Pro	Gly	Ile	Thr	Gly	Gln	His	
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Cys	Glu	Arg	Cys	Glu	Thr	Asn	His	Phe	Gly	Phe	Gly	Pro	Glu	Gly	Cys	
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Lys	Pro	Cys	Asp	Cys	His	His	Glu	Gly	Ser	Leu	Ser	Leu	Gln	Cys	Lys	
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Asp	Asp	Gly	Arg	Cys	Glu	Cys	Arg	Glu	Gly	Phe	Val	Gly	Asn	Arg	Cys	
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Asp	Gln	Cys	Glu	Glu	Asn	Tyr	Phe	Tyr	Asn	Arg	Ser	Trp	Pro	Gly	Cys	
		980					985						990			
cag	gag	tgt	ccg	gct	tgt	tac	cga	ctt	gtg	aag	gat	aag	gct	gct	gag	3024
Gln	Glu	Cys	Pro	Ala	Cys	Tyr	Arg	Leu	Val	Lys	Asp	Lys	Ala	Ala	Glu	
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His	Arg	Val	Lys	Leu	Gln	Glu	Leu	Glu	Ser	Leu	Ile	Ala	Asn	Leu	Gly	
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Thr	Gly	Asp	Asp	Met	Val	Thr	Asp	Gln	Ala	Phe	Glu	Asp	Arg	Leu	Lys	
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Glu	Ala	Glu	Arg	Glu	Val	Thr	Asp	Leu	Leu	Arg	Glu	Ala	Gln	Glu	Val	
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Lys	Asp	Val	Asp	Gln	Asn	Leu	Met	Asp	Arg	Leu	Gln	Arg	Val	Asn	Ser	

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Thr Glu Gln Leu Ile Glu Ile Ala Ser Arg Glu Leu Glu Lys Ala Lys			
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Met Ala Ala Asn Val Ser Ile Thr Gln Pro Glu Ser Thr Gly Glu Pro			
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Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg Arg Leu Ala Glu Arg			
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His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala Val Glu Ile Tyr Ala			
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Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp Met Arg Gly Lys			
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Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala Lys Ala Leu Ala			
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aca gcc gcg gaa gaa gct cta agg aga att ccc gcc atc aac cgg acc Thr Ala Ala Glu Glu Ala Leu Arg Arg Ile Pro Ala Ile Asn Arg Thr 1345 1350 1355 1360	4080
ata gct gaa gcc aat gag aag aca agg gag gcc cag cta gcg ctg ggc Ile Ala Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln Leu Ala Leu Gly 1365 1370 1375	4128
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gag agg atc gcc agc gcc gcg cag aag aat gcc acc agt acc aag gcg Glu Arg Ile Ala Ser Ala Ala Gln Lys Asn Ala Thr Ser Thr Lys Ala 1395 1400 1405	4224
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 Ile Glu Lys Pro
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 <213> Mus musculus

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 35 40 45
 Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Gln His Leu
 50 55 60
 Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala Asp Thr
 65 70 75 80
 Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr Pro Asn
 85 90 95
 Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile Thr Tyr
 100 105 110
 Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala Ile Tyr
 115 120 125

Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln Tyr Tyr Ser
 130 135 140
 Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly Phe Ile Arg
 145 150 155 160
 Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu Phe Ser Asp
 165 170 175
 Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser Thr Leu Glu Gly
 180 185 190
 Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val Leu Gln Glu Trp
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 Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg Leu Asn Thr Phe
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 Gly Asp Glu Val Phe Asn Asp Pro Lys Val Leu Lys Ser Tyr Tyr Tyr
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 Ala Ile Ser Asp Phe Ala Val Gly Gly Arg Cys Lys Cys Asn Gly His
 245 250 255
 Ala Ser Glu Cys Val Lys Asn Glu Phe Asp Lys Leu Met Cys Asn Cys
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 Lys His Asn Thr Tyr Gly Val Asp Cys Glu Lys Cys Leu Pro Phe Phe
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 305 310 315 320
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 Pro Gly Val Met Gly Asp Lys Cys Asp Arg Cys Gln Pro Gly Phe His
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 His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val Tyr Asp Ile
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 Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Val Glu Gln Arg
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 Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Asp Arg Gln Tyr Ile
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 Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile Ala Pro Val
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 Asp Gly Tyr Tyr Gly Asp Ser Thr Leu Gly Thr Ser Ser Asp Cys Gln
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Phe	Phe	Gly	Asn	Pro	Leu	Ala	Pro	Asn	Pro	Ala	Asp	Lys	Cys	Lys	Ala
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	850					855					860				
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Glu	Arg	Cys	Asp	Cys	His	Ala	Leu	Gly	Ser	Thr	Asn	Gly	Gln	Cys	Asp
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1570