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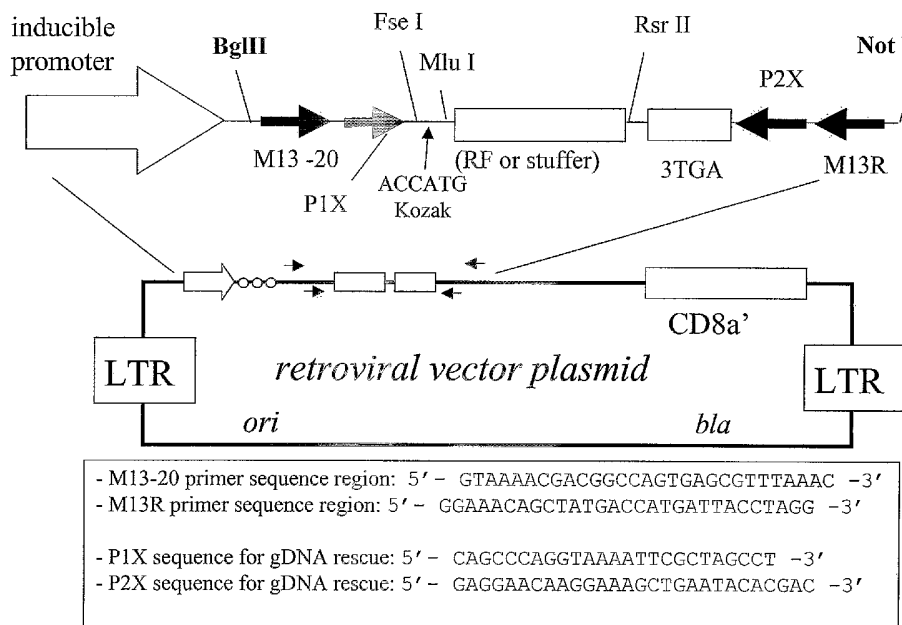
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(54) Title: TARGETS FOR CONTROLLING CELLULAR GROWTH AND FOR DIAGNOSTIC METHODS



(57) Abstract: A method of identifying a compound that induces apoptosis is disclosed. The method includes identifying compounds that inhibit the expression and/or activity of a target. Also disclosed are methods for inducing apoptosis by inhibiting one of the targets. The invention further includes methods for the diagnosis of a tumor that include determining the level of at least one of the targets as a biomarker in a patient sample, the level of the biomarker being indicative of the presence of tumor cells.



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TARGETS FOR CONTROLLING CELLULAR GROWTH AND FOR DIAGNOSTIC METHODS

FIELD OF THE INVENTION

5 The present invention relates to methods for inducing apoptosis in cells by inhibiting targets involved in the suppression of apoptosis, and to identifying compounds useful in such methods. The present invention also relates to methods for the diagnosis of cancer in a patient using the targets identified by the present invention as biomarkers.

10 BACKGROUND OF THE INVENTION

 The p53 tumor suppressor protein is an essential component in the regulation of the cell cycle, senescence, and programmed cell death (apoptosis). This protein regulates transcription of many genes in response to DNA damage and various transforming stimuli. The functional inactivation of p53 can occur through the action of viral
15 oncoproteins, or through over-expression of the hdm2 (human) or mdm2 (murine) oncogene protein. Additional tumor suppressors, such as the p14^{ARF} product of the INK4a gene, regulate the functional activity of p53. In the case of p14^{ARF}, the suppressor interacts with hdm2 and thereby prevents the mentioned oncoprotein from inhibiting p53. An alternative translation product of the INK4a locus, p16INK4a, a cyclin-dependent
20 kinase inhibitor, also contributes to normal growth control through its regulation of the Rb pathway.

 When regulation of the cell cycle, senescence, and apoptosis is not functioning properly, uncontrolled cell growth and tumor formation occurs. Because of the complicated regulation of these cell functions, there are many potential points in a variety
25 of regulatory pathways of a cell for intervention. By inhibiting the expression of genes important to cell growth and to suppression of apoptosis or the proteins encoded by them, it is possible to induce control cell growth and apoptosis in a cell, thereby preventing tumor formation. Once such genes or proteins are identified as targets, assays can be conducted for drug discovery to find inhibitors suitable for use as therapeutic agents. In
30 addition, such genes or proteins are useful as markers of tumor formation.

 There is an ongoing need to identify new targets and develop new assays for the identification of therapeutic compounds useful in the control of cell growth and tumor formation.

SUMMARY OF THE INVENTION

This invention provides methods for identifying compounds that induce apoptosis by inhibiting target genes or gene products involved in the control of cell growth. The present invention also includes a method for inducing apoptosis in a cell by inhibiting
5 such a target gene or gene product by, in one embodiment, contacting cells susceptible to uncontrolled growth with an inhibitory compound in an amount sufficient to inhibit said biochemical activity or expression. More particularly, targets of the present invention include any of the genes or gene products set forth in Table 1, which can also be identified as genes and gene products comprising SEQ ID NOs:1-80 (with odd numbered
10 identifiers referring to nucleic acid sequences and even numbered identifiers referring to amino acid sequences).

In one embodiment, the present invention relates to a method of identifying a compound that induces apoptosis in a cell that includes contacting the cell with a putative apoptosis-inducing compound and determining whether the compound inhibits the
15 expression and/or activity of a target selected from the group consisting of any of the targets listed in Table 1 (or comprising any of SEQ ID NOs:1-80). The target can have been validated as being involved in tumor cell growth, such as by a process of inhibiting the target in a cell by a method selected from gene knock-out, anti-sense oligonucleotide expression, use of RNAi molecules and GSE expression, or assaying the cell for the
20 ability of the cell to grow. The cell can be a tumor cell line. The step of determining can be selected from assaying for reduced expression of the target and assaying for reduced activity of the target. The expression of the target can be measured by methods including, but not limited to, polymerase chain reaction or by using an antibody that specifically recognizes the target. The activity of the target can be measured by methods including,
25 but not limited to, measuring the amount of a product generated in a biochemical reaction mediated by the target or by measuring the amount of a substrate consumed in a biochemical reaction mediated by the target. The inhibitor can be identified by methods including, but not limited to, determining the three-dimensional structure of the target or by determining the three-dimensional structure of an inhibitor by using computer
30 software capable of modeling the interaction of the target and putative test compounds.

Another embodiment of the present invention is a method for inducing apoptosis in a cell by inhibiting a target selected from any of the genes or products encoded thereby

listed in Table 1 (also represented herein as genes or gene products comprising any of SEQ ID NOs:1-80).

A further embodiment of the present invention is a method for the diagnosis of a tumor that includes determining the level of a biomarker selected from any of the genes or products encoded thereby listed in Table 1 (also represented herein as genes or gene products comprising any of SEQ ID NOs:1-80) in a patient test sample. In this method, the level of the biomarker is indicative of the presence of tumor cells. The presence of the biomarker at an increased level as compared to a normal baseline control is an indication of the presence a tumor, a possible predisposition to such tumor or a susceptibility to an anti-cancer therapeutic treatment. The level of the biomarker can be determined by conventional methods such as expression assays to determine the level of expression of the gene, by biochemical assays to determine the level of the gene product, or by immunoassays. In one embodiment of this method, the level of the biomarker can be determined by identifying the biomarker as a cell surface molecule in tissue or by detecting the biomarker in soluble form in a bodily fluid, such as serum, that can be immobilized. The biomarker level can be determined by contacting a patient test sample with an antibody, or a fragment thereof, that binds specifically to the biomarker and determining whether the anti-biomarker antibody or fragment has bound to the biomarker. The biomarker level can be determined by using a first monoclonal antibody that binds specifically to the biomarker and a second antibody that binds to the first antibody. This method can be used to determine the prognosis for cancer in the patient or to determine the susceptibility of the patient to a therapeutic treatment.

BRIEF DESCRIPTION OF THE DRAWINGS OF THE INVENTION

- Fig. 1 illustrates a schematic of the features of the V98 vector.
Fig. 2 illustrates a schematic drawing of the construction of the V87 vector.
Fig. 3 illustrates a schematic drawing of the construction of the V98 vector

DETAILED DESCRIPTION OF THE INVENTION

- The present invention includes methods for identifying protective compounds that control cell growth and induce apoptosis by using genes that encode products that are necessary for protecting cells from apoptosis as targets in the design of therapeutic agents. The invention further includes compounds for use in the treatment or prevention of tumor

growth. Such compounds include chemical compounds and biological compounds. Chemical compounds or biological compounds include any chemical or biological compound that disrupts or inhibits one or more biological functions required for controlling cell growth. Preferred chemical compounds include small molecule inhibitor
5 or substrate compounds, such as products of chemical combinatorial libraries. Preferred biological compounds include peptides, anti-sense molecules and antibodies.

The invention also includes methods for the diagnosis of cancer or for a prognosis of cancer or for determination of susceptibility to cancer treatments, by determining the level of expression of target genes and proteins of the present invention (also referred to
10 as tumor antigens (TAGs)) in patient samples. The targets may originate from different parts of the cell and may be cell surface proteins, intracellular proteins or proteins that are secreted from the cell. There is a distinction between tissue, individual and species-specific cellular markers that may also be present physiologically as differentiation antigens on cells. There may be targets that are intermediate products released, over
15 expressed or under expressed during the growth of a tumor cell type which can change upon further differentiation. The level of the target gene or protein can be determined by conventional methods such as expression assays to determine the level of expression of the gene, by biochemical assays to determine the level of the gene product, or by immunoassays. If appropriate, the marker can be identified as a cell surface molecule in
20 tissue or in a bodily fluid, such as serum. These methods are described in detail below. The present invention provides much needed markers that permit an improved and more specific diagnosis of cancer, including the possible distinction between various tumor types, the prediction of tumor formation and the patient susceptibility to certain known cancer treatments.

25 The present invention is based, in part, on the present inventors' isolation of certain GSEs from human cells that prevent cell growth, and the discovery that such nucleic acid molecules correspond to fragments of certain genes. In that regard, any cellular phenotype or protein associated with cell growth can be used to select for such nucleic acid molecules or proteins encoded thereby.

30 More specifically, targets of the present invention have been identified as corresponding to genetic suppressor elements (GSEs) that control cell growth. The GSX™ System technology allows rapid screening for the inhibitors of gene function in the form of genetic suppressor elements. Briefly, a Genetic Suppressor Element (GSE), is

a gene fragment, which, when expressed in cells, acts as a genetic inhibitor of the corresponding intact gene in those cells. A GSE can exert its effect through either an antisense, or a dominant negative peptide mechanism. GSEs are selected from libraries of DNA fragments, generated by random breakage of sets of test genes, cloned in a retroviral or other expression vector. The RFL clones are introduced into a population of test cells at approximately one test fragment per cell. Cells with a desired new phenotype, resulting from the expression of a GSE, are isolated on the basis of any selectable parameter. The GSEs are recovered from the selected cells and characterized by DNA sequence analysis and further functional assays.

GSEs having the ability to control cell growth can be functional in the sense orientation (and encode a peptide thereby), and can be functional in the antisense orientation (and encode antisense RNAs thereby). These GSEs are believed to down-regulate the corresponding gene from which they were derived by different mechanisms. Such a corresponding gene is referred to herein as a "target gene" and its product (*i.e.*, protein encoded by the coding region of the gene) is referred to as a "target product" or "target protein". As used herein, the term "target" alone can refer collectively to a target gene and its corresponding target product, or to useful portions thereof. Sense-oriented GSEs exert their effects as transdominant mutants or RNA decoys. Transdominant mutants are expressed proteins or peptides that competitively inhibit the normal function of a wild-type protein in a dominant fashion. RNA decoys are protein binding sites that titrate out these wild-type proteins. Anti-sense oriented GSEs exert their effects as antisense RNA molecules, *i.e.*, nucleic acid molecules complementary to the mRNA of the target gene. These nucleic acid molecules bind to mRNA and block the translation of the mRNA. In addition, some antisense nucleic acid molecules can act directly at the DNA level to inhibit transcription.

Specific targets of the present invention are shown below in the Examples section in Table 1. The targets include the genes and products of the genes or any useful portion thereof. Methods of the present invention for identifying therapeutic compounds by identifying an inhibitor of a target include identifying an inhibitor of: a target gene from Table 1, as well as target products encoded by any of the foregoing. Diagnostic methods for detecting cancer in a patient include detection of a target gene from Table 1, as well as target products encoded by any of the foregoing, and useful portions thereof. More specifically, the targets of the present invention include genes comprising all or a portion

of any of the nucleic acid sequences represented by SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, or 79. These nucleic acid molecules encode the following target proteins, respectively: angio-associated, migratory cell protein (AAMP; SEQ ID NO:2), a disintegrin and metalloproteinase domain 8 (ADAM8; SEQ ID NO:4), a disintegrin-like and metalloprotease (reporlysin type) with thrombospondin type 1 motif, 17 (ADAMTS17; SEQ ID NO:6), adenylate cyclase 3 (ADCY3; SEQ ID NO:8), adrenergic beta receptor kinase 1 (ADRBK1; SEQ ID NO:10), bladder cancer associated protein (BLCAP; SEQ ID NO:12), chromosome 22 open reading frame 5 (C22orf5; SEQ ID NO:14), CD81 antigen (target of antiproliferative antibody 1 (CD81; SEQ ID NO:16), CD9 antigen (p24) (CD9; SEQ ID NO:18), claudin 4 (CLDN4; SEQ ID NO:20), chloride intracellular channel 1 (CLIC1; SEQ ID NO:22), collagen, type VI, alpha 2 (COL6A2; SEQ ID NO:24), CTL2 (CTL2; SEQ ID NO:26), endothelin converting enzyme 1 (ECE1; SEQ ID NO:28), ephrin-B1 (EFNB1; SEQ ID NO:30), flotillin 2 (FLOT2; SEQ ID NO:32), intercellular adhesion molecule 3 (ICAM3; SEQ ID NO:34), iduronate 2-sulfatase (Hunter syndrome) (IDS; SEQ ID NO:36), jagged 2 (JAG2; SEQ ID NO:38), junctional adhesion molecule 1 (JAM1; SEQ ID NO:40), lectin, galactoside-binding soluble 3 binding protein (LGALS3BP; SEQ ID NO:42), similar to possible G-protein receptor (LOC146330; SEQ ID NO:44), CGI-78 protein (LOC51107; SEQ ID NO:46), lipoprotein lipase (LPL; SEQ ID NO:48), low density lipoprotein receptor-related protein 5 (LRP5; SEQ ID NO:50), Lutheran blood group (Auberger b antigen included) (LU; SEQ ID NO:52), membrane component, chromosome 11, surface marker 1 (M11S1; SEQ ID NO:54), serum constituent protein (MSE55; SEQ ID NO:56), neuropathy target esterase (NTE; SEQ ID NO:58), Homo sapiens cDNA FL31043 fis, clone HSYRA2000248 (PLEXIN A1) or Homo sapiens cDNA FLJ44113 fis, clone TESTI4046487, highly similar to Mus musculus plexin A1 (PLXNA1; SEQ ID NO:60), protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 3 (PPFIA3; SEQ ID NO:62), Homo sapiens peptide-histidine transporter 4 (PTR4), mRNA (PTR4; SEQ ID NO:64), solute carrier family 16 (monocarboxylic acid transporters) member 3 (SLC16A3; SEQ ID NO:66), solute carrier family 1 (neutral amino acid transporter) member 5 (SLC1A5; SEQ ID NO:68), solute carrier family 39 (zinc transporter) member 3 (SLC39A1; SEQ ID NO:70), serine protease inhibitor, Kunitz type 2 (SPINT2; SEQ ID NO:72), stanniocalcin 2 (STC2; SEQ ID NO:74), tumor

necrosis receptor superfamily member 21 (TNFRSF21; SEQ ID NO:76), tumor rejection antigen (gp96) 1 (TRA1; SEQ ID NO:78), and transient receptor potential cation channel, subfamily M member 4 (TRPM4; SEQ ID NO:80). In any of the assays described herein, one can use a full-length gene, including a regulatory region of the gene, or a nucleic acid molecule encoding the gene product (protein encoded by the gene) or any fragment of such nucleic acid molecules, or any gene product or fragment thereof that is suitable for use in an assay to identify inhibitors of the target for the purpose of regulating apoptosis or inhibition of tumor growth, or to detect cancer in a patient sample.

In one embodiment of the invention, the down-regulation of the concentration or activity of a target gene or product by an inhibitor (including a GSE) depletes a cellular component required for protecting cells from apoptosis resulting in control of cell growth. In another embodiment of the invention, the down-regulation of the concentration or activity of one target gene or product by an inhibitor (including a GSE) depletes a cellular component that interacts with another gene or gene product required for protecting cells from apoptosis resulting in control of cell growth. In a preferred embodiment of the invention, the two genes are members of the same biological pathway and one gene or gene product regulates the expression or activity of the other gene or gene product. In another preferred embodiment of the invention, the two genes are members of the same biological pathway and the substrate of a protein encoded by one gene is a product of a biochemical reaction mediated by the protein encoded by the other gene. In still another preferred embodiment of the invention, the two genes are members of the same biological pathway and the product of a protein encoded by one gene is a substrate of a biochemical reaction mediated by the protein encoded by the other gene. In another embodiment, the two genes encode proteins that are isozymes of each other. In a preferred embodiment, at least one of the genes encodes an enzyme.

Target genes or proteins identified using GSEs can be further evaluated using a variety of methods to validate their involvement in cell growth, suppression of apoptosis and tumor formation. Such methods include methods that disrupt or "knock out" the expression of a target gene in a cell capable of apoptosis. Knock-out methods include somatic cell knock-outs and inhibitory RNA molecules including anti-sense oligonucleotides, siRNA molecules, RNAi molecules and RNA decoys. Target genes or proteins can also be evaluated by methods that include nucleic acid-based experiments such as Northern Blots, Real Time polymerase chain reaction or high density microarrays.

Further evaluation can also be achieved using human/mouse xenograft models. For example, human tumor cells can be transfected with a GSE such that the GSE is expressed. Preferred tumor cells include HCT15, HT29, HCT116, SW480 and SW620 and MDA-MB-231 (*e.g., see Examples*). The transfected cells can then be implanted into mice, preferably nude mice. The growth of the tumor cells in the mouse can then be measured.

Once a gene has been identified as a potential target for supporting cell growth, assays can be used for associating a potential target with different tumor types. These assays include determining gene and protein expression of potential targets in different tumor cell types at different points of differentiation. Another assay can include determining the presence of a potential marker in patient samples using standard protein detection methods known to those of skill in the art. Targets that have been associated with cancer are also referred to as biomarkers. Preferred biomarkers of the present invention are listed in Table 1 (*see Examples section*).

Once one or more members of a biological pathway are identified as required for cell growth, the present invention can include identifying additional members of a biological pathway that are also required for cell growth. Such subsequent identification is within the skill of one in the art. GSEs, and therefore preferred targets of the present invention, are identified by selecting cells that exhibit certain hallmarks of apoptosis upon expression of the GSEs. Isolated GSEs are further prioritized based on their specificity for a neoplastic transformation state, such as their activity in transformed and non-transformed cells, and based on the p53 pathway status in cells expressing the GSEs. For example, GSEs can be prioritized by determining if the GSEs have activity in a p53 dependent and/or independent manner. GSEs specific for the neoplastic transformation state are preferred for identifying targets for anti-cancer drugs.

It will be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, constructs, or reagents described herein, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the invention that will be limited only by the appended claims. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

As used herein, the term "isolated nucleic acid molecule" refers to a nucleic acid molecule that has been removed from its natural milieu (*i.e.*, a molecule that has been subject to human manipulation) and can include DNA, RNA, or derivatives of either DNA or RNA. An isolated nucleic acid molecule can be isolated from its natural source or can be produced using recombinant DNA technology (*e.g.*, polymerase chain reaction amplification) or chemical synthesis. Isolated nucleic acid molecules include natural nucleic acid molecules and homologs thereof, including, but not limited to, natural allelic variants and modified nucleic acid molecules in which nucleotides have been inserted, deleted, substituted, or inverted in such a manner that such modifications do not substantially interfere with the nucleic acid molecule's ability to control cell growth or encode a protein that controls cell growth.

It should also be appreciated that reference to an isolated nucleic acid molecule does not necessarily reflect the extent of purity of the nucleic acid molecule. Nucleic acid molecules can be isolated and obtained in substantial purity, generally as other than an intact chromosome. Usually, the nucleic acid molecule will be obtained substantially free of other nucleic acid sequences, generally being at least about 50%, and usually at least about 90% pure. Although the phrase "nucleic acid molecule" primarily refers to the physical nucleic acid molecule and the phrase "nucleic acid sequence" primarily refers to the sequence of nucleotides on the nucleic acid molecule, the two phrases can be used interchangeably.

According to the invention, reference to an "isolated nucleic acid molecule" refers to a nucleic acid molecule that is the size of or is smaller than a gene. Thus, an isolated nucleic acid molecule does not encompass isolated total genomic DNA or an isolated chromosome. As used herein, the term "gene" has the meaning that is well known in the art, that is, a nucleic acid sequence that includes the translated sequences that code for a protein ("exons") and the untranslated intervening sequences ("introns"), and any regulatory elements necessary to transcribe and/or translate the protein. Included in the invention are nucleic acid molecules that are less than a full-length gene or less than a full-length coding sequence, such as fragments of a gene or coding sequence comprising, consisting essentially of, or consisting of, for example, a fragment of any of the nucleic acid sequences for target genes described in the present invention. A coding sequence can include genomic DNA without introns, cDNA or RNA that encodes a protein. An isolated nucleic acid molecule can also include a specified nucleic acid sequence flanked

by (*i.e.*, at the 5' and/or the 3' end of the sequence) additional nucleic acids that do not normally flank the specified nucleic acid sequence in nature (*i.e.*, are heterologous sequences).

In one embodiment, an isolated nucleic acid molecule useful in a method of the present invention is produced using recombinant DNA technology (*e.g.*, polymerase chain reaction (PCR) amplification, cloning) or chemical synthesis. A nucleic acid molecule homologue can be produced using a number of methods known to those skilled in the art (see, for example, Sambrook et al., *ibid.*). For example, nucleic acid molecules can be modified using a variety of techniques including, but not limited to, classical mutagenesis techniques and recombinant DNA techniques, such as site-directed mutagenesis, chemical treatment of a nucleic acid molecule to induce mutations, restriction enzyme cleavage of a nucleic acid fragment, ligation of nucleic acid fragments, PCR amplification and/or mutagenesis of selected regions of a nucleic acid sequence, synthesis of oligonucleotide mixtures and ligation of mixture groups to "build" a mixture of nucleic acid molecules and combinations thereof. Nucleic acid molecule homologues can be selected from a mixture of modified nucleic acids by screening for the function of the protein encoded by the nucleic acid and/or by hybridization with a wild-type gene.

The term isolated nucleic acid molecule does not necessarily connote any specific minimum length unless set forth by reference to a minimum number of nucleotides or by a function of the nucleic acid molecule. The minimum size of a nucleic acid molecule of the present invention is generally a size sufficient to encode a protein having the desired biological activity, a size sufficient to inhibit the expression and/or activity of a target as described herein (*e.g.*, as in a GSE), a size sufficient for use in a screening assay or diagnostic method of the invention, or a size sufficient to form a probe or oligonucleotide primer that is capable of forming a stable hybrid with the complementary sequence of a nucleic acid molecule. As such, the size of a nucleic acid molecule of the present invention can be dependent on nucleic acid composition and percent homology or identity between the nucleic acid molecule and complementary sequence as well as upon hybridization conditions *per se* (*e.g.*, temperature, salt concentration, and formamide concentration) and the intended use of the nucleic acid molecule. The minimal size of a nucleic acid molecule that is used as an oligonucleotide primer or as a probe is typically at least about 12 to about 15 nucleotides in length if the nucleic acid molecules are GC-rich and at least about 15 to about 18 bases in length if they are AT-rich. There is no

limit, other than a practical limit, on the maximal size of a nucleic acid molecule of the present invention, in that the nucleic acid molecule can include a fragment of a gene, a portion of a protein encoding sequence, or a nucleic acid sequence encoding a full-length protein (including a complete gene).

5 Some embodiments of the present invention may include the production and/or use of a recombinant nucleic acid molecule comprising a recombinant vector and a nucleic acid molecule comprising a nucleic acid sequence encoding a gene or fragment thereof as described herein. According to the present invention, a recombinant vector is an engineered (*i.e.*, artificially produced) nucleic acid molecule that is used as a tool for
10 manipulating a nucleic acid sequence of choice and for introducing such a nucleic acid sequence into a host cell. The recombinant vector is therefore suitable for use in cloning, sequencing, and/or otherwise manipulating the nucleic acid sequence of choice, such as by expressing and/or delivering the nucleic acid sequence of choice into a host cell to form a recombinant cell. Such a vector typically contains heterologous nucleic acid
15 sequences, that is nucleic acid sequences that are not naturally found adjacent to nucleic acid sequence to be cloned or delivered, although the vector can also contain regulatory nucleic acid sequences (*e.g.*, promoters, untranslated regions) which are naturally found adjacent to nucleic acid molecules of the present invention or which are useful for expression of the nucleic acid molecules of the present invention (discussed in detail
20 below). The vector can be either RNA or DNA, either prokaryotic or eukaryotic, and typically is a plasmid. The vector can be maintained as an extrachromosomal element (*e.g.*, a plasmid) or it can be integrated into the chromosome of a recombinant organism (*e.g.*, a microbe or a plant). The entire vector can remain in place within a host cell, or under certain conditions, the plasmid DNA can be deleted, leaving behind the nucleic
25 acid molecule of the present invention. The integrated nucleic acid molecule can be under chromosomal promoter control, under native or plasmid promoter control, or under a combination of several promoter controls. Single or multiple copies of the nucleic acid molecule can be integrated into the chromosome. A recombinant vector of the present invention can contain at least one selectable marker.

30 In one embodiment, a recombinant vector used in a recombinant nucleic acid molecule of the present invention is an expression vector. As used herein, the phrase "expression vector" is used to refer to a vector that is suitable for production of an encoded product (*e.g.*, a protein of interest). In this embodiment, a nucleic acid sequence

encoding the product to be produced is inserted into the recombinant vector to produce a recombinant nucleic acid molecule. The nucleic acid sequence encoding the protein to be produced is inserted into the vector in a manner that operatively links the nucleic acid sequence to regulatory sequences in the vector that enable the transcription and translation of the nucleic acid sequence within the recombinant host cell.

In another embodiment, a recombinant vector used in a recombinant nucleic acid molecule of the present invention is a targeting vector. As used herein, the phrase "targeting vector" is used to refer to a vector that is used to deliver a particular nucleic acid molecule into a recombinant host cell, wherein the nucleic acid molecule is used to delete or inactivate an endogenous gene within the host cell or microorganism (*i.e.*, used for targeted gene disruption or knock-out technology). Such a vector may also be known in the art as a "knock-out" vector. In one aspect of this embodiment, a portion of the vector, but more typically, the nucleic acid molecule inserted into the vector (*i.e.*, the insert), has a nucleic acid sequence that is homologous to a nucleic acid sequence of a target gene in the host cell (*i.e.*, a gene which is targeted to be deleted or inactivated). The nucleic acid sequence of the vector insert is designed to bind to the target gene such that the target gene and the insert undergo homologous recombination, whereby the endogenous target gene is deleted, inactivated or attenuated (*i.e.*, by at least a portion of the endogenous target gene being mutated or deleted).

Typically, a recombinant nucleic acid molecule includes at least one nucleic acid molecule of the present invention operatively linked to one or more expression control sequences, including transcription control sequences and translation control sequences. As used herein, the phrase "recombinant molecule" or "recombinant nucleic acid molecule" primarily refers to a nucleic acid molecule or nucleic acid sequence operatively linked to an expression control sequence, but can be used interchangeably with the phrase "nucleic acid molecule", when such nucleic acid molecule is a recombinant molecule as discussed herein. According to the present invention, the phrase "operatively linked" refers to linking a nucleic acid molecule to an expression control sequence (*e.g.*, a transcription control sequence and/or a translation control sequence) in a manner such that the molecule is able to be expressed when transfected (*i.e.*, transformed, transduced, transfected, conjugated or conducted) into a host cell. Transcription control sequences are sequences that control the initiation, elongation, or termination of transcription. Particularly important transcription control sequences are those that control transcription

initiation, such as promoter, enhancer, operator and repressor sequences. Suitable transcription control sequences include any transcription control sequence that can function in a host cell or organism into which the recombinant nucleic acid molecule is to be introduced.

5 According to the present invention, the term "transfection" is used to refer to any method by which an exogenous nucleic acid molecule (*i.e.*, a recombinant nucleic acid molecule) can be inserted into a cell. The term "transformation" can be used interchangeably with the term "transfection" when such term is used to refer to the introduction of nucleic acid molecules into microbial cells. In microbial systems, the
10 term "transformation" is used to describe an inherited change due to the acquisition of exogenous nucleic acids by the microorganism and is essentially synonymous with the term "transfection." However, in animal cells, transformation has acquired a second meaning that can refer to changes in the growth properties of cells in culture (described above) after they become cancerous, for example. Therefore, to avoid confusion, the
15 term "transfection" is preferably used with regard to the introduction of exogenous nucleic acids into animal cells, including human cells, and is used herein to generally encompass transfection of animal cells and transformation of microbial cells, to the extent that the terms pertain to the introduction of exogenous nucleic acids into a cell. Therefore, transfection techniques include, but are not limited to, transformation,
20 chemical treatment of cells, particle bombardment, electroporation, microinjection, lipofection, adsorption, infection and protoplast fusion.

 A recombinant cell is preferably produced by transforming a host cell with one or more recombinant molecules, each comprising one or more nucleic acid molecules operatively linked to an expression vector containing one or more expression control
25 sequences.

 "Hybridization" has the meaning that is well known in the art, that is, the formation of a duplex structure by two single-stranded nucleic acids due to complementary base pairing. Hybridization can occur between exactly complementary nucleic acid strands or between nucleic acid strands that contain some regions of
30 mismatch. As used herein, reference to hybridization conditions refers to standard hybridization conditions under which nucleic acid molecules are used to identify similar nucleic acid molecules. Such standard conditions are disclosed, for example, in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs

Press, 1989. Sambrook et al., *ibid.*, is incorporated by reference herein in its entirety (*see* specifically, pages 9.31-9.62). In addition, formulae to calculate the appropriate hybridization and wash conditions to achieve hybridization permitting varying degrees of mismatch of nucleotides are disclosed, for example, in Meinkoth et al., 1984, *Anal. Biochem.* 138, 267-284; Meinkoth et al., *ibid.*, is incorporated by reference herein in its entirety. "Stringent hybridization" has a meaning well-established in the art, that is, hybridization performed at a salt concentration of no more than 1M and a temperature of at least 25 degrees Celsius. For example, conditions of 5X SSPE (750 mM NaCl, 50 mM Sodium Phosphate, 5 mM EDTA, pH 7.4) and a temperature of 55 degrees to 60 degrees Celsius are suitable. For example, in one embodiment, "moderately stringent conditions" can be defined as hybridizations carried out as described above, followed by washing in 0.2X SSC and 0.1% SDS at 42 degrees Celsius (Ausubel *et al.*, 1989, *Current Protocols for Molecular Biology*, *ibid.*).

More particularly, moderate stringency hybridization and washing conditions, as referred to herein, refer to conditions which permit isolation of nucleic acid molecules having at least about 70% nucleic acid sequence identity with the nucleic acid molecule being used to probe in the hybridization reaction (*i.e.*, conditions permitting about 30% or less mismatch of nucleotides). High stringency hybridization and washing conditions, as referred to herein, refer to conditions which permit isolation of nucleic acid molecules having at least about 80% nucleic acid sequence identity with the nucleic acid molecule being used to probe in the hybridization reaction (*i.e.*, conditions permitting about 20% or less mismatch of nucleotides). Very high stringency hybridization and washing conditions, as referred to herein, refer to conditions which permit isolation of nucleic acid molecules having at least about 90% nucleic acid sequence identity with the nucleic acid molecule being used to probe in the hybridization reaction (*i.e.*, conditions permitting about 10% or less mismatch of nucleotides). As discussed above, one of skill in the art can use the formulae in Meinkoth et al., *ibid.* to calculate the appropriate hybridization and wash conditions to achieve these particular levels of nucleotide mismatch. Such conditions will vary, depending on whether DNA:RNA or DNA:DNA hybrids are being formed. Calculated melting temperatures for DNA:DNA hybrids are 10°C less than for DNA:RNA hybrids. In particular embodiments, stringent hybridization conditions for DNA:DNA hybrids include hybridization at an ionic strength of 6X SSC (0.9 M Na⁺) at a temperature of between about 20°C and about 35°C (low stringency), more preferably,

between about 28°C and about 42°C (more stringent), and even more preferably, between about 35°C and about 45°C (even more stringent), with appropriate wash conditions. In particular embodiments, stringent hybridization conditions for DNA:RNA hybrids include hybridization at an ionic strength of 6X SSC (0.9 M Na⁺) at a temperature of
5 between about 30°C and about 45°C, more preferably, between about 38°C and about 50°C, and even more preferably, between about 45°C and about 55°C, with similarly stringent wash conditions. These values are based on calculations of a melting temperature for molecules larger than about 100 nucleotides, 0% formamide and a G + C content of about 40%. Alternatively, T_m can be calculated empirically as set forth in
10 Sambrook et al., *supra*, pages 9.31 to 9.62. In general, the wash conditions should be as stringent as possible, and should be appropriate for the chosen hybridization conditions. For example, hybridization conditions can include a combination of salt and temperature conditions that are approximately 20-25°C below the calculated T_m of a particular hybrid, and wash conditions typically include a combination of salt and temperature conditions
15 that are approximately 12-20°C below the calculated T_m of the particular hybrid. One example of hybridization conditions suitable for use with DNA:DNA hybrids includes a 2-24 hour hybridization in 6X SSC (50% formamide) at about 42°C, followed by washing steps that include one or more washes at room temperature in about 2X SSC, followed by additional washes at higher temperatures and lower ionic strength (*e.g.*, at least one wash
20 as about 37°C in about 0.1X-0.5X SSC, followed by at least one wash at about 68°C in about 0.1X-0.5X SSC).

In one embodiment of the present invention, any amino acid sequence described herein can be produced with from at least one, and up to about 20, additional heterologous amino acids flanking each of the C- and/or N-terminal ends of the specified
25 amino acid sequence. The resulting protein or polypeptide can be referred to as "consisting essentially of" the specified amino acid sequence. According to the present invention, the heterologous amino acids are a sequence of amino acids that are not naturally found (*i.e.*, not found in nature, *in vivo*) flanking the specified amino acid sequence, or that are not related to the function of the specified amino acid sequence, or
30 that would not be encoded by the nucleotides that flank the naturally occurring nucleic acid sequence encoding the specified amino acid sequence as it occurs in the gene, if such nucleotides in the naturally occurring sequence were translated using standard codon

usage for the organism from which the given amino acid sequence is derived. Similarly, the phrase "consisting essentially of", when used with reference to a nucleic acid sequence herein, refers to a nucleic acid sequence encoding a specified amino acid sequence that can be flanked by from at least one, and up to as many as about 60, additional heterologous nucleotides at each of the 5' and/or the 3' end of the nucleic acid sequence encoding the specified amino acid sequence. The heterologous nucleotides are not naturally found (*i.e.*, not found in nature, *in vivo*) flanking the nucleic acid sequence encoding the specified amino acid sequence as it occurs in the natural gene or do not encode a protein that imparts any additional function to the protein or changes the function of the protein having the specified amino acid sequence.

As discussed above, one embodiment of the present invention relates to methods for identifying compounds that induce or increase or upregulate apoptosis in a cell by inhibiting genes or gene products involved in the control of cell growth. Once a gene has been identified as a target for supporting cell growth, an assay can be used for screening and selecting a chemical compound or a biological compound having activity as an anti-tumor therapeutic based on the ability of the compound to down-regulate expression of the gene or inhibit activity of its gene product. Reference herein to inhibiting a target, can refer to one or both of inhibiting expression of a target gene and inhibiting the translation and/or activity of its corresponding expression product. Such a compound can be referred to herein as therapeutic compound. For example, a cell line that naturally expresses the gene of interest or has been transfected with the gene or other recombinant nucleic acid molecule encoding the protein of interest is incubated with various compounds, also referred to as candidate compounds, test compounds, or putative regulatory compounds. A reduction of the expression of the gene of interest or an inhibition of the activities of its encoded product (*e.g.*, biological activity, which can include the involvement of the protein in the protection of the cell from apoptotic processes) may be used to identify a therapeutic compound. Therapeutic compounds identified in this manner can then be re-tested, if desired, in other assays to confirm their activities against cellular apoptotic processes.

In general, the biological activity or biological action of a protein refers to any function(s) exhibited or performed by the protein that is ascribed to the naturally occurring form of the protein as measured or observed *in vivo* (*i.e.*, in the natural physiological environment of the protein) or *in vitro* (*i.e.*, under laboratory conditions).

Modifications, activities or interactions which result in a decrease in protein expression or a decrease in the activity of the protein, can be referred to as inactivation (complete or partial), down-regulation, reduced action, or decreased action or activity of a protein. Similarly, modifications, activities or interactions which result in an increase in protein expression or an increase in the activity of the protein, can be referred to as amplification, overproduction, activation, enhancement, up-regulation or increased action of a protein. The biological activity of a protein according to the invention can be measured or evaluated using any assay for the biological activity of the protein as known in the art. Such assays can include, but are not limited to, binding assays, assays to determine internalization of the protein and/or associated proteins, enzyme assays, cell signal transduction assays (e.g., phosphorylation assays), and/or assays for determining downstream cellular events that result from activation or binding of the cell surface protein (e.g., expression of downstream genes, production of various biological mediators, etc.). The assay can also measure the ability of the protein to contribute to the regulation of apoptosis in a cell. Such assays are described in detail herein. According to the present invention, a biologically active fragment or homologue of a gene or protein maintains the ability to be useful in a method of the present invention. Therefore, the biologically active fragment or homologue maintains the ability to be used to identify regulators (e.g., inhibitors) of the native gene or protein when, for example, the biologically active fragment or homologue is expressed by a cell. Therefore, the biologically active fragment or homologue has a structure that is sufficiently similar to the structure of the native gene or protein that a regulatory compound can be identified by its ability to bind to and/or regulate the expression or activity of the fragment or homologue in a manner consistent with the regulation of the native gene or protein.

Compounds to be screened in the methods of the invention include known organic compounds such as antibodies, products of peptide libraries, and products of chemical combinatorial libraries. Compounds may also be identified using rational drug design relying on the structure of the product of a gene. Such methods are known to those of skill in the art and involve the use of three-dimensional imaging software programs. For example, various methods of drug design, useful to design or select mimetics or other therapeutic compounds useful in the present invention are disclosed in Maulik et al., 1997, *Molecular Biotechnology: Therapeutic Applications and Strategies*, Wiley-Liss, Inc., which is incorporated herein by reference in its entirety.

As used herein, a mimetic refers to any peptide or non-peptide compound that is able to mimic the biological action of a naturally occurring peptide, often because the mimetic has a basic structure that mimics the basic structure of the naturally occurring peptide and/or has the salient biological properties of the naturally occurring peptide.

5 Mimetics can include, but are not limited to: peptides that have substantial modifications from the prototype such as no side chain similarity with the naturally occurring peptide (such modifications, for example, may decrease its susceptibility to degradation); anti-idiotypic and/or catalytic antibodies, or fragments thereof; non-proteinaceous portions of an isolated protein (*e.g.*, carbohydrate structures); or synthetic or natural organic

10 molecules, including nucleic acids and drugs identified through combinatorial chemistry, for example. Such mimetics can be designed, selected and/or otherwise identified using a variety of methods known in the art.

A mimetic can be obtained, for example, from molecular diversity strategies (a combination of related strategies allowing the rapid construction of large, chemically

15 diverse molecule libraries), libraries of natural or synthetic compounds, in particular from chemical or combinatorial libraries (*i.e.*, libraries of compounds that differ in sequence or size but that have the similar building blocks) or by rational, directed or random drug design. *See* for example, Maulik et al., *supra*.

In a molecular diversity strategy, large compound libraries are synthesized, for

20 example, from peptides, oligonucleotides, carbohydrates and/or synthetic organic molecules, using biological, enzymatic and/or chemical approaches. The critical parameters in developing a molecular diversity strategy include subunit diversity, molecular size, and library diversity. The general goal of screening such libraries is to utilize sequential application of combinatorial selection to obtain high-affinity ligands for a desired target, and then to optimize the lead molecules by either random or directed

25 design strategies. Methods of molecular diversity are described in detail in Maulik, et al., *ibid*.

Maulik et al. also disclose, for example, methods of directed design, in which the user directs the process of creating novel molecules from a fragment library of

30 appropriately selected fragments; random design, in which the user uses a genetic or other algorithm to randomly mutate fragments and their combinations while simultaneously applying a selection criterion to evaluate the fitness of candidate ligands; and a grid-based approach in which the user calculates the interaction energy between three dimensional

receptor structures and small fragment probes, followed by linking together of favorable probe sites.

As used herein, the term "test compound", "putative inhibitory compound" or "putative regulatory compound" refers to compounds having an unknown or previously unappreciated regulatory activity in a particular process. As such, the term "identify" with regard to methods to identify compounds is intended to include all compounds, the usefulness of which as a regulatory compound for the purposes of inhibiting cell growth is determined by a method of the present invention.

In one embodiment of the invention, inhibitors of cell growth are identified by exposing a target gene to a test compound; measuring the expression of a target; and selecting a compound that down-regulates (reduces, decreases, inhibits, blocks) the expression of the target. For example, the putative inhibitor can be exposed to a cell that expresses the target gene (endogenously or recombinantly). A preferred cell to use in an assay includes a mammalian cell that either naturally expresses the target gene or has been transformed with a recombinant form of the target gene, such as a recombinant nucleic acid molecule comprising a nucleic acid sequence encoding the target protein or a useful fragment thereof. Methods to determine expression levels of a gene are well known in the art.

The conditions under which a cell, cell lysate, nucleic acid molecule or protein of the present invention is exposed to or contacted with a putative regulatory compound, such as by mixing, are any suitable culture or assay conditions. In the case of a cell-based assay, the conditions include an effective medium in which the cell can be cultured or in which the cell lysate can be evaluated in the presence and absence of a putative regulatory compound. Cells of the present invention can be cultured in a variety of containers including, but not limited to, tissue culture flasks, test tubes, microtiter dishes, and petri plates. Culturing is carried out at a temperature, pH and carbon dioxide content appropriate for the cell. Such culturing conditions are also within the skill in the art. Cells are contacted with a putative regulatory compound under conditions which take into account the number of cells per container contacted, the concentration of putative regulatory compound(s) administered to a cell, the incubation time of the putative regulatory compound with the cell, and the concentration of compound administered to a cell. Determination of effective protocols can be accomplished by those skilled in the art based on variables such as the size of the container, the volume of liquid in the container,

conditions known to be suitable for the culture of the particular cell type used in the assay, and the chemical composition of the putative regulatory compound (*i.e.*, size, charge etc.) being tested. A preferred amount of putative regulatory compound(s) can comprise between about 1 nM to about 10 mM of putative regulatory compound(s) per well of a 96-well plate.

As used herein, the term "expression", when used in connection with detecting the expression of a target of the present invention, can refer to detecting transcription of the target gene and/or to detecting translation of the target protein encoded by the target gene. To detect expression of a target refers to the act of actively determining whether a target is expressed or not. This can include determining whether the target expression is upregulated as compared to a control, downregulated as compared to a control, or unchanged as compared to a control. Therefore, the step of detecting expression does not require that expression of the target actually is upregulated or downregulated, but rather, can also include detecting that the expression of the target has not changed (*i.e.*, detecting no expression of the target or no change in expression of the target). Expression of transcripts and/or proteins is measured by any of a variety of known methods in the art. For RNA expression, methods include but are not limited to: extraction of cellular mRNA and Northern blotting using labeled probes that hybridize to transcripts encoding all or part of one or more of the genes of this invention; amplification of mRNA expressed from one or more of the genes of this invention using gene-specific primers, polymerase chain reaction (PCR), and reverse transcriptase-polymerase chain reaction (RT-PCR), followed by quantitative detection of the product by any of a variety of means; extraction of total RNA from the cells, which is then labeled and used to probe cDNAs or oligonucleotides encoding all or part of the genes of this invention, arrayed on any of a variety of surfaces; *in situ* hybridization; and detection of a reporter gene. The term "quantifying" or "quantitating" when used in the context of quantifying transcription levels of a gene can refer to absolute or to relative quantification. Absolute quantification may be accomplished by inclusion of known concentration(s) of one or more target nucleic acids and referencing the hybridization intensity of unknowns with the known target nucleic acids (*e.g.* through generation of a standard curve). Alternatively, relative quantification can be accomplished by comparison of hybridization signals between two or more genes, or between two or more treatments to quantify the changes in hybridization intensity and, by implication, transcription level.

In a preferred embodiment, the expression of the target gene is measured by the polymerase chain reaction. In another embodiment, the expression of the target gene is measured using polyacrylamide gel analysis, chromatography or spectroscopy.

In another preferred embodiment, the expression of the target gene is measured by measuring the production of the encoded protein (measuring translation of the protein). Measurement of translation of a protein includes any suitable method for detecting and/or measuring proteins from a cell or cell extract. Such methods include, but are not limited to, immunoblot (*e.g.*, Western blot), enzyme-linked immunosorbant assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunohistochemistry, immunofluorescence, fluorescence activated cell sorting (FACS) and immunofluorescence microscopy. Particularly preferred methods for detection of proteins include any single-cell assay, including immunohistochemistry and immunofluorescence assays. For example, one can use a detection agent, such as an antibody that specifically recognizes (selectively binds to) the protein encoded by the gene. Such methods are well known in the art.

Designing a compound for testing in a method of the present invention can include creating a new chemical compound or searching databases of libraries of known compounds (*e.g.*, a compound listed in a computational screening database containing three dimensional structures of known compounds). Designing can also be performed by simulating chemical compounds having substitute moieties at certain structural features. The step of designing can include selecting a chemical compound based on a known function of the compound. A preferred step of designing comprises computational screening of one or more databases of compounds in which the three dimensional structure of the compound is known and is interacted (*e.g.*, docked, aligned, matched, interfaced) with the three dimensional structure of a target by computer (*e.g.* as described by Humblet and Dunbar, *Animal Reports in Medicinal Chemistry*, vol. 28, pp. 275-283, 1993, M Venuti, ed., Academic Press). Methods to synthesize suitable chemical compounds are known to those of skill in the art and depend upon the structure of the chemical being synthesized. Methods to evaluate the bioactivity of the synthesized compound depend upon the bioactivity of the compound (*e.g.*, inhibitory or stimulatory).

Accordingly, in another embodiment of the invention, therapeutic compounds can be selected by determining the three-dimensional structure of a target; and determining or designing the three-dimensional structure of a therapeutic or regulatory compound by

rational drug design or detecting a structure that interacts with the target structure from a library of known compound structures. Preferably, the structure of the therapeutic compound is determined using computer software capable of modeling the interaction of a therapeutic compound with the target. One of skill in the art can select the appropriate
5 three-dimensional structure, therapeutic or regulatory compound, and analytical software based on the identity of the target.

For example, suitable candidate chemical compounds can align to a subset of residues described for a target site. Preferably, a candidate chemical compound comprises a conformation that promotes the formation of covalent or noncovalent
10 crosslinking between the target site and the candidate chemical compound. Preferably, a candidate chemical compound binds to a surface adjacent to a target site to provide an additional site of interaction in a complex. When designing an antagonist, for example, the antagonist should bind with sufficient affinity to the binding site or to substantially prohibit a ligand (*i.e.*, a molecule that specifically binds to the target site) from binding to
15 a target area. It will be appreciated by one of skill in the art that it is not necessary that the complementarity between a candidate chemical compound and a target site extend over all residues specified here in order to inhibit or promote binding of a ligand.

In general, the design of a chemical compound possessing stereochemical complementarity can be accomplished by techniques that optimize, chemically or
20 geometrically, the "fit" between a chemical compound and a target site. Such techniques are disclosed by, for example, Sheridan and Venkataraghavan, *Acc. Chem Res.*, vol. 20, p. 322, 1987; Goodford, *J. Med. Chem.*, vol. 27, p. 557, 1984; Beddell, *Chem. Soc. Reviews*, vol. 279, 1985; Hol, *Angew. Chem.*, vol. 25, p. 767, 1986; and Verlinde and Hol, *Structure*, vol. 2, p. 577, 1994, each of which are incorporated by this reference herein in
25 their entirety.

As another example, a "geometric approach" is used. In a geometric approach, the number of internal degrees of freedom (and the corresponding local minima in the molecular conformation space) is reduced by considering only the geometric (hard sphere) interactions of two rigid bodies, where one body (the active site) contains
30 "pockets" or "grooves" that form binding sites for the second body (the complementing molecule, such as a ligand). The geometric approach is described by Kuntz et al., *J. Mol. Biol.*, vol. 161, p. 269, 1982, which is incorporated by this reference herein in its entirety. The algorithm for chemical compound design can be implemented using the software

program DOCK Package, Version 1.0 (available from the Regents of the University of California). Pursuant to the Kuntz algorithm, the shape of the cavity or groove on the surface of a structure at a binding site or interface is defined as a series of overlapping spheres of different radii. One or more extant databases of crystallographic data (e.g., the
5 Cambridge Structural Database System maintained by University Chemical Laboratory, Cambridge University, Lensfield Road, Cambridge CB2 1EW, U.K.) or the Protein Data Bank maintained by Brookhaven National Laboratory, is then searched for chemical compounds that approximate the shape thus defined. Chemical compounds identified by the geometric approach can be modified to satisfy criteria associated with chemical
10 complementarity, such as hydrogen bonding, ionic interactions or Van der Waals interactions.

As yet another example, one can determine the interaction of chemical groups ("probes") with an active site at sample positions within and around a binding site or interface, resulting in an array of energy values from which three dimensional contour
15 surfaces at selected energy levels can be generated. This method is referred to herein as a "chemical-probe approach." The chemical-probe approach to the design of a chemical compound useful of the present invention is described by, for example, Goodford, *J. Med. Chem.*, vol. 28, p. 849, 1985, which is incorporated by this reference herein in its entirety, and is implemented using an appropriate software package, including for example, GRID
20 (available from Molecular Discovery Ltd., Oxford OX2 9LL, U.K.). The chemical prerequisites for a site-complementing molecule can be identified at the outset, by probing the active site of a protein with different chemical probes, e.g., water, a methyl group, an amine nitrogen, a carboxyl oxygen and/or a hydroxyl. Preferred sites for interaction between an active site and a probe are determined. Putative complementary
25 chemical compounds can be generated using the resulting three dimensional patterns of such sites.

Candidate compounds identified or designed by the above-described methods can be synthesized using techniques known in the art, and depending on the type of compound. Synthesis techniques for the production of non-protein compounds, including
30 organic and inorganic compounds are well known in the art. For example, for smaller peptides, chemical synthesis methods are preferred. For example, such methods include well known chemical procedures, such as solution or solid-phase peptide synthesis, or semi-synthesis in solution beginning with protein fragments coupled through

conventional solution methods. Such methods are well known in the art and may be found in general texts and articles in the area such as: Merrifield, 1997, *Methods Enzymol.* 289:3-13; Wade et al., 1993, *Australas Biotechnol.* 3(6):332-336; Wong et al., 1991, *Experientia* 47(11-12):1123-1129; Carey et al., 1991, *Ciba Found Symp.* 158:187-203; Plaue et al., 1990, *Biologicals* 18(3):147-157; Bodanszky, 1985, *Int. J. Pept. Protein Res.* 25(5):449-474; or H. Dugas and C. Penney, *BIOORGANIC CHEMISTRY*, (1981) at pages 54-92, all of which are incorporated herein by reference in their entirety. For example, peptides may be synthesized by solid-phase methodology utilizing a commercially available peptide synthesizer and synthesis cycles supplied by the manufacturer. One skilled in the art recognizes that the solid phase synthesis could also be accomplished using the Fmoc strategy and a TFA/scavenger cleavage mixture. A compound that is a protein or peptide can also be produced using recombinant DNA technology and methods standard in the art, particularly if larger quantities of a protein are desired.

In still another embodiment of the invention, inhibitors of cell growth are identified by exposing a target to a candidate compound; measuring the binding of the candidate compound to the target; and selecting a compound that binds to the target at a desired concentration, affinity, or avidity. In a preferred embodiment, the assay is performed under conditions conducive to promoting the interaction or binding of the compound to the target. One of skill in the art can determine such conditions based on the target and the compound being used in the assay. In one embodiment, a BIAcore machine can be used to determine the binding constant of a complex between the target protein (a protein encoded by the target gene) and a natural ligand in the presence and absence of the candidate compound. For example, the target protein or a ligand binding fragment thereof can be immobilized on a substrate. A natural or synthetic ligand is contacted with the substrate to form a complex. The dissociation constant for the complex can be determined by monitoring changes in the refractive index with respect to time as buffer is passed over the chip (O'Shannessy et al. *Anal. Biochem.* 212:457-468 (1993); Schuster et al., *Nature* 365:343-347 (1993)). Contacting a candidate compound at various concentrations with the complex and monitoring the response function (*e.g.*, the change in the refractive index with respect to time) allows the complex dissociation constant to be determined in the presence of the test compound and indicates whether the candidate compound is either an inhibitor or an agonist of the complex. Alternatively, the

candidate compound can be contacted with the immobilized target protein at the same time as the ligand to see if the candidate compound inhibits or stabilizes the binding of the ligand to the target protein.

Other suitable assays for measuring the binding of a candidate compound to a target protein or for measuring the ability of a candidate compound to affect the binding of the target protein to another protein or molecule include, but are not limited to, Western blot, immunoblot, enzyme-linked immunosorbant assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, microcytometry, microarray, microscopy, fluorescence activated cell sorting (FACS), and flow cytometry. Other assays include those that are suitable for monitoring the effects of protein binding, including, but not limited to, cell-based assays such as: cytokine secretion assays, or intracellular signal transduction assays that determine, for example, protein or lipid phosphorylation, mediator release or intracellular Ca^{++} mobilization.

In yet another embodiment, inhibitors of cellular growth are identified by exposing a target protein of the present invention (or a cell expressing the protein naturally or recombinantly) to a candidate compound and measuring the ability of the compound to inhibit (reduce, decrease, block) a biological activity of the protein. In one embodiment, the biological activity of a protein encoded by the target gene is measured by measuring the amount of product generated in a biochemical reaction mediated by the protein encoded by the target gene. In still another embodiment, the activity of the protein encoded by the target gene is measured by measuring the amount of substrate generated in a biochemical reaction mediated by the protein encoded by the target gene. In another embodiment, a biological activity is measured by measuring a specific event in a cell-based assay, such as release or secretion of a biological mediator or compound that is regulated by the activity of the target protein, measuring intracellular signal transduction assays that determine, for example, protein or lipid phosphorylation, mediator release or intracellular Ca^{++} mobilization. Preferably, the activity of the protein is measured in the presence and absence of the candidate compound, or in the presence of another suitable control compound.

In one embodiment of the invention, when the protein encoded by a target gene is an enzyme, a therapeutic compound is identified by exposing the enzyme encoded by a target gene to a test compound; measuring the activity of the enzyme encoded by the target gene in the presence and absence of the compound; and selecting a compound that
5 down-regulates or inhibits the activity of the enzyme encoded by the target gene. Methods to measure enzymatic activity are well known to those skilled in the art and are selected based on the identity of the enzyme being tested. For example, if the enzyme is a kinase, phosphorylation assays can be used.

In addition to methods for identifying and producing a biological compound that
10 inhibits cell growth, the present invention includes methods known in the art that down-regulate expression or function of a target gene. For example, antisense RNA and DNA molecules may be used to directly block translation of mRNA encoded by these genes by binding to targeted mRNA and preventing protein translation. Polydeoxyribonucleotides can form sequence-specific triple helices by hydrogen bonding to specific complementary
15 sequences in duplexed DNA to effect specific down-regulation of target gene expression. Formation of specific triple helices may selectively inhibit the replication or expression of a target gene by prohibiting the specific binding of functional trans-acting factors.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozyme action involves sequence specific hybridization of the
20 ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. Within the scope of the invention are ribozyme embodiments including engineered hammerhead motif ribozyme molecules that specifically and efficiently catalyze endonucleolytic cleavage of RNA sequences. Antisense RNA molecules showing high-affinity binding to target sequences can also be used as ribozymes by addition of
25 enzymatically active sequences known to those skilled in the art.

Polynucleotides to be used in triplex helix formation should be single-stranded and composed of deoxynucleotides. The base composition of these polynucleotides must be designed to promote triple helix formation via Hoogsteen base pairing rules, which generally require sizeable stretches of either purines or pyrimidines to be present on one
30 strand of a duplex. Polynucleotide sequences may be pyrimidine-based, which will result in TAT and CGC triplets across the three associated strands of the resulting triple helix. The pyrimidine-rich polynucleotides provide base complementarity to a purine-rich region of a single strand of the duplex in a parallel orientation to that strand. In addition,

polynucleotides may be chosen that are purine-rich, for example, containing a stretch of G residues. These polynucleotides will form a triple helix with a DNA duplex that is rich in GC pairs, in which the majority of the purine residues are located on a single strand of the targeted duplex, resulting in GGC triplets across the three strands in the triplex.

5 Alternatively, sequences that can be targeted for triple helix formation can be increased by creating a so-called "switchback" polynucleotide. Switchback polynucleotides are synthesized in an alternating 5'-3', 3'-5' manner, so that they base pair with first one strand of a duplex and then the other, eliminating the necessity for a sizeable stretch of either purines or pyrimidines to be present on one strand of a duplex.

10 Both antisense RNA and DNA molecules, and ribozymes of the invention may be prepared by any method known in the art. These include techniques for chemically synthesizing polynucleotides well known in the art such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding the antisense RNA molecule. Such DNA
15 sequences may be incorporated into a wide variety of vectors that incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly, depending on the promoter used, can be introduced stably into host cells.

 Various modifications to the nucleic acid molecules may be introduced as a means
20 of increasing intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences of ribonucleotides or deoxyribonucleotides to the 5' or 3' ends of the molecule or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the oligodeoxyribonucleotide backbone.

25 Preferably, methods used to identify therapeutic compounds are customized for each target gene or product. If the target product is an enzyme, then the enzyme will be expressed in cell culture and purified. The enzyme will then be screened *in vitro* against therapeutic compounds to look for inhibition of that enzymatic activity. If the target is a non-catalytic protein, then it will also be expressed and purified. Therapeutic compounds
30 will then be tested for their ability to prevent, for example, the binding of a site-specific antibody or a target-specific ligand to the target product.

 In a preferred embodiment, therapeutic compounds that bind to target products are identified, then those compounds can be further tested in biological assays that test for

characteristics such as apoptosis, tumor suppressor status (*e.g.*, p53 status), tumor cell growth and any other customary measure of anti-cancer activity.

In one embodiment of the invention, a therapeutic compound is not toxic to a human host cell. In another embodiment, the therapeutic compound is cytostatic or
5 cytotoxic.

In one embodiment of the invention, a pharmaceutical composition is prepared from a therapeutically-effective amount of a therapeutic compound of the invention and a pharmaceutically-acceptable carrier. Pharmaceutically-acceptable carriers are well known to those with skill in the art. The pharmaceutical compositions of the present
10 invention can be manufactured in a manner that is itself known, *e.g.*, by means of a conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. As used herein, a pharmaceutically acceptable carrier refers to any substance suitable for delivering a therapeutic composition useful in the method of the present invention to a suitable *in vivo* or *ex vivo*
15 site. Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the compounds of the invention can be formulated in appropriate aqueous solutions, such as physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal and transcutaneous administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For oral administration, the
20 compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. For administration by inhalation, the compounds for use according to the present
25 invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The compounds can be formulated for parenteral
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administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

According to the present invention, an effective administration protocol (*i.e.*, administering a composition of the present invention in an effective manner) comprises suitable dose parameters and modes of administration that result in delivery of the compound or composition to a patient or to a target site, cell or tissue in the patient, and subsequent inhibition of the growth of the target cell, preferably so that the patient obtains some measurable, observable or perceived benefit from such administration. In some situations, where the target cell population is accessible for sampling, effective dose parameters can be determined using methods as described herein for assessment of tumor growth. Such methods include removing a sample of the target cell population from the patient prior to and after the compound or composition is administered, and measuring changes expression or biological activity of a target, as well as measuring inhibition of the growth of the cell. Alternatively, effective dose parameters can be determined by experimentation using *in vitro* cell cultures, *in vivo* animal models, and eventually, clinical trials if the patient is human. Effective dose parameters can be determined using methods standard in the art. Such methods include, for example, determination of

survival rates, side effects (*i.e.*, toxicity) and progression or regression of disease. Compounds which exhibit high therapeutic indices are preferred. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be
5 chosen by the individual physician in view of the patient's condition. (*See, e.g. Fingl et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch.1, p.1).

Dosage amount and interval can be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the inhibitory effects. Usual patient dosages for systemic administration range from 100 - 2000 mg/day. Stated in terms of
10 patient body surface areas, usual dosages range from 50 - 910 mg/m²/day. Usual average plasma levels should be maintained within 0.1-1000 μ M. In cases of local administration or selective uptake, the effective local concentration of the compound can not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the
15 subject being treated, on the subject's body surface area, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

Suitable routes of administration can, for example, include oral, rectal, transmucosal, transcutaneous, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct
20 intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. Alternatively, one can administer the compound in a local rather than systemic manner, for example, *via* injection of the compound directly into a specific tissue, often in a depot or sustained release formulation. Furthermore, one can administer the compound in a targeted drug delivery system, for example, in a liposome and/or conjugated with a cell-
25 specific antibody. The liposomes and cell-specific antibody will be targeted to and taken up selectively by tumor cells.

Accordingly, a further embodiment of the invention is a method for inducing apoptosis in a cell by inhibiting a target of the present invention, *i.e.*, a target selected from the group consisting of any of the targets listed in Table 1 and/or represented by any
30 of SEQ ID NOs:1-80. For example, this method can be conducted *in vivo* by administering to an individual an inhibitory or therapeutic compound as generally discussed herein. In addition, the method can be conducted *in vitro* or *ex vivo*.

A further embodiment of the present invention is a method for the diagnosis of a tumor or the monitoring of a tumor growth or regression or a tumor therapy in a patient. The methods include determining the level of a marker (also referred to as a biomarker) in a patient sample, wherein the marker is selected from any of the biomarkers listed in Table 1 or represented by any of SEQ ID NOs:1-80.

The first step of this method of the present invention includes detecting the expression or biological activity of a biomarker in a test sample from a patient (also called a patient sample). Suitable methods of obtaining a patient sample are known to a person of skill in the art. A patient sample can include any bodily fluid or tissue from a patient that may contain tumor cells or proteins of tumor cells. More specifically, according to the present invention, the term "test sample" or "patient sample" can be used generally to refer to a sample of any type which contains cells or products that have been secreted from cells to be evaluated by the present method, including but not limited to, a sample of isolated cells, a tissue sample and/or a bodily fluid sample. According to the present invention, a sample of isolated cells is a specimen of cells, typically in suspension or separated from connective tissue which may have connected the cells within a tissue *in vivo*, which have been collected from an organ, tissue or fluid by any suitable method which results in the collection of a suitable number of cells for evaluation by the method of the present invention. The cells in the cell sample are not necessarily of the same type, although purification methods can be used to enrich for the type of cells that are preferably evaluated. Cells can be obtained, for example, by scraping of a tissue, processing of a tissue sample to release individual cells, or isolation from a bodily fluid.

A tissue sample, although similar to a sample of isolated cells, is defined herein as a section of an organ or tissue of the body which typically includes several cell types and/or cytoskeletal structure which holds the cells together. One of skill in the art will appreciate that the term "tissue sample" may be used, in some instances, interchangeably with a "cell sample", although it is preferably used to designate a more complex structure than a cell sample. A tissue sample can be obtained by a biopsy, for example, including by cutting, slicing, or a punch. A bodily fluid sample, like the tissue sample, contains the cells to be evaluated for marker expression or biological activity and/or may contain a soluble biomarker that is secreted by cells, and is a fluid obtained by any method suitable for the particular bodily fluid to be sampled. Bodily fluids suitable for sampling include, but are not limited to, blood, mucous, seminal fluid, saliva, breast milk, bile and urine.

In general, the sample type (*i.e.*, cell, tissue or bodily fluid) is selected based on the accessibility and structure of the organ or tissue to be evaluated for tumor cell growth and/or on what type of cancer is to be evaluated. For example, if the organ/tissue to be evaluated is the breast, the sample can be a sample of epithelial cells from a biopsy (*i.e.*, a cell sample) or a breast tissue sample from a biopsy (a tissue sample). The sample that is most useful in the present invention will be cells, tissues or bodily fluids isolated from a patient by a biopsy or surgery or routine laboratory fluid collection.

Once a sample is obtained from the patient, the sample is evaluated for detection of the expression or biological activity of the biomarker of the present invention in the cells of the sample. Expression and biological activity of biomarkers of the invention and methods of detecting or measuring the same have been described in detail above with regard to the description of the use of the biomarkers as targets.

For example, the level of the marker can be determined by conventional methods such as expression assays to determine the level of expression of the gene, by biochemical assays to determine the level of the gene product, or by immunoassays. If appropriate, the marker can be identified as a cell surface molecule in tissue or in a bodily fluid, such as serum. For example, a patient sample, which can be immobilized, can be contacted with an antibody, or an antibody fragment, that selectively binds to the marker and determining whether the anti-marker antibody or fragment thereof has bound to the marker. As used herein, the term "selectively binds to" refers to the specific binding of one protein to another (*e.g.*, an antibody, fragment thereof, or binding partner to an antigen), wherein the level of binding, as measured by any standard assay (*e.g.*, an immunoassay), is statistically significantly higher than the background control for the assay. For example, when performing an immunoassay, controls typically include a reaction well/tube that contain antibody or antigen binding fragment alone (*i.e.*, in the absence of antigen), wherein an amount of reactivity (*e.g.*, non-specific binding to the well) by the antibody or antigen binding fragment thereof in the absence of the antigen is considered to be background. Binding can be measured using a variety of methods standard in the art, including, but not limited to: Western blot, immunoblot, enzyme-linked immunosorbant assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, microcytometry,

microarray, microscopy, fluorescence activated cell sorting (FACS), and flow cytometry. In a particular immunoassay, the marker level is determined using a first monoclonal antibody that binds specifically to the marker and a second antibody that binds to the first antibody.

5 In one embodiment, the amino acid sequence of a biomarker or the nucleic acid sequence of the corresponding gene can be used as a basis for detection. For example, detection can refer to detection of gene expression by determining the concentration of messenger RNA using common methods such as northern blot analysis, gene chip array analysis, Taqman analysis or other DNA/RNA hybridization platforms. The over or under
10 expression of a biomarker can be an indication of the presence of a tumor or the predisposition for such tumor. Expression can be compared in patient samples versus samples isolated from healthy individuals.

 In one embodiment of the method of the present invention, the level of a biomarker of the present invention is determined by determining the protein level of that
15 biomarker in tissue. Suitable tissue tissues include tumor tissue and cell material obtained by biopsy.

 In another embodiment of the method of the present invention, the level of a biomarker of the present invention is determined by determining a soluble form of a biomarker in a bodily fluid. Suitable bodily fluids include serum, ascitic or pleural fluid,
20 serum being preferred. Levels of biomarker can be determined using various methods known in the art, including antibody binding assays, mass spectrometry analysis, 2-dimensional gel analysis and other methods used to quantify the presence of protein in solution. One preferred method of the present invention is to immobilize a biomarker to a solid substrate and then incubate the biomarker with a patient's serum. Bound antibodies
25 to the biomarker are then detected by means of an enzyme-conjugated second antibody and a color reaction. Another preferred method is to immobilize an antibody that binds to a biomarker to a solid substrate and incubate the antibody with patient serum. Biomarker in the serum binds to the immobilized antibody and is detected using a second different antibody that binds to the biomarker and a color reaction. Another preferred method of
30 the present invention is to contact an antibody that binds to a biomarker with a patient sample and then determining whether the antibody has been bound to the biomarker. Such method can be achieved using known methods including fluorescence cell sorter (FACS) analysis.

Suitable detection methods of a biomarker, an antibody that binds to a biomarker, or suitable nucleic acid probes, are known to those of skill in the art. The detection of biomarkers using antibodies is preferred, the same antibody being useful for both the soluble form and the form on the cell surface. Suitable antibodies for the method of the present invention include monoclonal antibodies, polyclonal antibodies, and fragments thereof. The antibody fragment refers to all parts of the antibody that bind to the biomarker including Fab, Fv or single-chain Fv fragments. Methods to produce such fragments are known to those of skill in the art. Preferred antibodies include monoclonal antibodies. Such antibodies can be produced using standard methods in the art.

Another method of the present invention can include immobilizing patient tissue in, for example, paraffin. The immobilized tissue can be sectioned and then contacted with an antibody that binds to a biomarker.

In the diagnostic/prognostic methods of the invention, if the level of the marker is greater than a normal level, the level of the marker is considered to be indicative of the presence of tumor cells. A normal level can be determined in a variety of ways. For example, if a patient history is known, a baseline level of the marker can be determined and higher levels will be indicative of tumor cells. Alternatively, a normal level can be based on the level for a healthy (*i.e.*, without tumor) individual in a given population. That is, a normal level can be based on a population having similar characteristics (*e.g.*, age, sex, race, medical history) as the patient in question.

More specifically, according to the present invention, a "baseline level" is a control level, and in some embodiments (but not all embodiments, depending on the method), a normal level, of biomarker expression or activity against which a test level of biomarker expression or biological activity (*i.e.*, in the test sample) can be compared. Therefore, it can be determined, based on the control or baseline level of biomarker expression or biological activity, whether a sample to be evaluated for tumor cell growth has a measurable increase, decrease, or substantially no change in biomarker expression or biological activity, as compared to the baseline level. In one aspect, the baseline level can be indicative of the cell growth expected in a normal (*i.e.*, healthy, negative control, non-tumor) cell sample. Therefore, the term "negative control" used in reference to a baseline level of biomarker expression or biological activity typically refers to a baseline level established in a sample from the patient or from a population of individuals which is believed to be normal (*i.e.*, non-tumorous, not undergoing neoplastic transformation, not

exhibiting inappropriate cell growth). It is noted that the "negative control" most typically has a lower level of biomarker expression or activity than would be detected in an experimental cell having inappropriate, increased cell growth, because the expression/biological activity of the biomarkers described herein are correlated with cell growth in most tumor cell types. In another embodiment, a baseline can be indicative of a positive diagnosis of tumor cell growth. Such a baseline level, also referred to herein as a "positive control" baseline, refers to a level of biomarker expression or biological activity established in a cell sample from the patient, another patient, or a population of individuals, wherein the sample was believed, based on data for that cell sample, to be neoplastically transformed (*i.e.*, tumorous, exhibiting inappropriate cell growth, cancerous). It is noted that this "positive control" will most typically have a higher level of biomarker expression or activity than in a normal cell, again due to the correlative relationship between the biomarkers of the present invention and cell growth in the majority of tumor cells. In yet another embodiment, the baseline level can be established from a previous sample from the patient being tested, so that the tumor growth of a patient can be monitored over time and/or so that the efficacy of a given therapeutic protocol can be evaluated over time. Methods for detecting biomarker expression or biological activity are described in detail above.

The method for establishing a baseline level of biomarker expression or activity is selected based on the sample type, the tissue or organ from which the sample is obtained, the status of the patient to be evaluated, and, as discussed above, the focus or goal of the assay (*e.g.*, diagnosis, staging, monitoring). Preferably, the method is the same method that will be used to evaluate the sample in the patient. In a most preferred embodiment, the baseline level is established using the same cell type as the cell to be evaluated.

In one embodiment, the baseline level of biomarker expression or biological activity is established in an autologous control sample obtained from the patient. The autologous control sample can be a sample of isolated cells, a tissue sample or a bodily fluid sample, and is preferably a cell sample or tissue sample. According to the present invention, and as used in the art, the term "autologous" means that the sample is obtained from the same patient from which the sample to be evaluated is obtained. The control sample should be of or from the same cell type and preferably, the control sample is obtained from the same organ, tissue or bodily fluid as the sample to be evaluated, such that the control sample serves as the best possible baseline for the sample to be evaluated.

In one embodiment, when the goal of the assay is diagnosis of abnormal cell growth, it is desirable to take the control sample from a population of cells, a tissue or a bodily fluid which is believed to represent a "normal" cell, tissue, or bodily fluid, or at a minimum, a cell or tissue which is least likely to be undergoing or potentially be predisposed to develop tumor cell growth. For example, if the sample to be evaluated is an area of apparently abnormal cell growth, such as a tumorous mass, the control sample is preferably obtained from a section of apparently normal tissue (*i.e.*, an area other than and preferably a reasonable distance from the tumorous mass) in the tissue or organ where the tumorous mass is growing. In one aspect, if a tumor to be evaluated is in the colon, the test sample would be obtained from the suspected tumor mass and the control sample would be obtained from a different section of the colon, which is separate from the area where the mass is located and which does not show signs of uncontrolled cellular proliferation.

In another embodiment, when the goal is to monitor tumor cell growth in the patient, the autologous baseline sample is typically a previous sample from the patient which was taken from an apparent or confirmed tumorous mass, and/or from apparently normal (*i.e.*, non-tumor) tissue in the patient (or a different type of baseline for normal can be used, as discussed below).

Therefore, a second method for establishing a baseline level of biomarker expression or biological activity is to establish a baseline level of biomarker expression or biological activity from at least one measurement of biomarker expression or biological activity in a previous sample from the same patient. Such a sample is also an autologous sample, but is taken from the patient at a different time point than the sample to be tested. Preferably, the previous sample(s) were of a same cell type, tissue type or bodily fluid type as the sample to be presently evaluated. In one embodiment, the previous sample resulted in a negative diagnosis (*i.e.*, no tumor cell growth, or potential therefore, was identified). In this embodiment, a new sample is evaluated periodically (*e.g.*, at annual physicals), and as long as the patient is determined to be negative for tumor development, an average or other suitable statistically appropriate baseline of the previous samples can be used as a "negative control" for subsequent evaluations. For the first evaluation, an alternate control can be used, as described below, or additional testing may be performed to confirm an initial negative diagnosis, if desired, and the value for biomarker expression or biological activity can be used thereafter. This type of baseline control is frequently

used in other clinical diagnosis procedures where a "normal" level may differ from patient to patient and/or where obtaining an autologous control sample at the time of diagnosis is not possible, not practical or not beneficial. For example, for a patient who has periodic mammograms, the previous mammograms serve as baseline controls for the mammary tissue of the individual patient. Similarly, for a patient who is regularly screened for prostate cancer by evaluation of levels of prostate cancer antigen (PCA), previous PCA levels are frequently used as a baseline for evaluating whether the individual patient experiences a change.

In another embodiment, the previous sample from the patient resulted in a positive diagnosis (*i.e.*, tumor growth was positively identified). In this embodiment, the baseline provided by the previous sample is effectively a positive control for tumor growth, and the subsequent samplings of the patient are compared to this baseline to monitor the progress of the tumor growth and/or to evaluate the efficacy of a treatment which is being prescribed for the cancer. In this embodiment, it may also be beneficial to have a negative baseline level of biomarker expression or biological activity (*i.e.*, a normal cell baseline control), so that a baseline for remission or regression of the tumor can be set. Monitoring of a patient's tumor growth can be used by the clinician to modify cancer treatment for the patient based on whether an increase or decrease in cell growth is indicated.

It will be clear to those of skill in the art that some samples to be evaluated will not readily provide an obvious autologous control sample, or it may be determined that collection of autologous control samples is too invasive and/or causes undue discomfort to the patient. In these instances, an alternate method of establishing a baseline level of biomarker expression or biological activity can be used, examples of which are described below.

Another method for establishing a baseline level of biomarker expression or biological activity is to establish a baseline level of biomarker expression or biological activity from control samples, and preferably control samples that were obtained from a population of matched individuals. It is preferred that the control samples are of the same sample type as the sample type to be evaluated for biomarker expression or biological activity (*e.g.*, the same cell type, and preferably from the same tissue or organ). According to the present invention, the phrase "matched individuals" refers to a matching of the control individuals on the basis of one or more characteristics which are suitable

for the type of cell or tumor growth to be evaluated. For example, control individuals can be matched with the patient to be evaluated on the basis of gender, age, race, or any relevant biological or sociological factor that may affect the baseline of the control individuals and the patient (*e.g.*, preexisting conditions, consumption of particular substances, levels of other biological or physiological factors). To establish a control or baseline level of biomarker expression or biological activity, samples from a number of matched individuals are obtained and evaluated for biomarker expression or biological activity. The sample type is preferably of the same sample type and obtained from the same organ, tissue or bodily fluid as the sample type to be evaluated in the test patient.

10 The number of matched individuals from whom control samples must be obtained to establish a suitable control level (*e.g.*, a population) can be determined by those of skill in the art, but should be statistically appropriate to establish a suitable baseline for comparison with the patient to be evaluated (*i.e.*, the test patient). The values obtained from the control samples are statistically processed using any suitable method of statistical analysis to establish a suitable baseline level using methods standard in the art for establishing such values.

A baseline such as that described above can be a negative control baseline, such as a baseline established from a population of apparently normal control individuals. Alternatively, as discussed above, such a baseline can be established from a population of individuals that have been positively diagnosed as having cancer, and particularly, cancer of a specified stage, as set forth by the medical community, so that one or more baseline levels can be established for use in staging a cancer in the patient to be evaluated. Therefore, in one embodiment, the baseline level is one or more tumor control samples that are correlated with a particular stage of tumor development for that type of tumor.

25 For example, tumor samples from an appropriate number of individuals that have been diagnosed as having a particular stage of a given cancer (*e.g.*, Stage I colon cancer) are tested for biomarker expression or biological activity. The values obtained from these control samples are statistically processed to establish a suitable baseline level using methods standard in the art for establishing such values, and the baseline is noted as being indicative of that particular stage of cancer. Preferably, a similar value is determined for each of the established stages of the given cancer, so that a panel of baseline values, each representing a different stage of the cancer, is formed. The level of biomarker expression or biological activity in the patient sample is then compared to each of the baseline levels

to determine to which baseline the biomarker level of the patient is statistically closest. It will be appreciated that a given patient sample may fall between baseline levels of two different stages such that the best diagnosis is that the patient tumor is at least at the lower stage, but is perhaps in the process of advancing to the higher stage. The data provided
5 by this method can be used in conjunction with current cancer staging methods to assist the physician in the evaluation of the patient and in prescribing suitable treatment for the cancer.

It will be appreciated by those of skill in the art that a baseline need not be established for each assay as the assay is performed but rather, a baseline can be
10 established by referring to a form of stored information regarding a previously determined baseline level of biomarker expression for a given control sample, such as a baseline level established by any of the above-described methods. Such a form of stored information can include, for example, but is not limited to, a reference chart, listing or electronic file of population or individual data regarding "normal" (negative control) or tumor positive
15 (including staged tumors) biomarker expression; a medical chart for the patient recording data from previous evaluations; or any other source of data regarding baseline biomarker expression that is useful for the patient to be diagnosed.

After the level of biomarker expression or biological activity is detected in the sample to be evaluated for tumor cell growth, such level is compared to the established
20 baseline level of biomarker expression or biological activity, determined as described above. Also, as mentioned above, preferably, the method of detecting used for the sample to be evaluated is the same or qualitatively and/or quantitatively equivalent to the method of detecting used to establish the baseline level, such that the levels of the test sample and the baseline can be directly compared. In comparing the test sample to the baseline
25 control, it is determined whether the test sample has a measurable decrease or increase in biomarker expression or biological activity over the baseline level, or whether there is no statistically significant difference between the test and baseline levels. After comparing the levels of biomarker expression or biological activity in the samples, the final step of making a diagnosis, monitoring, or staging of the patient can be performed as discussed
30 above.

According to the present invention, detection of an increased level of biomarker expression or biological activity in the sample to be evaluated (*i.e.*, the test sample) as compared to the baseline level indicates that, as compared to the baseline sample,

increased cell growth or tumorigenicity or a potential therefore is indicated in the cells corresponding to the test sample. This indication of increased tumorigenicity is evaluated based on what the baseline represents, and can mean: (1) a positive diagnosis of tumorigenicity (*i.e.*, neoplastic transformation) or potential for tumor cell growth in the patient; (2) continued or increased tumorigenicity in a patient previously diagnosed with a cancer; and/or (3) a higher stage of tumorigenicity than that represented by the baseline. More specifically, if the baseline is a normal or negative control sample (*i.e.*, autologous or otherwise established, such as from a population control), a detection of increased biomarker expression or biological activity in the test sample as compared to the control sample indicates that the cells in the test sample are undergoing (or are at risk of undergoing) increased, and likely inappropriate (*i.e.*, tumorous, neoplastic) cell growth. If the baseline sample is a previous sample from the patient (or a population control) and is representative of a positive diagnosis of tumor cell growth in the patient (*i.e.*, a positive control), a detection of increased biomarker expression or biological activity in the sample as compared to the baseline may indicate that the cells in the test sample are experiencing increased tumor growth or a potential therefore, which would suggest to a clinician that a treatment currently being prescribed, for example, is not controlling the tumor growth or that tumor growth in the patient has recurred. If the baseline sample is representative of a particular stage of tumor, a detection of increased biomarker expression or biological activity in the sample as compared to the baseline may indicate that the cells in the test sample are at a higher stage of tumor growth than the stage represented by the baseline sample.

Similarly, detection of a decreased level of biomarker expression or biological activity in the sample to be evaluated (*i.e.*, the test sample) as compared to the baseline level indicates that, as compared to the baseline sample, decreased cell growth or tumorigenicity or a potential therefore is indicated in the test cells. This indication of decreased tumorigenicity is evaluated based on what the baseline represents, and can mean: (1) a negative diagnosis of tumorigenicity (neoplastic transformation) or potential for tumor cell growth in the patient; (2) reduced tumorigenicity in a patient previously diagnosed with a cancer; and/or (3) a lower stage of tumorigenicity than that represented by the baseline. More specifically, if the baseline is a normal or negative control (autologous or otherwise established, such as from a population control), a detection of decreased biomarker expression or biological activity in the test sample as compared to

the control sample indicates that the cells in the test sample are also normal and are not predicted to be at risk of undergoing inappropriate (*i.e.*, tumorous, neoplastic) cell growth. If the baseline sample is a previous sample from the patient (or from a population control) and is representative of a positive diagnosis of tumorigenicity in the patient (*i.e.*, a positive control), a detection of decreased biomarker expression or biological activity in the sample as compared to the baseline indicates that the cells in the test sample are experiencing decreased tumorigenicity or a potential therefore, which suggests to a clinician, for a patient that has cancer, that a treatment currently being prescribed, for example, is successfully controlling the tumor growth or that a tumor in the patient is in remission or eliminated. If the baseline sample is representative of a particular stage of tumor, a detection of decreased biomarker expression or biological activity in the sample as compared to the baseline indicates that the cells in the test sample are at a lower stage of tumor growth than the stage represented by the baseline sample.

Finally, detection of biomarker expression that is not statistically significantly different than the biomarker expression or biological activity in the baseline sample indicates that, as compared to the baseline sample, no difference in tumorigenicity or a potential therefore is indicated in the test cells. This indication of effectively a "baseline level" of cell growth in the test cell is evaluated based on what the baseline represents, and can mean: (1) a negative or positive diagnosis of tumorigenicity (neoplastic transformation) or potential therefore in the patient; (2) unchanged tumorigenicity in a patient previously diagnosed with a cancer; and/or (3) a correlation with a stage of tumor growth that is represented by the baseline. More specifically, if the baseline is a normal or negative control (autologous or otherwise established, such as from a population control), detection of biomarker expression or biological activity in the test sample that is not statistically significantly different than the baseline sample indicates that the cells in the test sample are also normal and are not predicted to be at risk of undergoing inappropriate (*i.e.*, tumorous, neoplastic) cell growth. If the baseline sample is a previous sample from the patient (or from a population control) and is representative of a positive diagnosis of tumor cell growth in the patient (*i.e.*, a positive control), a detection of biomarker expression or biological activity in the sample that is not statistically significantly different than the baseline indicates that the cells in the test sample are experiencing tumor cell growth or a potential therefore, and the patient should be further

evaluated for cancer. In a patient who has cancer and is being monitored for tumor progression, a detection of biomarker expression or biological activity in the test sample that is not statistically significantly different than the baseline sample indicates that the tumor is neither increasing (progressing) nor decreasing (regressing). Such a diagnosis might suggest to a clinician that a treatment currently being prescribed, for example, is ineffective in controlling the tumor growth or is preventing accelerated tumor growth, but is not causing tumor growth to regress. Finally, if the baseline sample is representative of a particular stage of tumor, a detection of biomarker expression or biological activity in the test sample that is not statistically significantly different than the baseline sample indicates that the cells in the test sample are at substantially the same stage of tumor growth as the stage represented by the baseline sample.

As discussed above, a positive diagnosis indicates that increased cell growth, and possibly tumor cell growth (neoplastic transformation), has occurred, is occurring, or is statistically likely to occur in the cells or tissue from which the sample was obtained. In order to establish a positive diagnosis, the level of biomarker activity is increased over the established baseline by an amount that is statistically significant (*i.e.*, with at least a 95% confidence level, or $p < 0.05$). Preferably, detection of at least about a 10% change in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of increased cell growth for said sample, as compared to the baseline. More preferably, detection of at least about a 30% change in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of increased cell growth for said sample, as compared to the baseline. More preferably, detection of at least about a 50% change, and more preferably at least about a 70% change, and more preferably at least about a 90% change, or any percentage change between 5% and higher in 1% increments (*i.e.*, 5%, 6%, 7%, 8%...) in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of increased tumorigenicity for said sample. In one embodiment, a 1.5 fold change in biomarker expression or biological activity in the sample as compared to the baseline level results in a positive diagnosis of increased tumorigenicity for said sample. More preferably, detection of at least about a 3 fold change, and more preferably at least about a 6 fold change, and even more preferably, at least about a 12 fold change, and even more preferably, at least about a 24 fold change, or any fold change from 1.5 up in increments of 0.5 fold (*i.e.*, 1.5, 2.0, 2.5, 3.0...) in biomarker expression or biological

activity as compared to the baseline level, results in a positive diagnosis of increased tumorigenicity for said sample.

This method of diagnosis can be used specifically to determine the prognosis for cancer in the patient or to determine the susceptibility of the patient to a therapeutic treatment. In some embodiments, the method may be useful to monitor the progress of a patient undergoing therapeutic treatment for a tumor.

The present invention also includes a kit that utilizes the diagnostic methods of the present invention. The kit preferably contains any means of detecting the expression or activity of a biomarker of the present invention in a test sample, and preferably includes a probe, PCR primers, or an antibody, antigen binding peptide, or fragment thereof, that binds to a biomarker. The kit can include any reagent needed to perform a diagnostic method envisioned herein. The antibody, or fragment thereof, can be conjugated to another unit, for example a marker or immobilized to a solid carrier (substrate). The kit can also contain a second antibody for the detection of biomarker:antibody complexes. In one embodiment, the kit can contain a means for detecting a control marker characteristic of a cell type in the test sample. The antibody, or fragment thereof, may be present in free form or immobilized to a substrate such as a plastic dish, a test tube, a test rod and so on. The kit can also include suitable reagents for the detection of and/or for the labeling of positive or negative controls, wash solutions, dilution buffers and the like.

More specifically, according to the present invention, a means for detecting biomarker expression or biological activity can be any suitable reagent that can be used in a method for detection of biomarker expression or biological activity as described previously herein. Such reagents include, but are not limited to: a probe that hybridizes under stringent hybridization conditions to a nucleic acid molecule encoding the biomarker or a fragment thereof (including to a biomarker-specific regulatory region in the biomarker-encoding gene); RT-PCR primers for amplification of mRNA encoding the biomarker or a fragment thereof; and/or an antibody, antigen-binding fragment thereof or other antigen-binding peptide that selectively binds to the biomarker.

According to the present invention, a probe is a nucleic acid molecule which typically ranges in size from about 8 nucleotides to several hundred nucleotides in length. Such a molecule is typically used to identify a target nucleic acid sequence in a sample by hybridizing to such target nucleic acid sequence under stringent hybridization conditions. Hybridization conditions have been described in detail above.

PCR primers are also nucleic acid sequences, although PCR primers are typically oligonucleotides of fairly short length which are used in polymerase chain reactions. PCR primers and hybridization probes can readily be developed and produced by those of skill in the art, using sequence information from the target sequence. (See, for example, 5 Sambrook et al., *supra* or Glick et al., *supra*).

Antibodies that selectively bind to a biomarker in the sample can be produced using information available in the art. Antibodies useful in the assay kit and methods of the present invention can include polyclonal and monoclonal antibodies, divalent and monovalent antibodies, bi- or multi-specific antibodies, serum containing such antibodies, 10 antibodies that have been purified to varying degrees, and any functional equivalents of whole antibodies. Isolated antibodies of the present invention can include serum containing such antibodies, or antibodies that have been purified to varying degrees. Whole antibodies of the present invention can be polyclonal or monoclonal. Alternatively, functional equivalents of whole antibodies, such as antigen binding 15 fragments in which one or more antibody domains are truncated or absent (*e.g.*, Fv, Fab, Fab', or F(ab)₂ fragments), as well as genetically-engineered antibodies or antigen binding fragments thereof, including single chain antibodies or antibodies that can bind to more than one epitope (*e.g.*, bi-specific antibodies), or antibodies that can bind to one or more different antigens (*e.g.*, bi- or multi-specific antibodies), may also be employed in the 20 invention.

Genetically engineered antibodies include those produced by standard recombinant DNA techniques involving the manipulation and re-expression of DNA encoding antibody variable and/or constant regions. Particular examples include, chimeric antibodies, where the V_H and/or V_L domains of the antibody come from a 25 different source to the remainder of the antibody, and CDR grafted antibodies (and antigen binding fragments thereof), in which at least one CDR sequence and optionally at least one variable region framework amino acid is (are) derived from one source and the remaining portions of the variable and the constant regions (as appropriate) are derived from a different source. Construction of chimeric and CDR-grafted antibodies is 30 described, for example, in European Patent Applications: EP-A 0194276, EP-A 0239400, EP-A 0451216 and EP-A 0460617.

Generally, in the production of an antibody, a suitable experimental animal, such as, for example, but not limited to, a rabbit, a sheep, a hamster, a guinea pig, a mouse, a

rat, or a chicken, is exposed to an antigen against which an antibody is desired. Typically, an animal is immunized with an effective amount of antigen that is injected into the animal. An effective amount of antigen refers to an amount needed to induce antibody production by the animal. The animal's immune system is then allowed to
5 respond over a pre-determined period of time. The immunization process can be repeated until the immune system is found to be producing antibodies to the antigen. In order to obtain polyclonal antibodies specific for the antigen, serum is collected from the animal that contains the desired antibodies (or in the case of a chicken, antibody can be collected from the eggs). Such serum is useful as a reagent. Polyclonal antibodies can be further
10 purified from the serum (or eggs) by, for example, treating the serum with ammonium sulfate.

Monoclonal antibodies may be produced according to the methodology of Kohler and Milstein (*Nature* 256:495-497, 1975). For example, B lymphocytes are recovered from the spleen (or any suitable tissue) of an immunized animal and then fused with
15 myeloma cells to obtain a population of hybridoma cells capable of continual growth in suitable culture medium. Hybridomas producing the desired antibody are selected by testing the ability of the antibody produced by the hybridoma to bind to the desired antigen.

The invention also extends to non-antibody polypeptides, sometimes referred to as
20 antigen binding partners or antigen binding peptides, which have been designed to bind selectively to the protein of interest (a biomarker). Examples of the design of such polypeptides, which possess a prescribed ligand specificity, are given in Beste et al. (*Proc. Natl. Acad. Sci.* 96:1898-1903, 1999), incorporated herein by reference in its entirety.

25 In one embodiment, a means for detecting a control marker that is characteristic of the cell type being sampled can generally be any type of reagent that can be used in a method of detecting the presence of a known marker in a sample, such as by a method for detecting the presence of a biomarker described previously herein. Specifically, the means is characterized in that it identifies a specific marker of the cell type being
30 analyzed that positively identifies the cell type. For example, in a breast tumor assay, it is desirable to screen breast epithelial cells for the level of the biomarker expression and/or biological activity. Therefore, the means for detecting a control marker identifies a marker that is characteristic of an epithelial cell and preferably, a breast epithelial cell, so

that the cell is distinguished from other cell types, such as a fibroblast. Such a means increases the accuracy and specificity of the assay of the present invention. Such a means for detecting a control marker include, but are not limited to: a probe that hybridizes under stringent hybridization conditions to a nucleic acid molecule encoding a protein marker; PCR primers which amplify such a nucleic acid molecule; and/or an antibody, antigen binding fragment thereof, or antigen binding peptide that selectively binds to the control marker in the sample. Nucleic acid and amino acid sequences for many cell markers are known in the art and can be used to produce such reagents for detection.

The means for detecting a biomarker and/or a control marker of the assay kit of the present invention can be conjugated to a detectable tag or detectable label. Such a tag can be any suitable tag which allows for detection of the reagents used to detect the biomarker or control marker and includes, but is not limited to, any composition or label detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels in the present invention include biotin for staining with labeled streptavidin conjugate, magnetic beads (*e.g.*, Dynabeads™), fluorescent dyes (*e.g.*, fluorescein, texas red, rhodamine, green fluorescent protein, and the like), radiolabels (*e.g.*, ^3H , ^{125}I , ^{35}S , ^{14}C , or ^{32}P), enzymes (*e.g.*, horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (*e.g.*, polystyrene, polypropylene, latex, etc.) beads.

In addition, the means for detecting of the assay kit of the present invention can be immobilized on a substrate. Such a substrate can include any suitable substrate for immobilization of a detection reagent such as would be used in any of the previously described methods of detection. Briefly, a substrate suitable for immobilization of a means for detecting includes any solid support, such as any solid organic, biopolymer or inorganic support that can form a bond with the means for detecting without significantly effecting the activity and/or ability of the detection means to detect the desired target molecule. Exemplary organic solid supports include polymers such as polystyrene, nylon, phenol-formaldehyde resins, acrylic copolymers (*e.g.*, polyacrylamide), stabilized intact whole cells, and stabilized crude whole cell/membrane homogenates. Exemplary biopolymer supports include cellulose, polydextrans (*e.g.*, Sephadex®), agarose, collagen and chitin. Exemplary inorganic supports include glass beads (porous and nonporous),

stainless steel, metal oxides (*e.g.*, porous ceramics such as ZrO₂, TiO₂, Al₂O₃, and NiO) and sand.

According to the present invention, the method and assay for assessing the tumorigenicity of cells in a patient, as well as other methods disclosed herein, are suitable for use in a patient or cells from a patient or host that is a member of the Kingdom, Animalia, and particularly of the Vertebrate class, Mammalia, including, without limitation, primates, livestock and domestic pets (*e.g.*, a companion animal). Most typically, a patient will be a human patient or host cells will be derived from human patients, although the use of the methods of the invention in any suitable non-human animal model or host cell is also encompassed.

All publications cited herein are incorporated by reference in their entirety.

The Examples, which follow, are illustrative of specific embodiments of the invention, and various uses thereof. They are set forth for explanatory purposes only, and are not to be taken as limiting the invention.

EXAMPLES

Example 1

The purpose of this experiment was to perform a nearly saturated genome wide GSE screen in a tumor cell line model for GSEs that protect cells against apoptosis.

1. V98 Vector Design and Construction

Vector V98 was created through modification of p610SL, a derivative of pLNCO₃ (B-D Chang and I.B. Roninson, Gene 183 (1996) 137-142.) A schematic of V98 is shown in Figure 1. The region flanking the multiple cloning site (MCS) downstream of the inducible CMV promoter was re-engineered (1) to introduce restriction endonuclease sites for enzymes expected to occur with low frequency in the human genome [*e.g.*, Fse I (1 per 170 kbp), Mlu I (1 per 300 kbp), and Rsr II (1 per 260 kbp)], (2) to introduce a short sequence of nucleic acid containing stop codons in all three DNA reading frames downstream of the MCS, (3) to introduce between the Fse I and Mlu I sites on the re-engineered vector backbone a Kozak sequence for efficient translation initiation of peptides encoded by random fragments cloned into the MCS (4) to introduce sequences complementary to well established DNA primers used for DNA sequencing (*e.g.*, M13F-20 and M13R), to permit rapid and efficient sequencing of inserts cloned into the MCS, (5) to introduce sequences flanking the MCS, derived from the genome of *Zea mays*, and

(6) to introduce into the MCS a “stuffer” fragment of about 2.2 kBp, which permits easy assessment of the completeness of vector digestion and selection of the appropriate backbone fragment during vector preparation.

A cDNA encoding the open reading frame of the murine *Lyt-2-alpha'* gene was recovered from Marathon ready mouse spleen cDNA (Clontech) using PCR with the following conditions: 5 µL of marathon ready cDNA, 5 µL 10X cDNA PCR buffer, 1 µL 10 mM dNTP mix, 1 µL Advantage 2 polymerase mix (Clontech, #8430-1), 1 µL of 10 µM upstream primer 5'- ACC ATG GCC TCA CCG TTG ACC CGC TTT -3' (SEQ ID NO:81), 1 µL or 10 µM downstream primer 5'- CTA GCG GCT GTG GTA GCA GAT GAG A -3' (SEQ ID NO:82), and 36 µL of water. Cycling parameters were: 94°C for 3 min.; followed by 30 cycles of 94°C for 30 sec., 55°C for 30 sec., and 72°C for 2 minutes; followed by 72°C for 10 minutes; followed by a 4°C soak. The resultant PCR product of 669 nucleotides was subcloned into a pCRII TOPO vector (Invitrogen). Several independent clones were sequenced to confirm no mutations were introduced in the *Lyt-2-alpha'* ORF by the PCR. One pCRII-TOPO-*Lyt-2-alpha'* clone was shown to be free of mutations, clone #2. DNA from clone #2 was subjected to a second round of PCR (Vt = 50 µL) using the following conditions: 1 ng plasmid DNA, 5 µL 10X cDNA PCR buffer, 0.8 µL of 10 mM dNTP mix, 1 µL of Advantage 2 polymerase mix (Clontech, #8430-1), 2.5 µL of 10 µM upstream primer 5'- CTA CGG ATC CAC CAT GGC CTC ACC GTT GA -3' (SEQ ID NO:83) and 2.5 µL of 10 µM downstream primer 5'- GTA CAT CGA TCT AGC GGC TGT GGT AGC AGA TGA GA -3' (SEQ ID NO:84). These primers permitted recovery the ORF of the *Lyt-2-alpha'* gene flanked by BamH I (upstream) and Cla I restriction endonuclease sites. Cycling parameters were: 94°C for 3 min.; followed by 30 cycles of 94°C for 30 sec., 55°C for 30 sec., and 72°C for 2 minutes; followed by 72°C for 10 minutes; followed by a 4°C soak. The resulting 689-bp PCR product was purified from surrounding proteins and salts using a Qiagen PCR clean up kit following manufacturer's instructions. The purified Clone #2 DNA digested with Bam HI restriction endonuclease (NEB, #R0136S). The digested product was purified using a Qiagen PCR clean up kit and the buffer was changed. The digested DNA was then further digested with Cla I restriction endonuclease (NEB, #R0197S). The doubly restricted Clone #2 DNA was then subcloned into the backbone fragment of the 610SL retroviral vector produced by double digestion of 610SL with Bcl I (NEB, #R0160S) and

Sfu I (Roche, #1243497) restriction endonucleases. Sequencing of DNA harvested from several independent bacterial colonies that were produced from this subcloning step yielded a clone that showed no mutations in the Lyt-2-alpha' ORF. This clone was named V97.

5 The modifications to the MCS regions of vector 610SL were created by sequential cloning of various double stranded oligonucleotides containing the desired sequences into several precursor plasmids. Sequences designed to be located 5' to the Fse I GSE cloning site in V98, *e.g.*, M13F-20 primer site, primer site for P1X, were created by subcloning annealed oligonucleotides 5'- AGC TGT AAA ACG ACG GCC AGT GAG CGT TTA
10 AAC GAA TTC CAG ACT AGT GGC CGG CCG TGC A -3' (SEQ ID NO:85) and 5'- CGG CCG GCC ACT AGT CTG GAA TTC GTT TAA ACG CTC ACT GGC CGT CGT TTT AC -3' (SEQ ID NO:86) into the vector pEGFP-1 (ClonTech) between the HinD III and Pst I sites, to create pEGFP5'. The duplex produced by annealing primers 5'- AAT TCT GCA GCC CAG GTA AAA TTC GCT AGC CT -3' (SEQ ID NO:87) and
15 5'- CTA GAG GCT AGC GAA TTT TAC CTG GGC TGC AG -3' (SEQ ID NO:88), which contains the priming site for P1X sequence, was subcloned between the Eco RI and Spe I sites of pEGFP5' to yield pEGFP54. The modified 5' region of the MCS was recovered from plasmid pEGFP54 as a Bgl II – Not I flanked fragment, and subcloned between the Bgl II and Not I sites of p610SL, to yield p610-E54P1. Sequences designed
20 to be located 3' to the Rsr II GSE cloning site in V98, *e.g.*, 3 frame stop cassette, primer P2X, M13R sequencing primer, were created by subcloning of annealed oligonucleotides 5'- CGG TCC GTG AGT GAG TGA GGC GCG CC G GAT CCT AAC CTA GGT AAT CAT GGT CAT AGC TGT TTC CTG CAG GGC -3' (SEQ ID NO:89) and 5'- GGC CGC CCT GCA GGA AAC AGC TAT GAC CAT GAT TAC CTA GGT TAG GAT
25 CCG GCG CGC CTC ACT CAC TCA CGG ACC GTG CA -3' (SEQ ID NO:90) into the vector pBlueScript II (Stratagene) between the Pst I and Not I sites, to create plasmid pBS3.3'. The duplex produced by annealing primers 5'- GAT CCC GGG TCG TGT ATT CAG CTT TCC TTG TTC CT -3' (SEQ ID NO:91) and 5'- CTA GAG GAA CAA GGA AAG CTG AAT ACA CGA CCC GG -3' (SEQ ID NO:92), which contains the
30 priming site for P2X sequence, was subcloned between the BamH I and Avr II sites of pBS3.3' to yield pBS3.3'P12.

The stuffer fragment for V98 was designed to contain a luciferase ORF joined to a prokaryotic blastidicin S transferase (bsd) expression cassette, in order to yield a 2.2 kBp

DNA fragment. The luciferase ORF and was created by PCR using the following primers 5'- CAT CAA GCT TGG CCG GCC ACC ATG GAC GCG TCC GAA GAC GCC AAA AAC ATA AAG -3' (SEQ ID NO:93) and 5'- CAC GTG GAT ATC TTA CAA TTT GGA CTT TCC GCC CT -3' (SEQ ID NO:94) to amplify the luciferase ORF from the plasmid pNFκB-luc (Stratagene, #219078), while the bsd expression cassette was created by PCR using the primers 5'- TTG TAA GAT ATC CAC GTG TTG ACA ATT AAT C -3' (SEQ ID NO:95) and 5'- CAT CAG ATC TGT CGA CCG GAC CGA CGC GTC CAC GAA GTG CTT AGC -3' (SEQ ID NO:96) to amplify the E7-blasticidin S transferase open reading frame cassette from plasmid EM7-bsd. (InVitrogen, #V511-20).

Both reactions were performed using the following cycling parameters: 95°C for 3 min; followed by 30 cycles of 94°C for 30 sec., 60°C for 30 sec., 72°C for 2 min.; followed by 72°C for 10 min.; followed by a soak at 4°C. PCR products of the desired size were purified by agarose gel electrophoresis followed by recovery of the DNA from the gel using the Qiagen Gel Extraction kit according to manufacturer's instructions. The luciferase ORF and the bsd expression cassette were spliced together to generate a 2.2 kbp stuffer fragment using splice overlap extension PCR (Horton, R.M., Hunt, H.D., Ho, S.N., Pullen, J.K. and Pease, L.R. (1989)). Engineering hybrid genes without the use of restriction enzymes: gene splicing by overlap extension. Gene 77, 61-68) and the primers 5'- CAT CAA GCT TGG CCG GCC ACC ATG GAC GCG TCC GAA GAC GCC AAA AAC ATA AAG -3' (SEQ ID NO:97) and 5'- CAT CAG ATC TGT CGA CCG GAC CGA CGC GTC CAC GAA GTG CTT AGC -3' (SEQ ID NO:98). The resultant SOE PCR product was purified away from the proteins, primers, and salts using a Qiagen PCR clean up kit and following manufacturer's instructions. The product was digested with Hind III and Sal I restriction endonucleases, the restricted product was purified by agarose gel electrophoresis followed by recovery of the DNA from the gel using the Qiagen Gel Extraction kit according to manufacturer's instructions, and the purified DNA was subcloned between the Hind III (NEB, #R0104S) and Xho I (NEB, #R0146S) sites of plasmid pBluescript to yield pBSlucSOEK. Plasmid pBSlucSOEK was sequenced to confirm it was free of unwanted mutations, and the stuffer fragment recovered from the pBSlucSOEK as a Hind III and Rsr II fragment, which was purified by agarose gel electrophoresis, followed by recovery of the DNA from the gel using the Qiagen Gel Extraction kit according to manufacturer's instructions and subcloning of the fragment into the Hind III and Rsr II sites of plasmid pBS3.3'P12 to yield plasmid

pBS33P2lucSOEK. Plasmid V87 was then constructed by recovering from plasmid pBS33P2lucSOEK the luciferase-E7-bsd stuffer fragment along with the 3' flanking sequences as an Fse I – Not I flanked 2.2 kBp DNA product, which was purified by agarose gel electrophoresis followed by recovery of the DNA from the gel using the Qiagen Gel Extraction kit according to manufacturer's instructions. This 2.2 kBp DNA was subcloned between the Fse I and Not I site of plasmid p610-E54P1, to yield vector V87. A schematic drawing of the construction of V87 is shown in Figure 2.

The downstream Mlu I site was removed from V87 by PCR amplification of the stuffer fragment of V90, a derivative of V87 containing the same stuffer as V87, using 1 ng of V90 template DNA and 2.5 µL of primer 5'- CAT CAA GCT TGG CCG GCC ACG CGT GTT GGT AAA ATG GAA GAC G -3' (SEQ ID NO:99) and 2.5 µL of primer 5'- CAT GAG ATC TGT CGA CCG GAC CGC CAC GAA GTG CTT AAG C -3' (SEQ ID NO:100) in a standard 50 µL PCR reaction using Taq DNA polymerase (Roche, 1146165). Cycling parameters were: 94°C for 3 min.; followed by 30 cycles of 94°C for 20 sec., 55°C for 20 sec., and 72°C for 3 minutes; followed by 72°C for 10 minutes; followed by a 4°C soak. The resultant 2.2 kBp PCR product was purified from the proteins and salt using a Qiagen PCR clean up kit following manufacturer's instructions. The PCR product was digested with Fse I and Rsr II endonucleases, purified by agarose gel electrophoresis, and recovered from the gel using a Qiagen Gel Extraction kit according to manufacturer's instructions. The restricted and purified fragment was then subcloned into the Fse I and Rsr II sites of V86, a vector related to V87 but containing a stuffer fragment containing the luciferase ORF but not the bsd ORF, to yield V94. The MCS GSE cassette was recovered from V94 as a 2.2 kBp DNA fragment by digestion of V94 with Bgl II (NEB, #R0144S) and Not I (NEB, #R0189S) restriction endonucleases. Vector V98 was created by subcloning this 2.2 kBp DNA fragment from V94 into the Bgl II and Not I sites on the V97 backbone. A schematic of the construction of V98 is shown in Figure 3.

2. Random Fragment Library Construction

For construction of the starting AOLC1U library, V98 vector described above was restricted at 37°C for 3 hours, using Mlu I (NEB, #R0198S) and Rsr II restriction endonucleases. For construction of all other selected libraries, *e.g.*, AOLC1A, AOLC1B, AOLC1C, V98 vector DNA was restricted at 37°C for 3 hours, using Fse I and Rsr II restriction endonucleases. The vector DNA was purified from the digest using a Qiagen

PCR clean up spin column according to manufacturer's instructions, and the vector backbone DNA was purified by subjecting the eluate from the column to agarose gel electrophoresis to resolve the various DNA digestion products according to mass. A gel slice containing the 7.7 kbp backbone fragment was excised, and the DNA recovered from the agarose slice using the Qiagen Gel Extraction kit according to manufacturer's instructions. The concentration of DNA present in the vector preparations was determined by ethidium bromide staining in an 0.8% agarose gel following electrophoresis, by comparison to a DNA sample composed of various bands of known size and mass (High DNA Mass Ladder, Life Technologies, 10406-016). Vector preparations were quality controlled in series of test ligations as follows: vector alone control reaction, composed of x μ L vector DNA (30 fmol), z μ L water, 4 μ L 5X ligase buffer, 1 μ L T4 DNA ligase (BRL, 5 U/ μ L, #15224-041), where $x + z = 15 \mu$ L; and a vector + insert reaction, composed of x μ L vector DNA (30 fmol), y μ L insert DNA (90 fmol), z μ L water, 4 μ L 5X ligase buffer, 1 μ L T4 DNA ligase, where $x + y + z = 15 \mu$ L. Ligation reactions were incubated at 16°C for at least 16 hours. At the end of the incubation period, ligation products were precipitated under ethanol, the ethanol decanted and the precipitate washed three times with 70% EtOH, and the pellet dried and resuspended in 20 μ L of water. One microliter of resuspended DNA solution was electrotransformed into DH10B electrocompetent cells (Life Technologies, 18290-015) according to manufacturers instructions. Following transformation, bacteria was recovered in 960 μ L of room temperature SOC media, and recovery mixtures incubated at 37°C in a rotary shaker, 250-300 rpm, for at least 40 minutes. After the recovery period, 4 ten-fold serial dilutions of each transformation culture were created, *i.e.*, 1:10, 1:100, 1:1000, and 1:10000, and 50 μ L of each bacterial dilution mixture was plated on LB-agar plates containing carbenicillin. Plates were incubated at 37°C overnight, and scored the following morning. Stock solutions of the double-restricted vector were aliquoted and stored frozen at -20°C, preferably in 30 fmol / tube amounts.

3. Preparation of Randomly fragmented cDNAs from Cell Line mRNA

Total RNA was harvested from five colon cancer cell lines: HCT15, HT29, HCT116, SW480 and SW620, using a Qiagen RNeasy kit, according to manufacturer's instructions. Poly A+ mRNA was purified from the total RNA using an Oligotex kit (Qiagen) following manufacturer's instructions. The purified mRNA pools were fragmented by boiling the sample at 100° C for 8 minutes, a time empirically determined

to give a good distribution of cDNA fragments as demonstrated using a published fragmentation protocol (Gudkov and Roninson, "Isolation of Genetic Suppressor Elements (GSEs) from Random Fragment cDNA libraries in Retroviral Vectors," Chapter 18, in *Methods in Molecular Biology, Vol. 69: cDNA Library Protocols*, p. 228, I.G. Cowell and C. A. Austin, eds. Humana Press Inc., Totowa NJ, 1997). Two parallel first strand cDNA synthesis reactions were performed using the fragmented mRNAs as template, with either an Asc I-N₉ random primer 5'- GTA ATA CGA CTC ACT ATA GGC GCG CCN₉ -3' (SEQ ID NO:101) or an Rsr II-N₉ random primer 5'- GTA ATA CGA CTC ACT ATA GGC GGA CCG N₉ -3' (SEQ ID NO:102) and the SuperScript Choice Systems for cDNA synthesis (Gibco BRL) following manufacturer's instructions. Second strand synthesis was performed using the method of Gubler and Hoffman Gene 25:263-9, 1989) again using the SuperScript kit. The resultant double strand cDNAs were blunted using T4 DNA polymerase (NEB, #M0203S), then ligated to double stranded adapters, produced by annealing the oligonucleotides 5'- ATG ATT ACG CCA CGG ACC GTC -3' (SEQ ID NO:103) and 5'- GAC GGT CCG TGG CGT AAT CAT GGT CAT AGC -3' (SEQ ID NO:104) to yield adapters containing an Rsr II restriction site, or the oligonucleotides 5'- ATG ATT ACG CCA GGC GCG CCA C -3' (SEQ ID NO:105) and 5'- GTG GCG CGC CTG GCG TAA TCA TGG TCA TAG C -3' (SEQ ID NO:106) to yield adapters containing an Asc I restriction site. cDNA samples prepared using the Asc-N₉ primer were ligated to the adapters containing the Rsr II restriction site, while cDNA samples prepared using the Rsr II-N₉ primer were ligated to adapters containing the Asc I restriction site. After ligation of the adapters to the cDNA fragments, excess adapters were removed by spun column chromatography.

4. Preparation of Normalized Inserts for Starting AOLC1U Library

Eluted cDNAs ligated to appropriate adapters were subjected to 22 cycles of PCR to amplify the inserts and to generate large quantities of insert for self-normalization: those inserts ligated to Rsr II adapters were amplified using the primers 5'- GCT ATG ACC ATG ATT ACG CCA CGG ACC GTC -3' (SEQ ID NO:107) and 5'- GTA ATA CGA CTC ACT ATA GGC -3' (SEQ ID NO:108), while inserts ligated to the Asc I adapters were amplified using the primers 5'- GCT ATG ACC ATG ATT ACG CCA GGC GCG CCA C -3' (SEQ ID NO:109) and 5'- GTA ATA CGA CTC ACT ATA GGC GGA C -3' (SEQ ID NO:110). PCR products were pooled, purified using a Qiagen PCR

kit following manufacturer's instructions, evaporated to dryness using a rotary evaporator, and then resuspended in 25 μ L of 10 mM Tris-HCl (pH 8.5). The cDNA fragments were normalized by self-hybridization and batch binding hydroxyapatite (HAP) chromatography, essentially as described by Gudkov and Roninson (*op.cit.*), except that samples were collected at 24, 48, 72, 96 hours. The extent of normalization was evaluated using real-time PCR at five loci: ACTB, TP53, CASP3, 18S and a mitochondrial locus.

Purified, normalized ssDNA fractions from the HAP columns were reconverted to dsDNA and amplified using PCR: again, those inserts ligated to Rsr II adapters were amplified using the primers 5'- GCT ATG ACC ATG ATT ACG CCA CGG ACC GTC -3' (SEQ ID NO:111) and 5'- GTA ATA CGA CTC ACT ATA GGC -3' (SEQ ID NO:112), while inserts ligated to the Asc I adapters were amplified using the primers 5'- GCT ATG ACC ATG ATT ACG CCA GGC GCG CCA C -3' (SEQ ID NO:113) and 5'- GTA ATA CGA CTC ACT ATA GGC GGA C -3' (SEQ ID NO:114). PCR products were purified using Qiagen PCR clean up columns following manufacturer's instructions, and the PCR products from the two types of inserts (e.g, those with Rsr II adapters and those with Asc adapters) were mixed one-to-one molar ratio. Approximately 100 ng of mixed PCR product was digested with Asc I (NEB, #R0558S) and Rsr II restriction endonucleases for 2 hours at 37°C in multiple parallel reactions. DNA was recovered from the pooled digestions using a Qiagen PCR clean up kit following manufacturer's instructions. The concentration of restricted PCR products in the eluate was determined by resolving the DNA present in an aliquot of the eluate by 2% agarose gel electrophoresis. The fluorescent intensity of the PCR product band was compared to the intensity of bands in a DNA sample composed of a mixture of DNA fragments of known size and mass (Low DNA Mass Ladder, Life Technologies, 10068-013).

5. Isolation of GSEs for AOLC1A, AOLC1B, or AOLC1C Libraries.

Colon adenocarcinoma SW480 cells were engineered to stably express ecotropic retroviral receptor (EcoR), and the resulting cell line was termed SW480 E. Phoenix Eco retrovirus packaging cells were transfected with library plasmid DNA and SW480 E cells were transduced with viral supernatant harvested from the packaging cells. Floating SW480 E cells were collected at times 24, 48, 72 and 96 hours post-transduction and fixed with 100% methanol. Apoptotic cells were collected from all time points by

staining the fixed cells with a monoclonal antibody against caspase-cleaved cytokeratin 18 (M30 CytoDeath Antibody, Roche Diagnostics), and selecting stained cells by fluorescence activated cell sorting (FACS). Genomic DNA was isolated from the collected cells (typically between 1×10^5 and 2×10^6 cells, depending upon the selection round) using the Qiagen DNeasy kit (Qiagen). Recovered genomic DNA was quantitated using the PicoGreen DNA quantitation kit (Molecular Probes) in a fluorometric assay performed according to manufacturer's instructions.

GSEs were recovered from the integrated proviruses contained in the harvested genomic DNA using PCR and the following reaction recipe: 10 μ L genomic DNA solution, about 1 μ g DNA, 5 μ L of 3.3 μ M p5x primer 5'- TCT GCA GCC CAG GTA AAA TTC GCT AGC CTC TAG T -3' (SEQ ID NO:115), 5 μ L of 3.3 μ M p6x primer 5'- GAG GAA CAA GGA AAG CTG AAT ACA CGA CCC GTG AT -3' (SEQ ID NO:116), 2 μ L of 10 mM dNTP mix, 17 μ L of H₂O, 10 μ L 5X PCR buffer, 1 μ L of Thermozyme (Invitrogen E120-01). Cycling conditions for the PCR were: 95°C for 3 min.; followed by 30 cycles of 95°C for 30 sec., 68°C for 30 sec., 72°C for 1 min.; followed by 72°C for 10 min., followed by a soak at 4°C. At least 10, and typically 96 reactions were performed in parallel.

Two hundred μ L of pooled PCR product from the genomic PCR samples was purified from proteins and salts using a Qiagen PCR clean up kit following manufacturer's instructions. The concentration of PCR product in the eluate was determined by resolving the DNA present in an aliquot of the eluate by 2% agarose gel electrophoresis and then comparing the fluorescent intensity of the PCR product band to the intensity of bands in a DNA sample composed of a mixture of DNA fragments of known size and mass (Low DNA Mass Ladder, Life Technologies, 10068-013). Multiple parallel restriction digests were then set up using samples of the purified PCR product present in the eluate using the following recipe: 10 μ L 10X NEB buffer #4 (final 1X concentration: 20 mM Tris-acetate, 10 mM magnesium acetate, 50 mM potassium acetate, 1 mM dithiothreitol), 1 μ L 100X BSA (NEB), 7 μ L Fse I restriction endonuclease (2 U/ μ L, NEB #R0588S), 3 μ L Rsr II restriction endonuclease (4 U/ μ L, NEB #R0501S), X μ L aliquot of PCR product, about 100 ng, 79 μ L water, to bring total digestion volume up to 100 μ L. Restriction digests were incubated at 37°C for 3 hours. DNA products from the digest were separated from proteins and salts and concentrated using a Zymo DNA Clean & Concentrator-5 concentrator kit (#D4004), following the manufacturer's

instructions with the following modifications: after addition of DNA binding buffer to each of the digestion reactions, all of the reactions were spun through the same column to concentrate 600 to 800 ng of digested insert onto a single column. Columns were washed according to the manufacturer's protocols, and the DNA eluted from the column by two sequential additions of 8 μ L of 50 mM Tris-HCl, pH 8.5. DNA of desired sizes (100-500 bp) was recovered from the concentrated eluate by purification using gel electrophoresis on 1% low melting point agarose (NuSieve GTG agarose, FMC bioproducts) gels. DNA bands in the gel were visualized following ethidium bromide staining of the gel, using a hand-held shortwave ultraviolet light source. Gel slices containing the desired DNA were excised using clean razor blades, and DNA extracted from the gel slice using the Qiagen gel purification kit, following manufacturer's instructions. The concentration of restricted and purified PCR product was determined by ethidium bromide staining of an agarose gel containing an aliquot of the purified PCR product, and a DNA sample of known composition and mass, as described above.

5. cDNA Library Preparation

Ligation reactions for each batch of insert prepared were set up as follows: (reaction 1) Vector control reaction: x μ L vector DNA (150 ng), z μ L water, 4 μ L 5X ligase buffer, 1 μ L T4 DNA ligase (BRL, 5 U/ μ L, #15224-041), where $x + z = 15 \mu$ L; (reaction 2) Vector + insert: x μ L vector DNA (150 ng), y μ L insert DNA (12 ng); z μ L water; 4 μ L 5X ligase buffer; 1 μ L T4 DNA ligase, where $x + y + z = 15 \mu$ L. Ligation mixtures were incubated at 4°C for at least 16 hours. At the end of the ligation period, ligation products were precipitated under ethanol, the ethanol decanted and the precipitate washed three times with 70% EtOH, and the pellet dried and resuspended in 20 μ L of water. One μ L of resuspended ligation product was used to electrotransform DH10B electrocompetent cells (Life Technologies, 18290-015) according to manufacturers instructions; the balance of the ligation mixture was stored at -20°C. Following transformation, bacteria was recovered in 960 μ L of room temperature SOC media, and recovery mixtures incubated at 37°C in a rotary shaker, 250-300 rpm, for at least 40 minutes. After the recovery period, 4 ten-fold serially diluted samples (*i.e.*, 1:10, 1:100, 1:1000, and 1:10000) of each transformation culture were set up, and 50 μ L from each dilution was plated on LB-agar plates containing carbenicillin. Plates were incubated at 37°C overnight, and colony counts for each plate scored the following morning.

Insert sizes in a subset of clones were determined by performing PCR directly on bacterial colonies as follows. A disposable pipette tip was used to harvest a single bacterial colony from the LB plate of interest. The colony was transferred into 25 μ L of water, carefully swishing the tip to dislodge the bacterial colony. Five microliters of bacterial solution was spotted to an LB plate and allowed to incubate overnight. PCR was performed on the bacterial solution using the following recipe: 2 μ L 10 mM primer M13F(17) 5'-GTA AAA CGA CGG CCA GT -3' (SEQ ID NO:117), 2 μ L 10 mM primer p6X 5'-TCT GCA GCC CAG GTA AAA TTC GCT AGC CTC TAG T -3' (SEQ ID NO:118), 4 μ L 10X PCR buffer, 1 μ L 25 mM dNTP mix, 0.5 μ L Taq DNA polymerase (Roche, 1146165), 10.5 μ L PCR grade water, 20 μ L of bacterial solution. The cycling parameters were 95°C for 3 min., then 25 cycles of 95°C for 30 sec., 60°C for 30 sec., 72°C for 1 min., followed by 72°C for 5 min., and a 4°C soak. At the completion of the PCR, 10 μ L of each PCR product was resolved on a 2% agarose gel containing ethidium bromide. DNA mobility for each of the samples was evaluated. The balance of the PCR product was submitted for DNA sequencing to determine the sequence content of the inserts for these clones.

Ligations described above were used for further electro-transformations. The calculated cfu / μ g for each of the QC controlled ligations was used to compute the total number of electrotransformations required to achieve the required complexity for the library being constructed. Multiple electrotransformations were performed in parallel, using 1 μ L of ligation mix per transformation as described above. At the end of the 40-minute recovery period following the electrotransformation, up to 10 independent transformations were pooled, and 50 μ L from these pooled samples used to establish 4 ten-fold serially diluted samples (*i.e.*, 1:10, 1:100, 1:1000, and 1:10000). Fifty μ L of each serial dilution (*i.e.*, 1:10, 1:100, 1:1000, and 1:10000) was plated on LB-agar plates containing carbenicillin. The remaining volumes of undiluted and diluted transformation solutions were used to seed a bacterial culture flask containing 0.5L of LB broth, after which the seeded flask was incubated at 30°C overnight, about 14 – 16 hours, in a rotary shaker at 300 rpm. Plates from the serially diluted samples were incubated at 37°C overnight, and colony counts for each plate scored the following morning to determine the total number of colonies seeded into the 0.5L culture. Library plasmid DNA was recovered from the 0.5L cultures using a Qiagen Maxiprep plasmid kit, according to manufacturer's instructions.

The AOLC1U library was constructed using the normalized inserts prepared as described in section 4 above; the library was composed of greater than 80 million transformants. The AOLC1A library was constructed from GSEs recovered from apoptotic HCT116 cells collected 24, 48, 72 and 96 hours after transduction. The AOLC1B library was constructed from GSEs recovered from apoptotic HCT116 cells collected 24, 48, and 72 hours after transduction. The AOLC1C library was constructed from GSEs recovered from apoptotic HCT116 cells collected 48 hours after transduction. It was found that the AOLC1C library was highly enriched for RPX and *E. coli* sequences; with the RPL5, RPL36, RPL8, Fau, RPL13a species being the majority species. To subtract these sequences from AOLC1C library, the following procedure was performed: (1) library DNA was linearized using FseI restriction endonuclease, (2) primers specific to selected RPX and *E. coli* species were annealed to linearized DNA and (3) DNA synthesis extended from the primer using Bst DNA polymerase, a polymerase that lacks 3' exonuclease activity. Upon primer extension, the overhang of the FseI half-site adjacent to the insert will be lost, since extension products will yield blunt dsDNA. This blunted Fse I half-site will be incapable of adhering to the cohesive Fse I half-site present at the other end of the plasmid. Therefore, the DNA molecules to which primers have bound (*e.g.* the RPX and *E. coli* species) should have their Fse I sites blunted, and therefore be incapable of resealing by T4 DNA ligase. Hence, all linearized library DNA is treated with T4 DNA ligase, and the ligation products are transformed into electocompetent DH10B *E.coli* to generate a library enriched in sequences that do not contain RPX or *E coli* species. The enriched or subtracted library so created from the AOLC1C library was termed AOLC1CS. Sequencing of the AOLC1CS library showed that the targeted plasmids were substantially reduced in number, but they were still predominant species in the AOLC1CS library. Thus, the AOLC1CS library was subjected to another round of subtraction using the same method, with the resulting library termed AOLC1CS2 (AOLC1C library after 2 rounds of subtraction). The primers used in this method to make library AOLC1CS were: RPS5: 5'- TCG TTC GAG GAG CCC TTG GCA GCA T -3' (SEQ ID NO:119); RPL36A, 5'- CGC CCT TCC GCC ACG GCC GTC TCT -3' (SEQ ID NO:120); RPL18 5'- GAA AGG ACC CGT CGC CAT GGG CCG T -3' (SEQ ID NO:121); Fau, 5'- CAG TCG CCA ATA TGC AGC TCT TTG T -3' (SEQ ID NO:122); RPL13A , 5'- CGA GGT ATG CTG CCC CAC AA -3' (SEQ ID NO:123). For library AOLC1CS2, the above primers were used and these primers were

added as well: RPS5, 5'- CGA GCG CCT GTG CAC AGC AGC CAG A -3' (SEQ ID NO:124); RPL36A, 5'- GCG GGA CAT GAT TCG GGA GGT GTG T -3' (SEQ ID NO:125); RPL8, 5'- CTG CGC GCC TGC GCG CCG TGG ATT T -3' (SEQ ID NO:126); Fau, 5'- CTT CGA GGT GAC CGG CCA GGA AAC G -3' (SEQ ID NO:127);
 5 RPL13A, 5'- CAG GCC GCT CTG GAC CGT CTC AAG G -3' (SEQ ID NO:128); *E coli*, 5'- AAC GGT GGG CTT GTT GCT GCT CTG G -3' (SEQ ID NO:129), 5'- ATT GGT ATT GGT AAC GGG CGT CAG G -3' (SEQ ID NO:130), 5'- ACC ATC TTC CAG GCG CAG TTG AGT T -3' (SEQ ID NO:131).

The target genes and encoded proteins identified by the present invention are
 10 explicitly disclosed in Table 1, which contains a common name for the gene and the GENBANK accession number, which can be retrieved from public sequence databases, as well as a sequence identifier for the nucleic acid sequence (first number) and encoded amino acid sequence (second number).

15 **Table 1**

Accession Number	Common Name	Sequence Identifier (nucleic acid & protein)	Description
NM_001087	AAMP	SEQ ID NO:1 & 2	angio-associated, migratory cell protein
NM_001109	ADAM8	SEQ ID NO:3 & 4	a disintegrin and metalloproteinase domain 8
NM_139057	ADAMTS17	SEQ ID NO:5 & 6	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 17
NM_004036	ADCY3	SEQ ID NO:7 & 8	adenylate cyclase 3
NM_001619	ADRBK1	SEQ ID NO:9 & 10	adrenergic, beta, receptor kinase 1
NM_006698	BLCAP	SEQ ID NO:11 & 12	bladder cancer associated protein
NM_012264	C22orf5	SEQ ID NO:13 & 14	chromosome 22 open reading frame 5
NM_004356	CD81	SEQ ID NO:15 & 16	CD81 antigen (target of antiproliferative antibody 1)
NM_001769	CD9	SEQ ID NO:17 & 18	CD9 antigen (p24)
NM_001305	CLDN4	SEQ ID NO:19 & 20	claudin 4
NM_001288	CLIC1	SEQ ID NO:21 & 22	chloride intracellular channel 1
NM_058175	COL6A2	SEQ ID NO:23 & 24	collagen, type VI, alpha 2
AF070636 or NM_020428	CTL2	SEQ ID NO:25 & 26	CTL2 gene
NM_001397	ECE1	SEQ ID NO:27 & 28	endothelin converting enzyme 1
NM_004429	EFNB1	SEQ ID NO:29 & 30	ephrin-B1
NM_004475	FLOT2	SEQ ID NO:31 & 32	flotillin 2
AC011511 or BC058903	ICAM3	SEQ ID NO:33 & 34	intercellular adhesion molecule 3

Accession Number	Common Name	Sequence Identifier (nucleic acid & protein)	Description
NM_006123	IDS	SEQ ID NO:35 & 36	iduronate 2-sulfatase (Hunter syndrome)
NM_002226	JAG2	SEQ ID NO:37 & 38	jagged 2
BC001699	JAM1	SEQ ID NO:39 & 40	junctional adhesion molecule 1
NM_005567	LGALS3BP	SEQ ID NO:41 & 42	lectin, galactoside-binding, soluble, 3 binding protein
XM_085426	LOC146330	SEQ ID NO:43 & 44	similar to possible G-protein receptor
BC020590	LOC51107	SEQ ID NO:45 & 46	CGI-78 protein
NM_000237	LPL	SEQ ID NO:47 & 48	lipoprotein lipase
NM_002335	LRP5	SEQ ID NO:49 & 50	low density lipoprotein receptor-related protein 5
NM_005581	LU	SEQ ID NO:51 & 52	Lutheran blood group (Auberger b antigen included)
NM_005898	M11S1	SEQ ID NO:53 & 54	membrane component, chromosome 11, surface marker 1
NM_007061	MSE55	SEQ ID NO:55 & 56	serum constituent protein
NM_006702	NTE	SEQ ID NO:57 & 58	neuropathy target esterase
AK055605 or AK126101	PLXNA1	SEQ ID NO:59 & 60	Homo sapiens cDNA FLJ31043 fis, clone HSYRA2000248 (PLEXIN A1) or Homo sapiens cDNA FLJ44113 fis, clone TEST14046487, highly similar to Mus musculus plexin A1
AF034800	PPFIA3	SEQ ID NO:61 & 62	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 3
NM_145648	PTR4	SEQ ID NO:63 & 64	Homo sapiens peptide-histidine transporter 4 (PTR4), mRNA
NM_004207	SLC16A3	SEQ ID NO:65 & 66	solute carrier family 16 (monocarboxylic acid transporters), member 3
NM_005628	SLC1A5	SEQ ID NO:67 & 68	solute carrier family 1 (neutral amino acid transporter), member 5
NM_014437	SLC39A1	SEQ ID NO:69 & 70	solute carrier family 39 (zinc transporter), member 3
NM_021102	SPINT2	SEQ ID NO:71 & 72	serine protease inhibitor, Kunitz type, 2
NM_003714	STC2	SEQ ID NO:73 & 74	stanniocalcin 2
NM_014452	TNFRSF21	SEQ ID NO:75 & 76	tumor necrosis factor receptor superfamily, member 21
NM_003299	TRA1	SEQ ID NO:77 & 78	tumor rejection antigen (gp96) 1
NM_017636	TRPM4	SEQ ID NO:79 & 80	transient receptor potential cation channel, subfamily M, member 4

It should be understood that the foregoing disclosure emphasizes certain specific embodiments of the invention and that all modifications or alternatives equivalent thereto are within the spirit and scope of the invention as set forth in the appended claims.

WHAT WE CLAIM IS:

1. A method for identifying a compound for inducing apoptosis, comprising identifying an inhibitor of a target selected from the group consisting of: angio-associated, migratory cell protein (AAMP, comprising SEQ ID NO:2), a disintegrin and metalloproteinase domain 8 (ADAM8, comprising SEQ ID NO:4), a disintegrin-like and metalloprotease (reporlysin type) with thrombospondin type 1 motif, 17 (ADAMTS17, comprising SEQ ID NO:6), adenylate cyclase 3 (ADCY3, comprising SEQ ID NO:8), adrenergic beta receptor kinase 1 (ADRBK1, comprising SEQ ID NO:10), bladder cancer associated protein (BLCAP, comprising SEQ ID NO:12), chromosome 22 open reading frame 5 (C22orf5, comprising SEQ ID NO:14), CD81 antigen (target of antiproliferative antibody 1 (CD81, comprising SEQ ID NO:16), CD9 antigen (p24) (CD9, comprising SEQ ID NO:18), claudin 4 (CLDN4, comprising SEQ ID NO:20), chloride intracellular channel 1 (CLIC1, comprising SEQ ID NO:22), collagen, type VI, alpha 2 (COL6A2, comprising SEQ ID NO:24), CTL2 (CTL2, comprising SEQ ID NO:26), endothelin converting enzyme 1 (ECE1, comprising SEQ ID NO:28), ephrin-B1 (EFNB1, comprising SEQ ID NO:30), flotillin 2 (FLOT2, comprising SEQ ID NO:32), intercellular adhesion molecule 3 (ICAM3, comprising SEQ ID NO:34), iduronate 2-sulfatase (Hunter syndrome) (IDS, comprising SEQ ID NO:36), jagged 2 (JAG2, comprising SEQ ID NO:38), junctional adhesion molecule 1 (JAM1, comprising SEQ ID NO:40), lectin, galactoside-binding soluble 3 binding protein (LGALS3BP, comprising SEQ ID NO:42), similar to possible G-protein receptor (LOC146330, comprising SEQ ID NO:44), CGI-78 protein (LOC51107, comprising SEQ ID NO:46), lipoprotein lipase (LPL, comprising SEQ ID NO:48), low density lipoprotein receptor-related protein 5 (LRP5, comprising SEQ ID NO:50), Lutheran blood group (Auburger b antigen included) (LU, comprising SEQ ID NO:52), membrane component, chromosome 11, surface marker 1 (M11S1, comprising SEQ ID NO:54), serum constituent protein (MSE55, comprising SEQ ID NO:56), neuropathy target esterase (NTE, comprising SEQ ID NO:58), Homo sapiens cDNA FL31043 fis, clone HSYRA2000248 (PLEXIN A1) or Homo sapiens cDNA FLJ44113 fis, clone TESTI4046487, highly similar to Mus musculus plexin A1 (PLXNA1, comprising SEQ ID NO:60), protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein)(liprin), alpha 3 (PPFIA3, comprising SEQ ID NO:62), Homo sapiens peptide-histidine transporter 4 (PTR4), mRNA (PTR4, comprising SEQ ID NO:64), solute carrier family 16

(monocarboxylic acid transporters) member 3 (SLC16A3, comprising SEQ ID NO:66), solute carrier family 1 (neutral amino acid transporter) member 5 (SLC1A5, comprising SEQ ID NO:68), solute carrier family 39 (zinc transporter) member 3 (SLC39A1, comprising SEQ ID NO:70), serine protease inhibitor, Kunitz type 2 (SPINT2, comprising SEQ ID NO:72), stanniocalcin 2 (STC2, comprising SEQ ID NO:74), tumor necrosis receptor superfamily member 21 (TNFRSF21, comprising SEQ ID NO:76), tumor rejection antigen (gp96) 1 (TRA1, comprising SEQ ID NO:78), and transient receptor potential cation channel, subfamily M member 4 (TRPM4, comprising SEQ ID NO:80).

2. The method of Claim 1, further comprising assessing the ability of an identified inhibitor to induce apoptosis in a cell.

3. The method of Claim 2, further comprising detecting whether a compound identified as inducing apoptosis inhibits growth of tumor cells.

4. The method of Claim 1, wherein the step of identifying comprises identifying an inhibitor of expression or activity of the target.

5. The method of Claim 1, comprising the steps of:

a) contacting a host cell with a putative regulatory compound, wherein the host cell expresses the target or a biologically active fragment thereof; and

b) detecting whether the putative regulatory compound inhibits the target or biologically active fragment thereof, wherein a putative regulatory compound that inhibits the target as compared to in the absence of the compound is indicated to be a candidate compound for the induction of apoptosis in a host cell.

6. The method of Claim 5, wherein the host cell is a tumor cell line.

7. The method of Claim 5, wherein the step of detecting is selected from the group consisting of:

a) detecting expression of the target in the presence of the putative regulatory compound; and

b) detecting activity of the target in the presence of the putative regulatory compound.

8. The method of Claim 7, wherein the expression of the target is measured by polymerase chain reaction.

9. The method of Claim 7, wherein the expression of the target is measured using an antibody or antigen binding partner that selectively binds to the target.

10. The method of Claim 7, wherein the activity of the target is measured by measuring the amount of a product generated in a biochemical reaction mediated by the target.

11. The method of Claim 7, wherein the activity of the target is measured by
5 measuring the amount of a substrate consumed in a biochemical reaction mediated by the target.

12. The method of Claim 1, comprising the steps of:

a) determining the three-dimensional structure of the target;
b) identifying the three-dimensional structure of a putative inhibitor by using
10 computer software to model an interaction between the target structure and a structure of a test compound; and

c) synthesizing compounds identified in (b) and assaying the compounds in an *in vitro* assay to determine whether the compound inhibits the expression or activity of the target.

13. The method of Claim 1, wherein the target has been validated as being
15 involved in tumor cell growth.

14. The method of Claim 14, wherein the target has been validated as being involved in tumor cell growth by a process comprising:

a) inhibiting the target in a cell by a method selected from the group
20 consisting of gene knock-out, anti-sense oligonucleotide expression, use of RNAi molecules and GSE expression; and

b) assaying the cell for the ability of the cell to grow.

15. A method for inducing apoptosis, comprising inhibiting the expression or activity of a target or a gene encoding the target, wherein the target is selected from the
25 group consisting of: angio-associated, migratory cell protein (AAMP, comprising SEQ ID NO:2), a disintegrin and metalloproteinase domain 8 (ADAM8, comprising SEQ ID NO:4), a disintegrin-like and metalloprotease (reporlysin type) with thrombospondin type 1 motif, 17 (ADAMTS17, comprising SEQ ID NO:6), adenylate cyclase 3 (ADCY3, comprising SEQ ID NO:8), adrenergic beta receptor kinase 1 (ADRBK1, comprising
30 SEQ ID NO:10), bladder cancer associated protein (BLCAP, comprising SEQ ID NO:12), chromosome 22 open reading frame 5 (C22orf5, comprising SEQ ID NO:14), CD81 antigen (target of antiproliferative antibody 1 (CD81, comprising SEQ ID NO:16), CD9 antigen (p24) (CD9, comprising SEQ ID NO:18), claudin 4 (CLDN4, comprising SEQ ID

NO:20), chloride intracellular channel 1 (CLIC1, comprising SEQ ID NO:22), collagen, type VI, alpha 2 (COL6A2, comprising SEQ ID NO:24), CTL2 (CTL2, comprising SEQ ID NO:26), endothelin converting enzyme 1 (ECE1, comprising SEQ ID NO:28), ephrin-B1 (EFNB1, comprising SEQ ID NO:30), flotillin 2 (FLOT2, comprising SEQ ID NO:32), intercellular adhesion molecule 3 (ICAM3, comprising SEQ ID NO:34), iduronate 2-sulfatase (Hunter syndrome) (IDS, comprising SEQ ID NO:36), jagged 2 (JAG2, comprising SEQ ID NO:38), junctional adhesion molecule 1 (JAM1, comprising SEQ ID NO:40), lectin, galactoside-binding soluble 3 binding protein (LGALS3BP, comprising SEQ ID NO:42), similar to possible G-protein receptor (LOC146330, comprising SEQ ID NO:44), CGI-78 protein (LOC51107, comprising SEQ ID NO:46), lipoprotein lipase (LPL, comprising SEQ ID NO:48), low density lipoprotein receptor-related protein 5 (LRP5, comprising SEQ ID NO:50), Lutheran blood group (Auberger b antigen included) (LU, comprising SEQ ID NO:52), membrane component, chromosome 11, surface marker 1 (M11S1, comprising SEQ ID NO:54), serum constituent protein (MSE55, comprising SEQ ID NO:56), neuropathy target esterase (NTE, comprising SEQ ID NO:58), Homo sapiens cDNA FL31043 fis, clone HSYRA2000248 (PLEXIN A1) or Homo sapiens cDNA FLJ44113 fis, clone TESTI4046487, highly similar to Mus musculus plexin A1 (PLXNA1, comprising SEQ ID NO:60), protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein)(liprin), alpha 3 (PPFLA3, comprising SEQ ID NO:62), Homo sapiens peptide-histidine transporter 4 (PTR4), mRNA (PTR4, comprising SEQ ID NO:64), solute carrier family 16 (monocarboxylic acid transporters) member 3 (SLC16A3, comprising SEQ ID NO:66), solute carrier family 1 (neutral amino acid transporter) member 5 (SLC1A5, comprising SEQ ID NO:68), solute carrier family 39 (zinc transporter) member 3 (SLC39A1, comprising SEQ ID NO:70), serine protease inhibitor, Kunitz type 2 (SPINT2, comprising SEQ ID NO:72), stanniocalcin 2 (STC2, comprising SEQ ID NO:74), tumor necrosis receptor superfamily member 21 (TNFRSF21, comprising SEQ ID NO:76), tumor rejection antigen (gp96) 1 (TRA1, comprising SEQ ID NO:78), and transient receptor potential cation channel, subfamily M member 4 (TRPM4, comprising SEQ ID NO:80).

16. The method of Claim 15, wherein the step of inhibiting is conducted by contacting a cell with an inhibitor of the target, wherein the inhibitor induces apoptosis in the cell.

17. A method for the diagnosis of a tumor comprising:

- a) detecting a level of expression or activity of at least one biomarker in a test sample from a patient to be diagnosed, wherein the biomarker is selected from the group consisting of: angio-associated, migratory cell protein (AAMP, comprising SEQ ID NO:2), a disintegrin and metalloproteinase domain 8 (ADAM8, comprising SEQ ID NO:4), a disintegrin-like and metalloprotease (reporlysin type) with thrombospondin type 1 motif, 17 (ADAMTS17, comprising SEQ ID NO:6), adenylate cyclase 3 (ADCY3, comprising SEQ ID NO:8), adrenergic beta receptor kinase 1 (ADRBK1, comprising SEQ ID NO:10), bladder cancer associated protein (BLCAP, comprising SEQ ID NO:12), chromosome 22 open reading frame 5 (C22orf5, comprising SEQ ID NO:14), CD81 antigen (target of antiproliferative antibody 1 (CD81, comprising SEQ ID NO:16), CD9 antigen (p24) (CD9, comprising SEQ ID NO:18), claudin 4 (CLDN4, comprising SEQ ID NO:20), chloride intracellular channel 1 (CLIC1, comprising SEQ ID NO:22), collagen, type VI, alpha 2 (COL6A2, comprising SEQ ID NO:24), CTL2 (CTL2, comprising SEQ ID NO:26), endothelin converting enzyme 1 (ECE1, comprising SEQ ID NO:28), ephrin-B1 (EFNB1, comprising SEQ ID NO:30), flotillin 2 (FLOT2, comprising SEQ ID NO:32), intercellular adhesion molecule 3 (ICAM3, comprising SEQ ID NO:34), iduronate 2-sulfatase (Hunter syndrome) (IDS, comprising SEQ ID NO:36), jagged 2 (JAG2, comprising SEQ ID NO:38), junctional adhesion molecule 1 (JAM1, comprising SEQ ID NO:40), lectin, galactoside-binding soluble 3 binding protein (LGALS3BP, comprising SEQ ID NO:42), similar to possible G-protein receptor (LOC146330, comprising SEQ ID NO:44), CGI-78 protein (LOC51107, comprising SEQ ID NO:46), lipoprotein lipase (LPL, comprising SEQ ID NO:48), low density lipoprotein receptor-related protein 5 (LRP5, comprising SEQ ID NO:50), Lutheran blood group (Auberger b antigen included) (LU, comprising SEQ ID NO:52), membrane component, chromosome 11, surface marker 1 (M11S1, comprising SEQ ID NO:54), serum constituent protein (MSE55, comprising SEQ ID NO:56), neuropathy target esterase (NTE, comprising SEQ ID NO:58), Homo sapiens cDNA FL31043 fis, clone HSYRA2000248 (PLEXIN A1) or Homo sapiens cDNA FLJ44113 fis, clone TESTI4046487, highly similar to Mus musculus plexin A1 (PLXNA1, comprising SEQ ID NO:60), protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein)(liprin), alpha 3 (PPFLA3, comprising SEQ ID NO:62), Homo sapiens peptide-histidine transporter 4 (PTR4), mRNA (PTR4, comprising SEQ ID NO:64), solute carrier family 16

(monocarboxylic acid transporters) member 3 (SLC16A3, comprising SEQ ID NO:66), solute carrier family 1 (neutral amino acid transporter) member 5 (SLC1A5, comprising SEQ ID NO:68), solute carrier family 39 (zinc transporter) member 3 (SLC39A1, comprising SEQ ID NO:70), serine protease inhibitor, Kunitz type 2 (SPINT2, comprising SEQ ID NO:72), stanniocalcin 2 (STC2, comprising SEQ ID NO:74), tumor necrosis receptor superfamily member 21 (TNFRSF21, comprising SEQ ID NO:76), tumor rejection antigen (gp96) 1 (TRA1, comprising SEQ ID NO:78), and transient receptor potential cation channel, subfamily M member 4 (TRPM4, comprising SEQ ID NO:80);

b) comparing the level of expression or activity of the biomarker in the test sample to a baseline level of biomarker expression or activity established from a control sample; wherein detection of a statistically significant difference in the expression or activity of the biomarker in the test sample, as compared to the baseline level of the expression or biological activity of the biomarker, is an indicator of a difference in the tumorigenicity or potential therefore of cells in the patient.

18. The method of Claim 17, wherein the step of detecting comprises detecting biomarker mRNA transcription in the test sample.

19. The method of Claim 18, wherein the step of detecting is by a method selected from the group consisting of polymerase chain reaction (PCR), reverse transcriptase-PCR (RT-PCR), *in situ* hybridization, Northern blot, sequence analysis, gene microarray analysis, and detection of a reporter gene.

20. The method of Claim 17, wherein the step of detecting comprises detecting the biomarker protein in the test sample.

21. The method of Claim 20, wherein the step of detecting is by a method selected from the group consisting of immunoblot, enzyme-linked immunosorbant assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunohistochemistry and immunofluorescence.

22. The method of Claim 17, wherein the step of detecting comprises detecting biomarker biological activity in the test sample.

23. The method of Claim 17, wherein detection of a statistically significant difference in the level of biomarker expression or activity in the test sample as compared to the baseline level, with a confidence of $p < 0.05$, indicates that the cells in the test

sample have a difference in tumorigenicity or potential therefore as compared to the control sample.

24. The method of Claim 17, wherein the test sample is from a patient being diagnosed for cancer and wherein the baseline level is established from a control sample
5 that is established as non-tumorigenic.

25. The method of Claim 24, wherein an increase in the level of biomarker expression or activity of the test sample as compared to the baseline level of expression or activity indicates that cells from which the test sample was derived are predicted to be tumorigenic or predisposed to becoming tumorigenic.

10 26. The method of Claim 17, wherein the test sample is from a patient who is known to have cancer, and wherein the baseline level comprises a level of biomarker expression or activity from a previous tumor cell sample from the patient;

wherein a statistically significant decrease in the level of biomarker expression or activity in the test sample as compared to the first baseline level of expression or activity
15 from the previous tumor cell sample, indicates that the test sample is less tumorigenic than the previous tumor cell sample;

and wherein a statistically significant increase in the level of biomarker expression or activity in the test sample as compared to the first baseline level of expression or activity, indicates that the test sample is more tumorigenic than the previous tumor cell
20 sample.

27. The method of Claim 26, wherein the method further comprises a step (c) of modifying cancer treatment for the patient based on whether an increase or decrease in tumorigenicity is indicated in step (b).

28. The method of Claim 17, wherein the baseline level is established by a
25 method selected from the group consisting of:

(1) establishing a baseline level of biomarker expression or activity in an autologous control sample from the patient, wherein the autologous sample is from a same cell type, tissue type or bodily fluid type as the test sample of step (a);

(2) establishing a baseline level of biomarker expression or activity from at
30 least one previous detection of biomarker expression or activity in a previous test sample from the patient, wherein the previous test sample was of a same cell type, tissue type or bodily fluid type as the test sample of step (a); and

(3) establishing a baseline level of biomarker expression or activity from an average of control samples of a same cell type, tissue type or bodily fluid type as the test sample of step (a), the control samples having been obtained from a population of matched individuals.

5 29. The method of Claim 17, wherein the patient test sample is immobilized on a substrate.

 30. The method of Claim 17, wherein the test sample is a bodily fluid sample.

 31. The method of Claim 17, wherein the biomarker level is determined by contacting the patient test sample with an antibody or a fragment thereof that selectively
10 binds specifically to the biomarker, and determining whether the antibody or fragment thereof has bound to the marker.

 32. The method of Claim 17, wherein the method is used to determine the prognosis for cancer in the patient.

 33. The method of Claim 17, wherein the method is used to determine the
15 susceptibility of the patient to a therapeutic treatment.

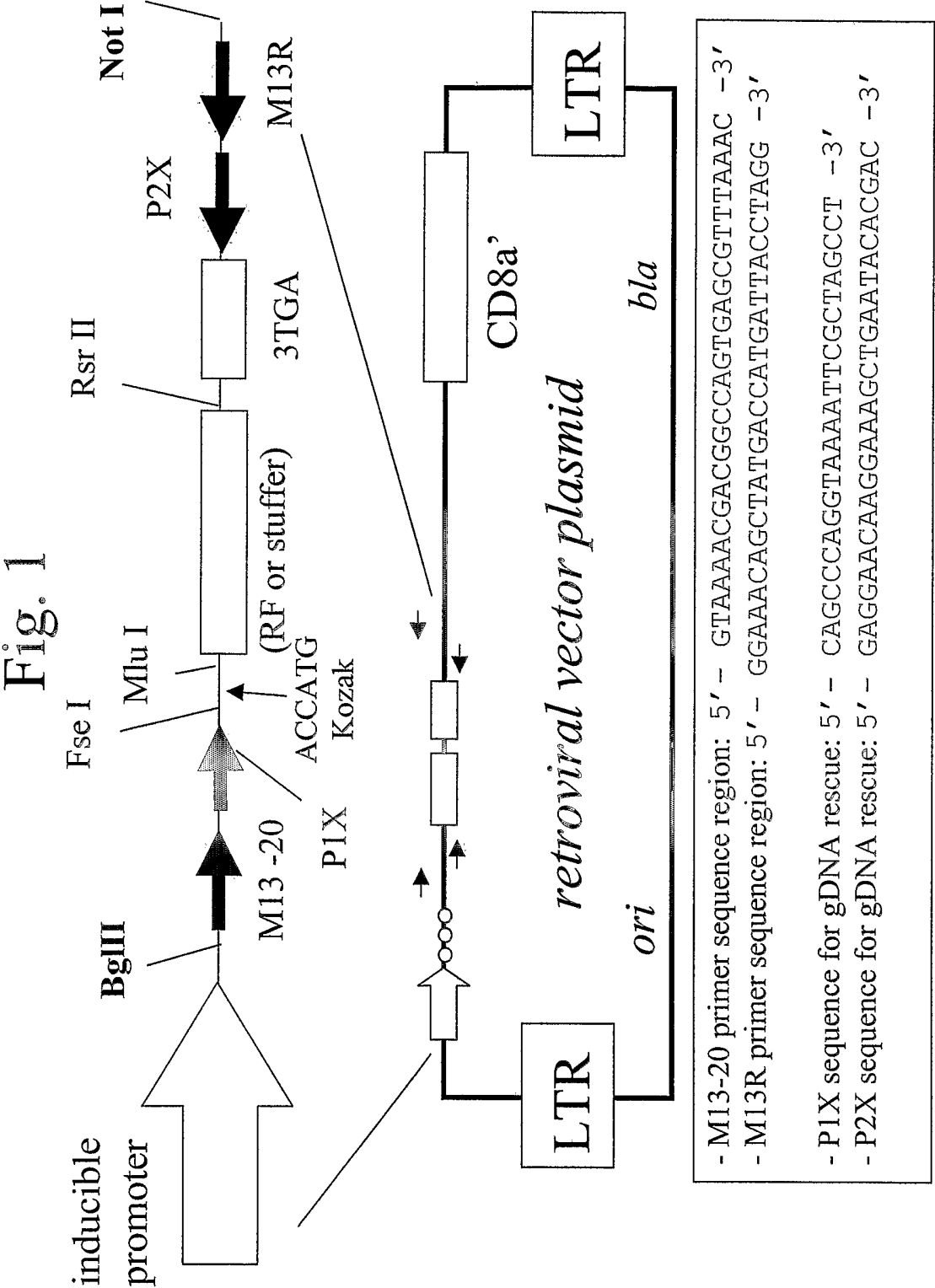
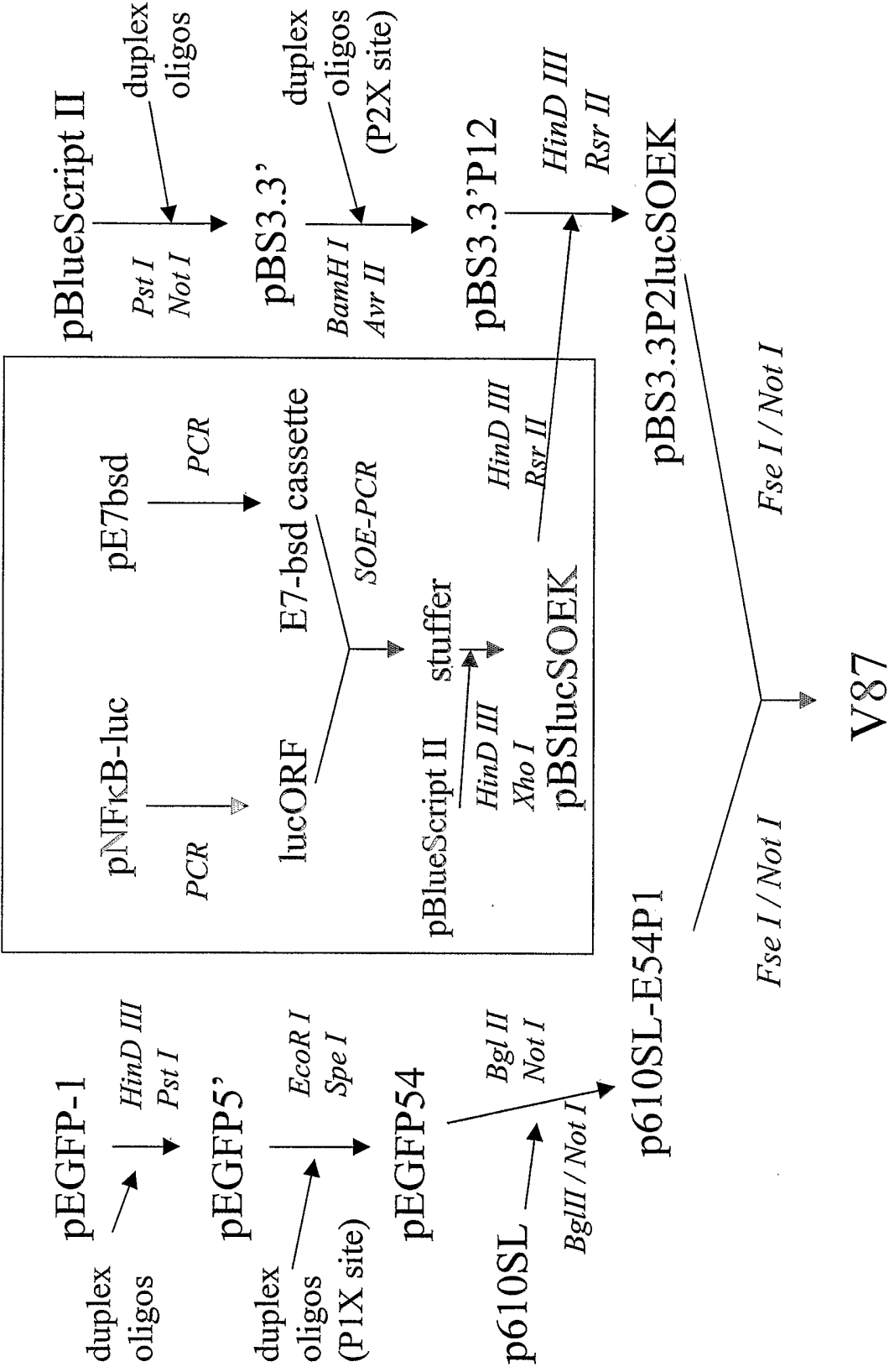
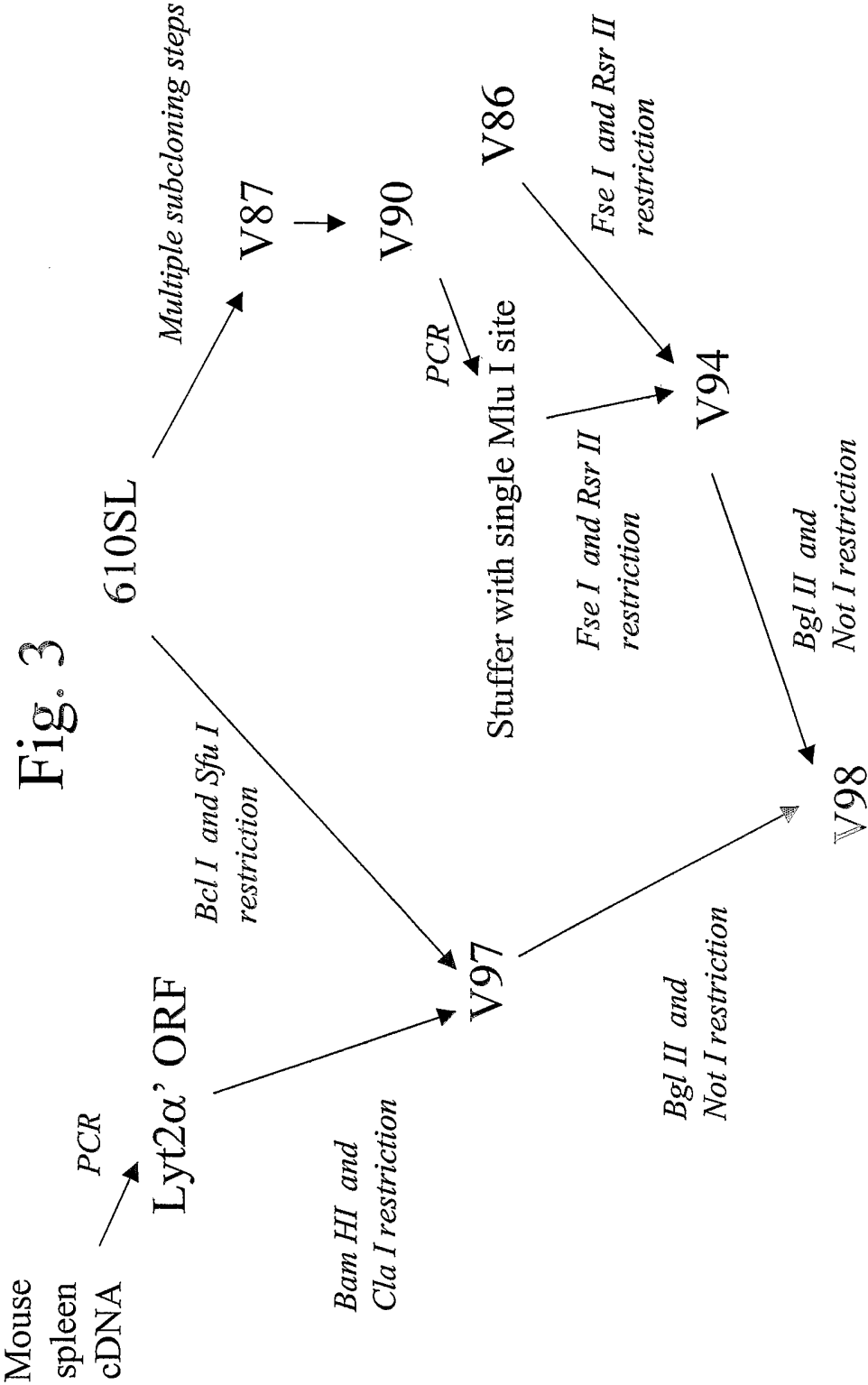


Fig. 2





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Axenovich, Sergey
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Gelman, Marina
Chui, Kitty
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 Leu Gln Thr Ala Gly₁₆₅ Thr Cys Gly Val Ser₁₇₀ Asp Asp Ser Leu Gly₁₇₅ Ser
 Leu Leu Gly Pro₁₈₀ Arg Thr Ala Ala Val₁₈₅ Phe Arg Pro Arg Pro₁₉₀ Gly Asp
 Ser Leu Pro₁₉₅ Ser Arg Glu Thr Arg₂₀₀ Tyr Val Glu Leu Tyr₂₀₅ Val Val Val
 Asp Asn₂₁₀ Ala Glu Phe Gln Met₂₁₅ Leu Gly Ser Glu Ala₂₂₀ Ala Val Arg His
 Arg₂₂₅ Val Leu Glu Val Val₂₃₀ Asn His Val Asp Lys₂₃₅ Leu Tyr Gln Lys Leu₂₄₀
 Asn Phe Arg Val Val₂₄₅ Leu Val Gly Leu Glu₂₅₀ Ile Trp Asn Ser Gln₂₅₅ Asp
 Arg Phe His Val₂₆₀ Ser Pro Asp Pro Ser₂₆₅ Val Thr Leu Glu Asn₂₇₀ Leu Leu
 Thr Trp Gln₂₇₅ Ala Arg Gln Arg Thr₂₈₀ Arg Arg His Leu His₂₈₅ Asp Asn Val
 Gln Leu₂₉₀ Ile Thr Gly Val Asp₂₉₅ Phe Thr Gly Thr Thr₃₀₀ Val Gly Phe Ala
 Arg₃₀₅ Val Ser Ala Met Cys₃₁₀ Ser His Ser Ser Gly₃₁₅ Ala Val Asn Gln Asp₃₂₀
 His Ser Lys Asn Pro₃₂₅ Val Gly Val Ala Cys₃₃₀ Thr Met Ala His Glu₃₃₅ Met
 Gly His Asn Leu₃₄₀ Gly Met Asp His Asp₃₄₅ Glu Asn Val Gln Gly₃₅₀ Cys Arg
 Cys Gln Glu₃₅₅ Arg Phe Glu Ala Gly₃₆₀ Arg Cys Ile Met Ala₃₆₅ Gly Ser Ile
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 Glu Arg Gly Glu Gln Cys Asp Cys Gly Pro Pro Glu Asp Cys Arg Asn
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 Arg Cys Cys Asn Ser Thr Thr Cys Gln Leu Ala Glu Gly Ala Gln Cys
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 Ala His Gly Thr Cys Cys Gln Glu Cys Lys Val Lys Pro Ala Gly Glu
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 Leu Cys Arg Pro Lys Lys Asp Met Cys Asp Leu Glu Glu Phe Cys Asp
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 Gly Arg His Pro Glu Cys Pro Glu Asp Ala Phe Gln Glu Asn Gly Thr
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 Pro Cys Ser Gly Gly Tyr Cys Tyr Asn Gly Ala Cys Pro Thr Leu Ala
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 Glu Asp Gly Thr Ala Tyr Glu Pro Val Pro Glu Gly Thr Arg Cys Gly
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 Pro Glu Lys Val Cys Trp Lys Gly Arg Cys Gln Asp Leu His Val Tyr
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 Ala Lys Leu Leu Thr Glu Val His Ala Ala Ser Gly Ser Leu Pro Val
 645 650 655
 Leu Val Val Val Val Leu Val Leu Leu Ala Val Val Leu Val Thr Leu
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 Asn Val Ala Pro Lys Thr Thr Met Gly Arg Ser Asn Pro Leu Phe His
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Pro Val Thr Val Ser Ser Pro Pro Phe Pro Val Pro Val Tyr Thr Arg
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Gln Ala Pro Lys Gln Val Ile Lys Pro Thr Phe Ala Pro Pro Val Pro
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Pro Val Lys Pro Gly Ala Gly Ala Ala Asn Pro Gly Pro Ala Glu Gly
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Val Leu Pro Val Leu Leu Leu Leu Val Trp Gly Leu Asp Pro Gly Thr
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Ala Val Gly Asp Ala Ala Ala Asp Val Glu Val Val Leu Pro Trp Arg
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Val Arg Pro Asp Asp Val His Leu Pro Pro Leu Pro Ala Ala Pro Gly
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Arg Pro Gly Glu Arg Ala Leu Leu Leu His Leu Pro Ala Phe Gly Arg
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Asp Leu Tyr Leu Gln Leu Arg Arg Asp Leu Arg Phe Leu Ser Arg Gly
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Phe Glu Val Glu Glu Ala Gly Ala Ala Arg Arg Arg Gly Arg Pro Ala
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Glu Leu Cys Phe Tyr Ser Gly Arg Val Leu Gly His Pro Gly Ser Leu
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gtt Val	cta Leu	aca Thr 205	gaa Glu	aag Lys	aag Lys	aag Lys	ccg Pro 210	acg Thr	tgg Trp	ggc Gly	agg Arg	cct Pro 215	tgc Ser	cgg Arg	gac Asp	677
tgg Trp	cgg Arg 220	gag Glu	cgg Arg	agg Arg	aac Asn	gct Ala 225	atc Ile	cgg Arg	ctc Leu	acc Thr	agc Ser 230	gag Glu	cac His	acg Thr	gtg Val	725
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gta Val	cgc Arg 460	ctc Leu	ccg Pro	cac His	aag Lys	ctg Leu 465	ccg Pro	ggc Gly	atg Met	cac His	tac Tyr 470	agt Ser	gcc Ala	aac Asn	gag Glu	1445
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 Pro Arg Thr Pro Pro Ala Ala Pro Arg Ala Arg Pro Gly Glu Arg Ala
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Gln Arg Pro Ala Lys Leu Ser Ile Gly His His Gly Glu Arg Ser Leu
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Glu Trp Ser Gln Cys Ser Ala Ser Cys Gly Lys Gly Val Trp Lys Arg
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 Thr Val Ala Cys Thr Asn Ser Gln Gly Lys Cys Asp Ala Ser Thr Arg
 945 950 955 960
 Pro Arg Ala Glu Glu Ala Cys Glu Asp Tyr Ser Gly Cys Tyr Glu Trp
 965 970 975
 Lys Thr Gly Asp Trp Ser Thr Cys Ser Ser Thr Cys Gly Lys Gly Leu
 980 985 990
 Gln Ser Arg Val Val Gln Cys Met His Lys Val Thr Gly Arg His Gly
 995 1000 1005
 Ser Glu Cys Pro Ala Leu Ser Lys Pro Ala Pro Tyr Arg Gln Cys
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 Tyr Gln Glu Val Cys Asn Asp Arg Ile Asn Ala Asn Thr Ile Thr
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 Ser Pro Arg Leu Ala Ala Leu Thr Tyr Lys Cys Thr Arg Asp Gln
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 Trp Thr Val Tyr Cys Arg Val Ile Arg Glu Lys Asn Leu Cys Gln
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 tagggccagt agcagacacc agccagt atg ccg agg aac cag ggc ttc tcc gag 174
 Met Pro Arg Asn Gln Gly Phe Ser Glu
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 ccc gaa tac tcg gcc gag tac tca gcc gag tac tcc gtc agc ctg ccc 222
 Pro Glu Tyr Ser Ala Glu Tyr Ser Ala Glu Tyr Ser Val Ser Leu Pro
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 tcc gac cct gac cgc ggg gtg ggc cgg acc cat gaa atc tcg gtc cgg 270
 Ser Asp Pro Asp Arg Gly Val Gly Arg Thr His Glu Ile Ser Val Arg
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 aac tcg ggc tcc tgc ctg tgc ctg cct cgc ttc atg cgg ctg act ttc 318
 Asn Ser Gly Ser Cys Leu Cys Leu Pro Arg Phe Met Arg Leu Thr Phe
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 gtg ccg gag tcc ttg gag aac ctc tac cag acc tac ttc aaa agg cag 366
 Val Pro Glu Ser Leu Glu Asn Leu Tyr Gln Thr Tyr Phe Lys Arg Gln
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 cgc cac gag acc ctg ctg gtg ctg gtg gtc ttt gca gcc ctc ttt gac 414

Arg	His	Glu	Thr	Leu	Leu	Val	Leu	Val	Val	Phe	Ala	Ala	Leu	Phe	Asp	
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tgc	tac	gtg	gtg	gtc	atg	tgt	gct	gtg	gtc	ttc	tcc	agc	gac	aag	ctg	462
Cys	Tyr	Val	Val	Val	Met	Cys	Ala	Val	Val	Phe	Ser	Ser	Asp	Lys	Leu	
90					95					100					105	
gct	ccc	ctc	gcc	gtg	gct	gga	att	gga	ctg	gtg	ttg	gac	atc	atc	ctc	510
Ala	Pro	Leu	Ala	Val	Ala	Gly	Ile	Gly	Leu	Val	Leu	Asp	Ile	Ile	Leu	
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ttc	gtg	ctc	tgc	aaa	aag	ggg	ctg	ctc	ccg	gac	cgg	gtc	acc	cgc	aga	558
Phe	Val	Leu	Cys	Lys	Lys	Gly	Leu	Leu	Pro	Asp	Arg	Val	Thr	Arg	Arg	
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gtg	ctg	ccc	tac	gtg	ctg	tgg	ctg	ctc	ata	acc	gcc	cag	atc	ttc	tcc	606
Val	Leu	Pro	Tyr	Val	Leu	Trp	Leu	Leu	Ile	Thr	Ala	Gln	Ile	Phe	Ser	
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Tyr	Leu	Gly	Leu	Asn	Phe	Ala	Arg	Ala	His	Ala	Ala	Ser	Asp	Thr	Val	
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ggc	tgg	cag	gtc	ttc	ttt	gtc	ttc	tcc	ttc	ttc	atc	acg	ctg	ccc	ctc	702
Gly	Trp	Gln	Val	Phe	Phe	Val	Phe	Ser	Phe	Phe	Ile	Thr	Leu	Pro	Leu	
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agc	ctc	agc	ccc	atc	gtg	atc	atc	tcc	gtg	gtc	tcc	tgt	gtg	gtg	cac	750
Ser	Leu	Ser	Pro	Ile	Val	Ile	Ile	Ser	Val	Val	Ser	Cys	Val	Val	His	
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acg	ttg	gtc	ctg	ggg	gtc	acc	gtg	gcc	cag	cag	cag	cag	gag	gag	ctc	798
Thr	Leu	Val	Leu	Gly	Val	Thr	Val	Ala	Gln	Gln	Gln	Gln	Glu	Glu	Leu	
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aag	ggg	atg	cag	ctg	ctg	cgg	gag	atc	ctg	gcc	aac	gtc	ttc	ctc	tac	846
Lys	Gly	Met	Gln	Leu	Leu	Arg	Glu	Ile	Leu	Ala	Asn	Val	Phe	Leu	Tyr	
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ctg	tgc	gcc	atc	gct	gtg	ggc	atc	atg	tcc	tac	tac	atg	gct	gac	cgc	894
Leu	Cys	Ala	Ile	Ala	Val	Gly	Ile	Met	Ser	Tyr	Tyr	Met	Ala	Asp	Arg	
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Lys	His	Arg	Lys	Ala	Phe	Leu	Glu	Ala	Arg	Gln	Ser	Leu	Glu	Val	Lys	
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atg	aac	ctg	gaa	gag	cag	agc	cag	cag	cag	gag	aac	ctc	atg	ctt	tcc	990
Met	Asn	Leu	Glu	Gln	Gln	Ser	Gln	Gln	Gln	Glu	Asn	Leu	Met	Leu	Ser	
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atc	ctg	ccc	aag	cac	gtg	gct	gac	gag	atg	ctg	aaa	gac	atg	aag	aaa	1038
Ile	Leu	Pro	Lys	His	Val	Ala	Asp	Glu	Met	Leu	Lys	Asp	Met	Lys	Lys	
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gac	gag	agc	cag	aag	gac	cag	cag	cag	ttc	aac	acc	atg	tac	atg	tac	1086
Asp	Glu	Ser	Gln	Lys	Asp	Gln	Gln	Gln	Phe	Asn	Thr	Met	Tyr	Met	Tyr	
		300				305						310				
cgt	cac	gag	aac	gtc	agc	atc	ctc	ttt	gcc	gac	atc	gtg	ggc	ttt	acc	1134
Arg	His	Glu	Asn	Val	Ser	Ile	Leu	Phe	Ala	Asp	Ile	Val	Gly	Phe	Thr	
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cag	ctg	tct	tct	gcc	tgc	agt	gcc	cag	gag	ctt	gtg	aag	ctg	ctc	aac	1182
Gln	Leu	Ser	Ser	Ala	Cys	Ser	Ala	Gln	Glu	Leu	Val	Lys	Leu	Leu	Asn	
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gag	ctc	ttt	gcc	cgc	ttt	gac	aag	ctg	gca	gct	aaa	tac	cac	cag	ctg	1230
Glu	Leu	Phe	Ala	Arg	Phe	Asp	Lys	Leu	Ala	Ala	Lys	Tyr	His	Gln	Leu	
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cgg	att	aag	atc	ctg	ggc	gac	tgc	tac	tac	tgc	atc	tgc	ggc	ttg	cct	1278
Arg	Ile	Lys	Ile	Leu	Gly	Asp	Cys	Tyr	Tyr	Cys	Ile	Cys	Gly	Leu	Pro	
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gac	tac	cgg	gag	gac	cac	gcc	gtc	tgc	tcc	atc	ctc	atg	ggg	ctg	gcc	1326
Asp	Tyr	Arg	Glu	Asp	His	Ala	Val	Cys	Ser	Ile	Leu	Met	Gly	Leu	Ala	
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atg	gtg	gag	gcc	atc	tcg	tat	gtg	cgg	gag	aag	acc	aag	act	ggg	gtg	1374

Met	Val	Glu	Ala	Ile	Ser	Tyr	Val	Arg	Glu	Lys	Thr	Lys	Thr	Gly	Val	
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ggc Gly	cag Gln	aag Lys	cgc Arg	tgg Trp 430	cag Gln	tac Tyr	gac Asp	gtg Val	tgg Trp 435	tcg Ser	act Thr	gat Asp	gtc Val	act Thr 440	gta Val	1470
gcc Ala	aac Asn	aag Lys	atg Met 445	gag Glu	gcc Ala	ggc Gly	ggc Gly	atc Ile 450	cct Pro	ggg Gly	cgc Arg	gtg Val	cac His 455	atc Ile	tcc Ser	1518
cag Gln	agc Ser	acc Thr 460	atg Met	gac Asp	tgc Cys	ctg Leu	aaa Lys 465	ggg Gly	gag Glu	ttt Phe	gat Asp	gtg Val 470	gag Glu	cca Pro	ggc Gly	1566
gat Asp	ggg Gly 475	ggc Gly	agc Ser	cgc Arg	tgt Cys	gat Asp 480	tac Tyr	cta Leu	gaa Glu	gag Glu	aag Lys 485	ggt Gly	att Ile	gaa Glu	acc Thr	1614
tac Tyr 490	ctc Leu	atc Ile	att Ile	gcc Ala	tcc Ser 495	aag Lys	cca Pro	gag Glu	gtg Val	aag Lys 500	aaa Lys	aca Thr	gcc Ala	acc Thr	cag Gln 505	1662
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ccc Pro	gag Glu	atg Met 620	gaa Glu	acc Thr	cgc Arg	tac Tyr	tcg Ser 625	gtg Val	gag Glu	aag Lys	gag Glu	aag Lys 630	cag Gln	agt Ser	ggg Gly	2046
gct Ala	gcc Ala 635	ttc Phe	agc Ser	tgc Cys	tcc Ser	tgc Cys 640	gtc Val	gtc Val	ctg Leu	ctc Leu	tgc Cys 645	acg Thr	gcc Ala	ctg Leu	gtc Val	2094
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gtg Val	ggg Gly	gag Glu	att Ile	ctg Leu 670	ctc Leu	ctc Leu	atc Ile	ctg Leu	acc Thr 675	atc Ile	tgc Cys	tcc Ser	ctg Leu	gct Ala 680	gcc Ala	2190
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ttc	atc	ctg	gtg	atg	gca	aat	gtc	gtg	gac	atg	ctc	agc	tgt	ctc	cag	2334

Phe ⁷¹⁵	Ile ⁷¹⁵	Leu	Val	Met	Ala	Asn ⁷²⁰	Val	Val	Asp	Met	Leu ⁷²⁵	Ser	Cys	Leu	Gln	
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cac His 810	gac Asp	tta Leu	cct Pro	atg Met	gtg Val 815	gcc Ala	tta Leu	gag Glu	cag Gln	atg Met 820	caa Gln	gga Gly	ttc Phe	aac Asn	cct Pro 825	2622
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gaa Glu	gac Asp	aag Lys	tcc Ser 1005	gag Glu	aga Arg	gag Glu	cgc Arg	tgg Trp 1010	cag Gln	cac His	ctg Leu	gct Ala	gac Asp 1015	ctg Leu		3195
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Leu Tyr Gln Thr Tyr Phe Lys Arg Gln Arg His Glu Thr Leu Leu Val
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 Ala Val Val Phe Ser Ser Asp Lys Leu Ala Pro Leu Ala Val Ala Gly
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 Ile Gly Leu Val Leu Asp Ile Ile Leu Phe Val Leu Cys Lys Lys Gly
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 Ala Gln Glu Leu Val Lys Leu Leu Asn Glu Leu Phe Ala Arg Phe Asp
 340 345 350
 Lys Leu Ala Ala Lys Tyr His Gln Leu Arg Ile Lys Ile Leu Gly Asp
 355 360 365
 Lys Tyr Tyr Cys Ile Cys Gly Leu Pro Asp Tyr Arg Glu Asp His Ala
 370 375 380

Val Cys Ser Ile Leu Met Gly Leu Ala Met Val Glu Ala Ile Ser Tyr
 385 390 395 400
 Val Arg Glu Lys Thr Lys Thr Gly Val Asp Met Arg Val Gly Val His
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 Thr Gly Thr Val Leu Gly Gly Val Leu Gly Gln Lys Arg Trp Gln Tyr
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 Asp Val Trp Ser Thr Asp Val Thr Val Ala Asn Lys Met Glu Ala Gly
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 Gly Ile Pro Gly Arg Val His Ile Ser Gln Ser Thr Met Asp Cys Leu
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 Lys Gly Glu Phe Asp Val Glu Pro Gly Asp Gly Gly Ser Arg Cys Asp
 465 470 475 480
 Tyr Leu Glu Glu Lys Gly Ile Glu Thr Tyr Leu Ile Ile Ala Ser Lys
 485 490 495
 Pro Glu Val Lys Lys Thr Ala Thr Gln Asn Gly Leu Asn Gly Ser Ala
 500 505 510
 Leu Pro Asn Gly Ala Pro Ala Ser Ser Lys Ser Ser Ser Pro Ala Leu
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 Ile Glu Thr Lys Glu Pro Asn Gly Ser Ala His Ser Ser Gly Ser Thr
 530 535 540
 Ser Glu Lys Pro Glu Glu Gln Asp Ala Gln Ala Asp Asn Pro Ser Phe
 545 550 555 560
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 Lys Pro Ile Glu Ser Ser Cys Met Tyr Gly Thr Cys Cys Leu Trp Gly
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Asp Glu Val Ile Lys Glu Val Gln Glu Phe Tyr Lys Asp Thr Tyr Asn
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Lys Leu Lys Thr Lys Asp Glu Pro Gln Arg Glu Thr Leu Lys Ala Ile
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Met Ile Phe Ser Met Ile Leu Cys Cys Ala Ile Arg Arg Asn Arg Glu
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Gly Ala Gly Ala Leu Met Met Leu Val Gly Phe Leu Gly Cys Cys Gly
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Ala Val Gln Glu Ser Gln Cys Met Leu Gly Leu Phe Phe Gly Phe Leu
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His Lys Asp Glu Val Ile Lys Glu Val Gln Glu Phe Tyr Lys Asp Thr
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Tyr Asn Lys Leu Lys Thr Lys Asp Glu Pro Gln Arg Glu Thr Leu Lys
 130 135 140

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

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 Lys Arg Arg Thr Glu Thr Val Gln Lys Leu Cys Pro Gly Gly Gln Leu
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 Lys Phe Ser Ala Tyr Ile Lys Asn Ser Asn Pro Ala Leu Asn Asp Asn
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 Thr Ser Pro Leu Pro Glu Glu Val Asp Glu Thr Ser Ala Glu Asp Glu
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 Gly Val Ser Gln Arg Lys Phe Leu Asp Gly Asn Glu Leu Thr Leu Ala
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 Asp Cys Asn Leu Leu Pro Lys Leu His Ile Val Gln Val Val Cys Lys
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 Lys Tyr Arg Gly Phe Thr Ile Pro Glu Ala Phe Arg Gly Val His Arg
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 Gly Ile Leu Gly Ala Ile Gln Ala Gln Gln Gln Glu Val Ile Ser Pro
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 Asp Thr Thr Glu Arg Asn Asn Asn Cys Pro Glu Lys Thr Asp Cys Pro
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 Ala Ser Thr Pro His Glu Leu Tyr Arg Asn Asp Tyr Ala Thr Met Leu
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 Pro Asp Ser Thr Glu Ile Asn Gln Asp Thr Ile Asn Arg Ile Ile Lys
 225 230 235

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gaa Glu	atc Ile	cct Pro 255	ggg Gly	ccc Pro	tct Ser	ggg Gly	ccc Pro 260	aag Lys	ggc Gly	tac Tyr	cgt Arg	gga Gly 265	cag Gln	aag Lys	ggt Gly	877
gcc Ala	aag Lys 270	ggc Gly	aac Asn	atg Met	ggt Gly	gag Glu 275	ccg Pro	gga Gly	gag Glu	cct Pro	ggc Gly 280	cag Gln	aag Lys	gga Gly	aga Arg	925
cag Gln 285	gga Gly	gac Asp	ccg Pro	ggc Gly	atc Ile 290	gaa Glu	ggc Gly	ccc Pro	att Ile	gga Gly 295	ttc Phe	cca Pro	gga Gly	ccc Pro	aag Lys 300	973
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Phe Val Leu Asp Thr Ser Glu Ser Val Thr Met Gln Ser Pro Thr Asp
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Ile Leu Leu Phe His Met Lys Gln Phe Val Pro Gln Phe Ile Ser Gln
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Gly Gly Leu His Phe Ser Asp Gln Val Glu Val Phe Ser Pro Pro Gly
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Arg Arg Gly Thr Phe Thr Asp Cys Ala Leu Ala Asn Met Thr Glu Gln
130    135    140
Ile Arg Gln Asp Arg Ser Lys Gly Thr Val His Phe Ala Val Val Ile
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Thr Asp Gly His Val Thr Gly Ser Pro Cys Gly Gly Ile Lys Leu Gln
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Ala Glu Arg Ala Arg Glu Glu Gly Ile Arg Leu Phe Ala Val Ala Pro
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Asn Gln Asn Leu Lys Glu Gln Gly Leu Arg Asp Ile Ala Ser Thr Pro
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His Glu Leu Tyr Arg Asn Asp Tyr Ala Thr Met Leu Pro Asp Ser Thr
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 Pro Ser Gly Pro Lys Gly Tyr Arg Gly Gln Lys Gly Ala Lys Gly Asn
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 Pro Arg Asp Asp Asp Leu Asn Leu Arg Ala Leu Cys Asp Arg Asp Val
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Arg Cys Phe Pro Ala Ile His Ala Tyr Lys Gly Val Leu Met Val Gly
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Gln Leu Ala Met Arg Ile Phe Glu Asp Tyr Thr Val Ser Trp Tyr Trp
                        220      225      230
att atc ata ggc ctg gtc att gcc atg gcg atg agc ctc ctg ttc atc      831
Ile Ile Ile Gly Leu Val Ile Ala Met Ala Met Ser Leu Leu Phe Ile
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Ile Leu Leu Arg Phe Leu Ala Gly Ile Met Val Trp Val Met Ile Ile
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atg gtg att ctg gtg ctg ggc tac gga ata ttt cac tgc tac atg gag      927
Met Val Ile Leu Val Leu Gly Tyr Gly Ile Phe His Cys Tyr Met Glu
                        270      275      280
tac tcc cga ctg cgt ggt gag gcc ggc tct gat gtc tct ttg gtg gac      975
Tyr Ser Arg Leu Arg Gly Glu Ala Gly Ser Asp Val Ser Leu Val Asp
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tgg Trp 315	ttg Leu	gcc Ala	ttt Phe	atg Met	atc Ile 320	att Ile	ctg Leu	agt Ser	atc Ile	ctt Leu 325	gaa Glu	gtc Val	att Ile	atc Ile	atc Ile 330	1071
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atc Ile	aaa Lys	gaa Glu	gcc Ala 350	agc Ser	agg Arg	gct Ala	gtg Val	gga Gly 355	tac Tyr	gtc Val	atg Met	tgc Cys	tcc Ser 360	ttg Leu	ctc Leu	1167
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gcc Ala	agc Ser 380	act Thr	gct Ala	gtc Val	ttc Phe	ctg Leu 385	tcc Ser	act Thr	tcc Ser	aac Asn	gaa Glu 390	gcg Ala	gtc Val	tat Tyr	aag Lys	1263
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635 640 645 650

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gag agg cct tac ttc atg tct tcc acc ctg aag aaa ccc ttg aac aag 2175
Glu Arg Pro Tyr Phe Met Ser Ser Thr Leu Lys Lys Pro Leu Asn Lys
685 690 695

acc aac aag aag gca gcg gag tcc tga agggcccggtg ctccccacct 2222
Thr Asn Lys Lys Ala Ala Glu Ser 700 705

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 Ala Val Gly Ile Ile Ala Trp Thr His Gly Asp Pro Arg Lys Val Ile
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 Ser Pro Leu Val Leu Leu Glu Phe Gln Cys Pro Thr Pro Gln Ile Cys
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 Val Glu Lys Cys Pro Asp Arg Tyr Leu Thr Tyr Leu Asn Ala Arg Ser
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 Ser Arg Asp Phe Glu Tyr Tyr Lys Gln Phe Cys Val Pro Gly Phe Lys
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 Gly Tyr Gly Ile Phe His Cys Tyr Met Glu Tyr Ser Arg Leu Arg Gly
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 Glu Ala Gly Ser Asp Val Ser Leu Val Asp Leu Gly Phe Gln Thr Asp
 290 295 300
 Phe Arg Val Tyr Leu His Leu Arg Gln Thr Trp Leu Ala Phe Met Ile
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 Ile Leu Ser Ile Leu Glu Val Ile Ile Ile Leu Leu Leu Ile Phe Leu
 325 330 335
 Arg Lys Arg Ile Leu Ile Ala Ile Ala Leu Ile Lys Glu Ala Ser Arg
 340 345 350

Ala Val Gly Tyr Val Met Cys Ser Leu Leu Tyr Pro Leu Val Thr Phe
 355 360 365
 Phe Leu Leu Cys Leu Cys Ile Ala Tyr Trp Ala Ser Thr Ala Val Phe
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 Leu Ser Thr Ser Asn Glu Ala Val Tyr Lys Ile Phe Asp Asp Ser Pro
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 Cys Pro Phe Thr Ala Lys Thr Cys Asn Pro Glu Thr Phe Pro Ser Ser
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 420 425 430
 Gly Gly Glu Ser Gly Tyr His Arg Ala Leu Leu Gly Leu Gln Ile Phe
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 Asn Ala Phe Met Phe Phe Trp Leu Ala Asn Phe Val Leu Ala Leu Gly
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 Lys Pro Asp Asp Leu Pro Ala Phe Pro Leu Phe Ser Ala Phe Gly Arg
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 Lys Cys Cys Phe Trp Cys Leu Glu Lys Phe Ile Lys Phe Leu Asn Arg
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 Val Leu Asp Lys Val Thr Asp Phe Leu Phe Leu Leu Gly Lys Leu Leu
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 Pro Ile Leu Thr Val Ile Val Gly Ser Tyr Leu Ile Ala His Gly Phe
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Gly Met Ser Thr Tyr Lys Arg Ala Thr Leu Asp Glu Glu Asp Leu Val
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Phe His Ser Pro Arg Ser Gly Gln Arg Cys Trp Ala Ala Arg Thr Gln
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Val Ala Cys Leu Ala Ala Leu Gly Ile Gln Tyr Gln Thr Arg Ser Pro
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Ser Val Cys Leu Ser Glu Ala Cys Val Ser Val Thr Ser Ser Ile Leu
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agc tcc atg gac ccc aca gtg gac ccc tgc cat gac ttc ttc agc tac 384
Ser Ser Met Asp Pro Thr Val Asp Pro Cys His Asp Phe Phe Ser Tyr
115 120 125
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Ala Cys Gly Gly Trp Ile Lys Ala Asn Pro Val Pro Asp Gly His Ser
130 135 140
cgc tgg ggg acc ttc agc aac ctc tgg gaa cac aac caa gca atc atc 480
Arg Trp Gly Thr Phe Ser Asn Leu Trp Glu His Asn Gln Ala Ile Ile
145 150 155 160
aag cac ctc ctc gaa aac tcc acg gcc agc gtg agc gag gca gag aga 528
Lys His Leu Leu Glu Asn Ser Thr Ala Ser Val Ser Glu Ala Glu Arg
165 170 175
aag gcg caa gta tac tac cgt gcg tgc atg aac gag acc agg atc gag 576
Lys Ala Gln Val Tyr Tyr Arg Ala Cys Met Asn Glu Thr Arg Ile Glu
180 185 190
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Glu Leu Arg Ala Lys Pro Leu Met Glu Leu Ile Glu Arg Leu Gly Gly
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tgg aac atc aca ggt ccc tgg gcc aag gac aac ttc cag gac acc ctg 672
Trp Asn Ile Thr Gly Pro Trp Ala Lys Asp Asn Phe Gln Asp Thr Leu
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Gln 225	Val	Val	Thr	Ala	His 230	Tyr	Arg	Thr	Ser	Pro 235	Phe	Phe	Ser	Val	Tyr 240	
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Phe₅₀ His Ser Pro Arg Ser Gly₅₅ Gln Arg Cys Trp Ala₆₀ Ala Arg Thr Gln
 Val₆₅ Glu Lys Arg Leu Val₇₀ Val Leu Val Val₇₅ Leu Leu Ala Ala Gly Leu₈₀
 Val Ala Cys Leu₈₅ Ala Ala Leu Gly Ile₉₀ Gln Tyr Gln Thr Arg Ser₉₅ Pro
 Ser Val Cys₁₀₀ Leu Ser Glu Ala Cys₁₀₅ Val Ser Val Thr Ser₁₁₀ Ser Ile Leu
 Ser Ser Met₁₁₅ Asp Pro Thr Val₁₂₀ Asp Pro Cys His Asp₁₂₅ Phe Phe Ser Tyr
 Ala Cys₁₃₀ Gly Gly Trp Ile₁₃₅ Ala Asn Pro Val₁₄₀ Pro Asp Gly His Ser
 Arg₁₄₅ Trp Gly Thr Phe₁₅₀ Asn Leu Trp Glu₁₅₅ Asn Gln Ala Ile₁₆₀ Ile
 Lys His Leu Leu₁₆₅ Glu Asn Ser Thr Ala₁₇₀ Ser Val Ser Glu Ala₁₇₅ Glu Arg
 Lys Ala Gln₁₈₀ Val Tyr Tyr Arg Ala₁₈₅ Cys Met Asn Glu Thr₁₉₀ Arg Ile Glu
 Glu Leu Arg₁₉₅ Ala Lys Pro Leu₂₀₀ Met Glu Leu Ile Glu₂₀₅ Arg Leu Gly Gly
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 Gln₃₀₅ Gln Ile Leu Asp Phe₃₁₀ Glu Thr Ala Leu₃₁₅ Ala Asn Ile Thr Ile₃₂₀ Pro
 Gln Glu Lys Arg₃₂₅ Arg Asp Glu Glu Leu₃₃₀ Ile Tyr His Lys Val₃₃₅ Thr Ala
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 Asn Thr₃₅₅ Ile Phe Tyr Pro Val₃₆₀ Glu Ile Asn Glu Ser₃₆₅ Glu Pro Ile Val

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 Gln Thr Glu Cys Met⁶⁴⁵ Val Glu Gln Tyr Ser⁶⁵⁰ Asn Tyr Ser Val Asn⁶⁵⁵ Gly
 Glu Pro Val Asn⁶⁶⁰ Gly Arg His Thr Leu⁶⁶⁵ Gly Glu Asn Ile Ala⁶⁷⁰ Asp Asn
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 aatggaggca gaagagccca ggacccaagc gtcttggcag ggggtgctgtg aatgtccagt 2346
 ggtccagct cccaccctg gccctgcccc agcctgtgta gctcttcctg catgtggatg 2406
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 aataaagaac tcttaatgcc cg 2488

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 <213> Homo sapiens

<400> 32

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

Gly Ile Glu Ile Leu Ser Phe Thr Ile Lys Asp Val Tyr Asp Lys Val
 100 105 110
 Asp Tyr Leu Ser Ser Leu Gly Lys Thr Gln Thr Ala Val Val Gln Arg
 115 120 125
 Asp Ala Asp Ile Gly Val Ala Glu Ala Glu Arg Asp Ala Gly Ile Arg
 130 135 140
 Glu Ala Glu Cys Lys Lys Glu Met Leu Asp Val Lys Phe Met Ala Asp
 145 150 155 160
 Thr Lys Ile Ala Asp Ser Lys Arg Ala Phe Glu Leu Gln Lys Ser Ala
 165 170 175
 Phe Ser Glu Glu Val Asn Ile Lys Thr Ala Glu Ala Gln Leu Ala Tyr
 180 185 190
 Glu Leu Gln Gly Ala Arg Glu Gln Gln Lys Ile Arg Gln Glu Glu Ile
 195 200 205
 Glu Ile Glu Val Val Gln Arg Lys Lys Gln Ile Ala Val Glu Ala Gln
 210 215 220
 Glu Ile Leu Arg Thr Asp Lys Glu Leu Ile Ala Thr Val Arg Arg Pro
 225 230 235 240
 Ala Glu Ala Glu Ala His Arg Ile Gln Gln Ile Ala Glu Gly Glu Lys
 245 250 255
 Val Lys Gln Val Leu Leu Ala Gln Ala Glu Ala Glu Lys Ile Arg Lys
 260 265 270
 Ile Gly Glu Ala Glu Ala Ala Val Ile Glu Ala Met Gly Lys Ala Glu
 275 280 285
 Ala Glu Arg Met Lys Leu Lys Ala Glu Ala Tyr Gln Lys Tyr Gly Asp
 290 295 300
 Ala Ala Lys Met Ala Leu Val Leu Glu Ala Leu Pro Gln Ile Ala Ala
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 Lys Ile Ala Ala Pro Leu Thr Lys Val Asp Glu Ile Val Val Leu Ser
 325 330 335
 Gly Asp Asn Ser Lys Val Thr Ser Glu Val Asn Arg Leu Leu Ala Glu
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 <213> Homo sapiens

<220>
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 <222> (7)..(1650)

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tgg Trp 15	act Thr	ctg Leu	ctg Leu	gtc Val	tgc Cys 20	tgt Cys	ctg Leu	ctg Leu	acc Thr	cca Pro 25	ggg Gly	gtc Val	cag Gln	ggg Gly	cag Gln 30	96
gag Glu	ttc Phe	ctt Leu	ttg Leu	cgg Arg 35	gtg Val	gag Glu	ccc Pro	cag Gln	aac Asn 40	cct Pro	gtg Val	ctc Leu	tct Ser	gct Ala 45	gga Gly	144
ggg Gly	tcc Ser	ctg Leu	ttt Phe 50	gtg Val	aac Asn	tgc Cys	agt Ser	act Thr 55	gat Asp	tgt Cys	ccc Pro	agc Ser	tct Ser 60	gag Glu	aaa Lys	192
atc Ile	gcc Ala	ttg Leu 65	gag Glu	acg Thr	tcc Ser	cta Leu	tca Ser 70	aag Lys	gag Glu	ctg Leu	gtg Val	gcc Ala 75	agt Ser	ggc Gly	atg Met	240
ggc Gly	tgg Trp 80	gca Ala	gcc Ala	ttc Phe	aat Asn	ctc Leu 85	agc Ser	aac Asn	gtg Val	act Thr	ggc Gly 90	aac Asn	agt Ser	cgg Arg	atc Ile	288
ctc Leu 95	tgc Cys	tca Ser	gtg Val	tac Tyr	tgc Cys 100	aat Asn	ggc Gly	tcc Ser	cag Gln	ata Ile 105	aca Thr	ggc Gly	tcc Ser	tct Ser	aac Asn 110	336
atc Ile	acc Thr	gtg Val	tac Tyr	agg Arg 115	ctc Leu	ccg Pro	gag Glu	cgt Arg	gtg Val 120	gag Glu	ctg Leu	gca Ala	ccc Pro	ctg Leu 125	cct Pro	384
cct Pro	tgg Trp	cag Gln	ccg Pro 130	gtg Val	ggc Gly	cag Gln	aac Asn	ttc Phe 135	acc Thr	ctg Leu	cgc Arg	tgc Cys	caa Gln 140	gtg Val	gag Glu	432
gat Asp	ggg Gly	tcg Ser 145	ccc Pro	cgg Arg	acc Thr	agc Ser	ctc Leu 150	acg Thr	gtg Val	gtg Val	ctg Leu	ctt Leu 155	cgc Arg	tgg Trp	gag Glu	480
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gcc Ala 175	act Thr	gtg Val	ctg Leu	gcc Ala	agc Ser 180	aga Arg	gac Asp	gac Asp	cac His	gga Gly 185	gcc Ala	cct Pro	ttc Phe	tca Ser	tgc Cys 190	576
cgc Arg	aca Thr	gaa Glu	ctg Leu	gac Asp 195	atg Met	cag Gln	ccc Pro	cag Gln	ggg Gly 200	ctg Leu	gga Gly	ctg Leu	ttc Phe	gtg Val 205	aac Asn	624
acc Thr	tca Ser	gcc Ala	ccc Pro 210	cgc Arg	cag Gln	ctc Leu	cga Arg	acc Thr 215	ttt Phe	gtc Val	ctg Leu	ccc Pro	gtg Val 220	acc Thr	ccc Pro	672
ccg Pro	cgc Arg	ctc Leu 225	gtg Val	gcc Ala	ccc Pro	cgg Arg	ttc Phe 230	ttg Leu	gag Glu	gtg Val	gaa Glu	acg Thr 235	tcg Ser	tgg Trp	ccg Pro	720
gtg Val	gac Asp 240	tgc Cys	acc Thr	cta Leu	gac Asp	ggg Gly 245	ctt Leu	ttt Phe	cca Pro	gcc Ala	tca Ser 250	gag Glu	gcc Ala	cag Gln	gtc Val	768
tac Tyr 255	ctg Leu	gcg Ala	ctg Leu	ggg Gly	gac Asp 260	cag Gln	atg Met	ctg Leu	aat Asn	gcg Ala 265	aca Thr	gtc Val	atg Met	aac Asn	cac His 270	816
ggg Gly	gac Asp	acg Thr	cta Leu	acg Thr 275	gcc Ala	aca Thr	gcc Ala	aca Thr	gcc Ala 280	acg Thr	gcg Ala	cgc Arg	gcg Ala	gat Asp 285	cag Gln	864
gag Glu	ggg Gly	gcc Ala	cgg Arg 290	gag Glu	atc Ile	gtc Val	tgc Cys	aac Asn 295	gtg Val	acc Thr	cta Leu	ggg Gly	ggc Gly 300	gag Glu	aga Arg	912
cgg	gag	gcc	cgg	gag	aac	ttg	acg	gtc	ttt	agc	ttc	cta	gga	ccc	att	960

Arg	Glu	Ala	Arg	Glu	Asn	Leu	Thr	Val	Phe	Ser	Phe	Leu	Gly	Pro	Ile	
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gtg	aac	ctc	agc	gag	ccc	acc	gcc	cat	gag	ggg	tcc	aca	gtg	acc	gtg	1008
Val	Asn	Leu	Ser	Glu	Pro	Thr	Ala	His	Glu	Gly	Ser	Thr	Val	Thr	Val	
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agt	tgc	atg	gct	ggg	gct	cga	gtc	cag	gtc	acg	ctg	gac	gga	gtt	ccg	1056
Ser	Cys	Met	Ala	Gly	Ala	Arg	Val	Gln	Val	Thr	Leu	Asp	Gly	Val	Pro	
		335			340					345					350	
gcc	gcg	gcc	ccg	ggg	cag	cca	gct	caa	ctt	cag	cta	aat	gct	acc	gag	1104
Ala	Ala	Ala	Pro	Gly	Gln	Pro	Ala	Gln	Leu	Gln	Leu	Asn	Ala	Thr	Glu	
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agt	gac	gac	gga	cgc	agc	ttc	ttc	tgc	agt	gcc	act	ctc	gag	gtg	gac	1152
Ser	Asp	Asp	Gly	Arg	Ser	Phe	Phe	Cys	Ser	Ala	Thr	Leu	Glu	Val	Asp	
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ggc	gag	ttc	ttg	cac	agg	aac	agt	agc	gtc	cag	ctg	cga	gtc	ctg	tat	1200
Gly	Glu	Phe	Leu	His	Arg	Asn	Ser	Ser	Val	Gln	Leu	Arg	Val	Leu	Tyr	
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ggt	ccc	aaa	att	gac	cga	gcc	aca	tgc	ccc	cag	cac	ttg	aaa	tgg	aaa	1248
Gly	Pro	Lys	Ile	Asp	Arg	Ala	Thr	Cys	Pro	Gln	His	Leu	Lys	Trp	Lys	
	400					405					410					
gat	aaa	acg	aga	cac	gtc	ctg	cag	tgc	caa	gcc	agg	ggc	aac	ccg	tac	1296
Asp	Lys	Thr	Arg	His	Val	Leu	Gln	Cys	Gln	Ala	Arg	Gly	Asn	Pro	Tyr	
					420					425					430	
ccc	gag	ctg	cgg	tgt	ttg	aag	gaa	ggc	tcc	agc	cgg	gag	gtg	ccg	gtg	1344
Pro	Glu	Leu	Arg	Cys	Leu	Lys	Glu	Gly	Ser	Ser	Arg	Glu	Val	Pro	Val	
				435					440					445		
ggg	atc	ccg	ttc	ttc	gtc	aac	gta	aca	cat	aat	ggt	act	tat	cag	tgc	1392
Gly	Ile	Pro	Phe	Phe	Val	Asn	Val	Thr	His	Asn	Gly	Thr	Tyr	Gln	Cys	
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caa	gcg	tcc	agc	tca	cga	ggc	aaa	tac	acc	ctg	gtc	gtg	gtg	atg	gac	1440
Gln	Ala	Ser	Ser	Ser	Arg	Gly	Lys	Tyr	Thr	Leu	Val	Val	Val	Met	Asp	
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att	gag	gct	ggg	agc	tcc	cac	ttt	gtc	ccc	gtc	ttc	gtg	gcg	gtg	tta	1488
Ile	Glu	Ala	Gly	Ser	Ser	His	Phe	Val	Pro	Val	Phe	Val	Ala	Val	Leu	
	480					485					490					
ctg	acc	ctg	ggc	gtg	gtg	act	atc	gta	ctg	gcc	tta	atg	tac	gtc	ttc	1536
Leu	Thr	Leu	Gly	Val	Val	Thr	Ile	Val	Leu	Ala	Leu	Met	Tyr	Val	Phe	
				500						505					510	
agg	gag	cac	caa	cgg	agc	ggc	agt	tac	cat	gtt	agg	gag	gag	agc	acc	1584
Arg	Glu	His	Gln	Arg	Ser	Gly	Ser	Tyr	His	Val	Arg	Glu	Glu	Ser	Thr	
				515					520					525		
tat	ctg	ccc	ctc	acg	tct	atg	cag	ccg	aca	gaa	gca	atg	ggg	gaa	gaa	1632
Tyr	Leu	Pro	Leu	Thr	Ser	Met	Gln	Pro	Thr	Glu	Ala	Met	Gly	Glu	Glu	
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ccg	tcc	aga	gct	gag	tga	cgctggg	atc	cgggatcaaa	g	g	g	g	g	g	g	1680
Pro	Ser	Arg	Ala	Glu												
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<400> 34

Met Ala Thr Met Val Pro Ser Val Leu Trp Pro Arg Ala Cys Trp Thr
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Leu	Leu	Arg ₃₅	Val	Glu	Pro	Gln	Asn ₄₀	Pro	Val	Leu	Ser	Ala ₄₅	Gly	Gly	Ser				
Leu	Phe ₅₀	Val	Asn	Cys	Ser	Thr ₅₅	Asp	Cys	Pro	Ser	Ser ₆₀	Glu	Lys	Ile	Ala				
Leu	Glu	Thr	Ser	Leu	Ser ₇₀	Lys	Glu	Leu	Val	Ala ₇₅	Ser	Gly	Met	Gly	Trp ₈₀				
Ala	Ala	Phe	Asn	Leu ₈₅	Ser	Asn	Val	Thr	Gly ₉₀	Asn	Ser	Arg	Ile	Leu ₉₅	Cys				
Ser	Val	Tyr	Cys ₁₀₀	Asn	Gly	Ser	Gln	Ile ₁₀₅	Thr	Gly	Ser	Ser	Asn ₁₁₀	Ile	Thr				
Val	Tyr	Arg ₁₁₅	Leu	Pro	Glu	Arg	Val ₁₂₀	Glu	Leu	Ala	Pro	Leu ₁₂₅	Pro	Pro	Trp				
Gln	Pro ₁₃₀	Val	Gly	Gln	Asn	Phe ₁₃₅	Thr	Leu	Arg	Cys	Gln ₁₄₀	Val	Glu	Asp	Gly				
Ser ₁₄₅	Pro	Arg	Thr	Ser	Leu ₁₅₀	Thr	Val	Val	Leu	Leu ₁₅₅	Arg	Trp	Glu	Glu	Glu ₁₆₀				
Leu	Ser	Arg	Gln	Pro ₁₆₅	Ala	Val	Glu	Glu	Pro ₁₇₀	Ala	Glu	Val	Thr	Ala ₁₇₅	Thr				
Val	Leu	Ala	Ser ₁₈₀	Arg	Asp	Asp	His	Gly ₁₈₅	Ala	Pro	Phe	Ser	Cys ₁₉₀	Arg	Thr				
Glu	Leu	Asp ₁₉₅	Met	Gln	Pro	Gln	Gly ₂₀₀	Leu	Gly	Leu	Phe	Val ₂₀₅	Asn	Thr	Ser				
Ala	Pro ₂₁₀	Arg	Gln	Leu	Arg	Thr ₂₁₅	Phe	Val	Leu	Pro	Val ₂₂₀	Thr	Pro	Pro	Arg				
Leu ₂₂₅	Val	Ala	Pro	Arg	Phe ₂₃₀	Leu	Glu	Val	Glu	Thr ₂₃₅	Ser	Trp	Pro	Val	Asp ₂₄₀				
Cys	Thr	Leu	Asp	Gly ₂₄₅	Leu	Phe	Pro	Ala	Ser ₂₅₀	Glu	Ala	Gln	Val	Tyr ₂₅₅	Leu				
Ala	Leu	Gly	Asp ₂₆₀	Gln	Met	Leu	Asn	Ala ₂₆₅	Thr	Val	Met	Asn	His ₂₇₀	Gly	Asp				
Thr	Leu	Thr ₂₇₅	Ala	Thr	Ala	Thr	Ala ₂₈₀	Thr	Ala	Arg	Ala	Asp ₂₈₅	Gln	Glu	Gly				
Ala	Arg ₂₉₀	Glu	Ile	Val	Cys	Asn ₂₉₅	Val	Thr	Leu	Gly	Gly ₃₀₀	Glu	Arg	Arg	Glu				
Ala ₃₀₅	Arg	Glu	Asn	Leu	Thr ₃₁₀	Val	Phe	Ser	Phe	Leu ₃₁₅	Gly	Pro	Ile	Val	Asn ₃₂₀				
Leu	Ser	Glu	Pro	Thr ₃₂₅	Ala	His	Glu	Gly	Ser ₃₃₀	Thr	Val	Thr	Val	Ser ₃₃₅	Cys				
Met	Ala	Gly	Ala	Arg	Val	Gln	Val	Thr	Leu	Asp	Gly	Val	Pro	Ala	Ala				

340 345 350

Ala Pro Gly Gln Pro Ala Gln Leu Gln Leu Asn Ala Thr Glu Ser Asp
 355 360 365

Asp Gly Arg Ser Phe Phe Cys Ser Ala Thr Leu Glu Val Asp Gly Glu
 370 375 380

Phe Leu His Arg Asn Ser Ser Val Gln Leu Arg Val Leu Tyr Gly Pro
 385 390 395 400

Lys Ile Asp Arg Ala Thr Cys Pro Gln His Leu Lys Trp Lys Asp Lys
 405 410 415

Thr Arg His Val Leu Gln Cys Gln Ala Arg Gly Asn Pro Tyr Pro Glu
 420 425 430

Leu Arg Cys Leu Lys Glu Gly Ser Ser Arg Glu Val Pro Val Gly Ile
 435 440 445

Pro Phe Phe Val Asn Val Thr His Asn Gly Thr Tyr Gln Cys Gln Ala
 450 455 460

Ser Ser Ser Arg Gly Lys Tyr Thr Leu Val Val Val Met Asp Ile Glu
 465 470 475 480

Ala Gly Ser Ser His Phe Val Pro Val Phe Val Ala Val Leu Leu Thr
 485 490 495

Leu Gly Val Val Thr Ile Val Leu Ala Leu Met Tyr Val Phe Arg Glu
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His Gln Arg Ser Gly Ser Tyr His Val Arg Glu Glu Ser Thr Tyr Leu
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Pro Leu Thr Ser Met Gln Pro Thr Glu Ala Met Gly Glu Glu Pro Ser
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Arg Ala Glu
 545

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 <222> (128)..(1159)
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 ggctgctaac tgcgccacct gctgcagcct gtccccgccg ctctgaagcg gccgcgtcga 120
 agccgaa atg ccg cca ccc cgg acc ggc cga ggc ctt ctc tgg ctg ggt 169
 Met Pro Pro Pro Arg Thr Gly Arg Gly Leu Leu Trp Leu Gly 10
 ctg gtt ctg agc tcc gtc tgc gtc gcc ctc gga tcc gaa acg cag gcc 217
 Leu Val Leu Ser Ser Val Cys Val Ala Leu Gly Ser Glu Thr Gln Ala 15 20 25 30
 aac tcg acc aca gat gct ctg aac gtt ctt ctc atc atc gtg gat gac 265
 Asn Ser Thr Thr Asp Ala Leu Asn Val Leu Leu Ile Ile Val Asp Asp

35								40					45					
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aat Asn	att Ile	gac Asp 65	caa Gln	ctg Leu	gca Ala	tcc Ser	cac His 70	agc Ser	ctc Leu	ctc Leu	ttc Phe	cag Gln 75	aat Asn	gcc Ala	ttt Phe	361		
gcg Ala	cag Gln 80	caa Gln	gca Ala	gtg Val	tgc Cys	gcc Ala 85	ccg Pro	agc Ser	cgc Arg	gtt Val	tct Ser 90	ttc Phe	ctc Leu	act Thr	ggc Gly	409		
agg Arg 95	aga Arg	cct Pro	gac Asp	acc Thr	acc Thr 100	cgc Arg	ctg Leu	tac Tyr	gac Asp	ttc Phe 105	aac Asn	tcc Ser	tac Tyr	tgg Trp	agg Arg 110	457		
gtg Val	cac His	gct Ala	gga Gly	aac Asn 115	ttc Phe	tcc Ser	acc Thr	atc Ile	ccc Pro 120	cag Gln	tac Tyr	ttc Phe	aag Lys	gag Glu 125	aat Asn	505		
ggc Gly	tat Tyr	gtg Val	acc Thr 130	atg Met	tcg Ser	gtg Val	gga Gly	aaa Lys 135	gtc Val	ttt Phe	cac His	cct Pro	ggg Gly 140	ata Ile	tct Ser	553		
tct Ser	aac Asn	cat His 145	acc Thr	gat Asp	gat Asp	tct Ser	ccg Pro 150	tat Tyr	agc Ser	tgg Trp	tct Ser	ttt Phe 155	cca Pro	cct Pro	tat Tyr	601		
cat His	cct Pro 160	tcc Ser	tct Ser	gag Glu	aag Lys	tat Tyr 165	gaa Glu	aac Asn	act Thr	aag Lys	aca Thr 170	tgt Cys	cga Arg	ggg Gly	cca Pro	649		
gat Asp 175	gga Gly	gaa Glu	ctc Leu	cat His	gcc Ala 180	aac Asn	ctg Leu	ctt Leu	tgc Cys	cct Pro 185	gtg Val	gat Asp	gtg Val	ctg Leu	gat Asp 190	697		
gtt Val	ccc Pro	gag Glu	ggc Gly	acc Thr 195	ttg Leu	cct Pro	gac Asp	aaa Lys	cag Gln 200	agc Ser	act Thr	gag Glu	caa Gln	gcc Ala 205	ata Ile	745		
cag Gln	ttg Leu	ttg Leu	gaa Glu 210	aag Lys	atg Met	aaa Lys	acg Thr	tca Ser 215	gcc Ala	agt Ser	cct Pro	ttc Phe	ttc Phe 220	ctg Leu	gcc Ala	793		
gtt Val	ggg Gly	tat Tyr 225	cat His	aag Lys	cca Pro	cac His	atc Ile 230	ccc Pro	ttc Phe	aga Arg	tac Tyr	ccc Pro 235	aag Lys	gaa Glu	ttt Phe	841		
cag Gln	aag Lys 240	ttg Leu	tat Tyr	ccc Pro	ttg Leu	gag Glu 245	aac Asn	atc Ile	acc Thr	ctg Leu	gcc Ala 250	ccc Pro	gat Asp	ccc Pro	gag Glu	889		
gtc Val 255	cct Pro	gat Asp	ggc Gly	cta Leu	ccc Pro 260	cct Pro	gtg Val	gcc Ala	tac Tyr	aac Asn 265	ccc Pro	tgg Trp	atg Met	gac Asp	atc Ile 270	937		
agg Arg	caa Gln	cgg Arg	gaa Glu	gac Asp 275	gtc Val	caa Gln	gcc Ala	tta Leu	aac Asn 280	atc Ile	agt Ser	gtg Val	ccg Pro	tat Tyr 285	ggt Gly	985		
cca Pro	att Ile	cct Pro	gtg Val 290	gac Asp	ttt Phe	cag Gln	cgg Arg	aaa Lys 295	atc Ile	cgc Arg	cag Gln	agc Ser	tac Tyr 300	ttt Phe	gcc Ala	1033		
tct Ser	gtg Val	tca Ser 305	tat Tyr	ttg Leu	gat Asp	aca Thr	cag Gln 310	gtc Val	ggc Gly	cgc Arg	ctc Leu	ttg Leu 315	agt Ser	gct Ala	ttg Leu	1081		
gac Asp	gat Asp 320	ctt Leu	cag Gln	ctg Leu	gcc Ala	aac Asn 325	agc Ser	acc Thr	atc Ile	att Ile	gca Ala 330	ttt Phe	acc Thr	tcg Ser	gat Asp	1129		
cat His 335	ggt Gly	ttc Phe	ctc Leu	atg Met	agg Arg 340	aca Thr	aat Asn	acc Thr	tga	ttttgaataa	agcagcattc					1179		
agttgaaata			accctttctg			tggttaattcc			aagtgaatat			ttttcttcta			ggtgatgagt			1239

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 <212> PRT
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<400> 36

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 Thr Thr Asp Ala Leu Asn Val Leu Leu Ile Ile Val Asp Asp Leu Arg
 35 40 45
 Pro Ser Leu Gly Cys Tyr Gly Asp Lys Leu Val Arg Ser Pro Asn Ile
 50 55 60
 Asp Gln Leu Ala Ser His Ser Leu Leu Phe Gln Asn Ala Phe Ala Gln
 65 70 75 80
 Gln Ala Val Cys Ala Pro Ser Arg Val Ser Phe Leu Thr Gly Arg Arg
 85 90 95
 Pro Asp Thr Thr Arg Leu Tyr Asp Phe Asn Ser Tyr Trp Arg Val His
 100 105 110
 Ala Gly Asn Phe Ser Thr Ile Pro Gln Tyr Phe Lys Glu Asn Gly Tyr
 115 120 125
 Val Thr Met Ser Val Gly Lys Val Phe His Pro Gly Ile Ser Ser Asn
 130 135 140
 His Thr Asp Asp Ser Pro Tyr Ser Trp Ser Phe Pro Pro Tyr His Pro
 145 150 155 160
 Ser Ser Glu Lys Tyr Glu Asn Thr Lys Thr Cys Arg Gly Pro Asp Gly
 165 170 175
 Glu Leu His Ala Asn Leu Leu Cys Pro Val Asp Val Leu Asp Val Pro
 180 185 190
 Glu Gly Thr Leu Pro Asp Lys Gln Ser Thr Glu Gln Ala Ile Gln Leu
 195 200 205
 Leu Glu Lys Met Lys Thr Ser Ala Ser Pro Phe Phe Leu Ala Val Gly
 210 215 220
 Tyr His Lys Pro His Ile Pro Phe Arg Tyr Pro Lys Glu Phe Gln Lys
 225 230 235 240
 Leu Tyr Pro Leu Glu Asn Ile Thr Leu Ala Pro Asp Pro Glu Val Pro
 245 250 255
 Asp Gly Leu Pro Pro Val Ala Tyr Asn Pro Trp Met Asp Ile Arg Gln
 260 265 270

Arg Glu Asp Val Gln Ala Leu Asn Ile Ser Val Pro Tyr Gly Pro Ile
 275 280 285

Pro Val Asp Phe Gln Arg Lys Ile Arg Gln Ser Tyr Phe Ala Ser Val
 290 295 300

Ser Tyr Leu Asp Thr Gln Val Gly Arg Leu Leu Ser Ala Leu Asp Asp
 305 310 315 320

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

Phe Leu Met Arg Thr Asn Thr
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 Met Arg Ala Gln
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 Val Asp Gln Val Asp₄₀₅ Gly Phe Glu Cys Ile₄₁₀ Cys Pro Glu Gln Trp₄₁₅ Val
 Gly Ala Thr Cys₄₂₀ Gln Leu Asp Ala Asn₄₂₅ Glu Cys Glu Gly Lys₄₃₀ Pro Cys
 Leu Asn Ala₄₃₅ Phe Ser Cys Lys Asn₄₄₀ Leu Ile Gly Gly Tyr₄₄₅ Tyr Cys Asp
 Cys Ile₄₅₀ Pro Gly Trp Lys Gly₄₅₅ Ile Asn Cys His Ile₄₆₀ Asn Val Asn Asp
 Cys₄₆₅ Arg Gly Gln Cys Gln₄₇₀ His Gly Gly Thr Cys₄₇₅ Lys Asp Leu Val Asn₄₈₀
 Gly Tyr Gln Cys Val₄₈₅ Cys Pro Arg Gly Phe₄₉₀ Gly Gly Arg His Cys₄₉₅ Glu
 Leu Glu Arg Asp₅₀₀ Glu Cys Ala Ser Ser₅₀₅ Pro Cys His Ser Gly₅₁₀ Gly Leu
 Cys Glu Asp₅₁₅ Leu Ala Asp Gly Phe₅₂₀ His Cys His Cys Pro₅₂₅ Gln Gly Phe
 Ser Gly₅₃₀ Pro Leu Cys Glu Val₅₃₅ Asp Val Asp Leu Cys₅₄₀ Glu Pro Ser Pro
 Cys₅₄₅ Arg Asn Gly Ala Arg₅₅₀ Cys Tyr Asn Leu Glu₅₅₅ Gly Asp Tyr Tyr Cys₅₆₀
 Ala Cys Pro Asp Asp₅₆₅ Phe Gly Gly Lys Asn₅₇₀ Cys Ser Val Pro Arg₅₇₅ Glu
 Pro Cys Pro Gly₅₈₀ Gly Ala Cys Arg Val₅₈₅ Ile Asp Gly Cys Gly₅₉₀ Ser Asp
 Ala Gly Pro₅₉₅ Gly Met Pro Gly Thr₆₀₀ Ala Ala Ser Gly Val₆₀₅ Cys Gly Pro
 His Gly₆₁₀ Arg Cys Val Ser Gln₆₁₅ Pro Gly Gly Asn Phe₆₂₀ Ser Cys Ile Cys
 Asp₆₂₅ Ser Gly Phe Thr Gly₆₃₀ Thr Tyr Cys His Glu₆₃₅ Asn Ile Asp Asp Cys₆₄₀

Leu Gly Gln Pro Cys₆₄₅ Arg Asn Gly Gly Thr₆₅₀ Cys Ile Asp Glu Val₆₅₅ Asp
 Ala Phe Arg Cys₆₆₀ Phe Cys Pro Ser Gly₆₆₅ Trp Glu Gly Glu Leu₆₇₀ Cys Asp
 Thr Asn Pro₆₇₅ Asn Asp Cys Leu Pro₆₈₀ Asp Pro Cys His Ser₆₈₅ Arg Gly Arg
 Cys Tyr₆₉₀ Asp Leu Val Asn Asp₆₉₅ Phe Tyr Cys Ala Cys₇₀₀ Asp Asp Gly Trp
 Lys₇₀₅ Gly Lys Thr Cys His₇₁₀ Ser Arg Glu Phe Gln₇₁₅ Cys Asp Ala Tyr Thr₇₂₀
 Cys Ser Asn Gly Gly₇₂₅ Thr Cys Tyr Asp Ser₇₃₀ Gly Asp Thr Phe Arg₇₃₅ Cys
 Ala Cys Pro Pro₇₄₀ Gly Trp Lys Gly Ser₇₄₅ Thr Cys Ala Val Ala₇₅₀ Lys Asn
 Ser Ser Cys₇₅₅ Leu Pro Asn Pro Cys₇₆₀ Val Asn Gly Gly Thr₇₆₅ Cys Val Gly
 Ser Gly₇₇₀ Ala Ser Phe Ser Cys₇₇₅ Ile Cys Arg Asp Gly₇₈₀ Trp Glu Gly Arg
 Thr₇₈₅ Cys Thr His Asn Thr₇₉₀ Asn Asp Cys Asn Pro₇₉₅ Leu Pro Cys Tyr Asn₈₀₀
 Gly Gly Ile Cys Val₈₀₅ Asp Gly Val Asn Trp₈₁₀ Phe Arg Cys Glu Cys₈₁₅ Ala
 Pro Gly Phe Ala₈₂₀ Gly Pro Asp Cys Arg₈₂₅ Ile Asn Ile Asp Glu₈₃₀ Cys Gln
 Ser Ser Pro₈₃₅ Cys Ala Tyr Gly Ala₈₄₀ Thr Cys Val Asp Glu₈₄₅ Ile Asn Gly
 Tyr Arg₈₅₀ Cys Ser Cys Pro Pro₈₅₅ Gly Arg Ala Gly Pro₈₆₀ Arg Cys Gln Glu
 Val₈₆₅ Ile Gly Phe Gly Arg₈₇₀ Ser Cys Trp Ser Arg₈₇₅ Gly Thr Pro Phe Pro₈₈₀
 His Gly Ser Ser Trp₈₈₅ Val Glu Asp Cys Asn₈₉₀ Ser Cys Arg Cys Leu₈₉₅ Asp
 Gly Arg Arg Asp₉₀₀ Cys Ser Lys Val Trp₉₀₅ Cys Gly Trp Lys Pro₉₁₀ Cys Leu
 Leu Ala Gly₉₁₅ Gln Pro Glu Ala Leu₉₂₀ Ser Ala Gln Cys Pro₉₂₅ Leu Gly Gln
 Arg Cys₉₃₀ Leu Glu Lys Ala Pro₉₃₅ Gly Gln Cys Leu Arg₉₄₀ Pro Pro Cys Glu
 Ala Trp Gly Glu Cys Gly₉₅₀ Ala Glu Glu Pro Pro₉₅₅ Ser Thr Pro Cys Leu₉₆₀

Pro Arg Ser Gly His Leu Asp Asn Asn Cys Ala Arg Leu Thr Leu His
 965 970 975
 Phe Asn Arg Asp His Val Pro Gln Gly Thr Thr Val Gly Ala Ile Cys
 980 985 990
 Ser Gly Ile Arg Ser Leu Pro Ala Thr Arg Ala Val Ala Arg Asp Arg
 995 1000 1005
 Leu Leu Val Leu Leu Cys Asp Arg Ala Ser Ser Gly Ala Ser Ala
 1010 1015 1020
 Val Glu Val Ala Val Ser Phe Ser Pro Ala Arg Asp Leu Pro Asp
 1025 1030 1035
 Ser Ser Leu Ile Gln Gly Ala Ala His Ala Ile Val Ala Ala Ile
 1040 1045 1050
 Thr Gln Arg Gly Asn Ser Ser Leu Leu Leu Ala Val Thr Glu Val
 1055 1060 1065
 Lys Val Glu Thr Val Val Thr Gly Gly Ser Ser Thr Gly Leu Leu
 1070 1075 1080
 Val Pro Val Leu Cys Gly Ala Phe Ser Val Leu Trp Leu Ala Cys
 1085 1090 1095
 Val Val Leu Cys Val Trp Trp Thr Arg Lys Arg Arg Lys Glu Arg
 1100 1105 1110
 Glu Arg Ser Arg Leu Pro Arg Glu Glu Ser Ala Asn Asn Gln Trp
 1115 1120 1125
 Ala Pro Leu Asn Pro Ile Arg Asn Pro Ile Glu Arg Pro Gly Gly
 1130 1135 1140
 His Lys Asp Val Leu Tyr Gln Cys Lys Asn Phe Thr Pro Pro Pro
 1145 1150 1155
 Arg Arg Ala Asp Glu Ala Leu Pro Gly Pro Ala Gly His Ala Ala
 1160 1165 1170
 Val Arg Glu Asp Glu Glu Asp Glu Asp Leu Gly Arg Gly Glu Glu
 1175 1180 1185
 Asp Ser Leu Glu Ala Glu Lys Phe Leu Ser His Lys Phe Thr Lys
 1190 1195 1200
 Asp Pro Gly Arg Ser Pro Gly Arg Pro Ala His Trp Ala Ser Gly
 1205 1210 1215
 Pro Lys Val Asp Asn Arg Ala Val Arg Ser Ile Asn Glu Ala Arg
 1220 1225 1230
 Tyr Ala Gly Lys Glu
 1235

<210> 39
 <211> 634
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (3)..(371)
 <223>

<400> 39
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 Arg Ala Ala Leu Arg Arg Leu Ala Val Ala Thr Arg Thr Met Ala
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 gga gcg ccc acg gtc tcg ctt cct gaa ctc cgt tca ctc cta gcc tcc 95
 Gly Ala Pro Thr Val Ser Leu Pro Glu Leu Arg Ser Leu Leu Ala Ser
 20 25 30
 gga cgg gcc cgg ctc ttc gac gtg cgc tct cgc gag gag gcg gca gct 143
 Gly Arg Ala Arg Leu Phe Asp Val Arg Ser Arg Glu Glu Ala Ala
 35 40 45
 ggg acc atc cca ggg gcg ctc aac atc ccg gtg tcc gag ttg gag agt 191
 Gly Thr Ile Pro Gly Ala Leu Asn Ile Pro Val Ser Glu Leu Glu Ser
 50 55 60
 gct ctg cag atg gag cca gct gcc ttc cag gct tta tat tct gct gag 239
 Ala Leu Gln Met Glu Pro Ala Ala Phe Gln Ala Leu Tyr Ser Ala Glu
 65 70 75
 aag cca aag ctg gaa gat gag cat ctc gtt ttc ttc tgt cag atg ggc 287
 Lys Pro Lys Leu Glu Asp Glu His Leu Val Phe Phe Cys Gln Met Gly
 80 85 90 95
 aag cgg ggc ctc cag gcc acg cag ctg gcc cgg agt ctt gga tac act 335
 Lys Arg Gly Leu Gln Ala Thr Gln Leu Ala Arg Ser Leu Gly Tyr Thr
 100 105 110
 ggg tac ggg gag gtg tgg ctg cta gct ggg agg tga tggggactgc 381
 Gly Tyr Gly Glu Val Trp Leu Leu Ala Gly Arg
 115 120
 ctgtcattcc tgtcagtcctc tcacgcttct ttgtctccac agggctcgca actacgctgg 441
 agcctataga gaatggttgg agaaagagag ttaggcagga ggcagcttac tgattgccac 501
 cccctggccc cttaatggcc accttaacta aggggtgtgaa cgggctgact tgggtgaattg 561
 ggcaactcct tatagtgttg tgcacacaaa agcatcaaat aaagaacatt taatcaaaaa 621
 aaaaaaaaaa aaa 634

<210> 40
 <211> 122
 <212> PRT
 <213> Homo sapiens

<400> 40
 Arg Ala Ala Leu Arg Arg Leu Ala Val Ala Thr Arg Thr Met Ala Gly
 1 5 10 15
 Ala Pro Thr Val Ser Leu Pro Glu Leu Arg Ser Leu Leu Ala Ser Gly
 20 25 30
 Arg Ala Arg Leu Phe Asp Val Arg Ser Arg Glu Glu Ala Ala Ala Gly
 35 40 45
 Thr Ile Pro Gly Ala Leu Asn Ile Pro Val Ser Glu Leu Glu Ser Ala
 50 55 60
 Leu Gln Met Glu Pro Ala Ala Phe Gln Ala Leu Tyr Ser Ala Glu Lys
 65 70 75 80
 Pro Lys Leu Glu Asp Glu His Leu Val Phe Phe Cys Gln Met Gly Lys
 85 90 95

Arg Gly Leu Gln Ala Thr Gln Leu Ala Arg Ser Leu Gly Tyr Thr Gly
 100 105 110

Tyr Gly Glu Val Trp Leu Leu Ala Gly Arg
 115 120

<210> 41
 <211> 2254
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (180)..(1937)
 <223>

<400> 41
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 gaggctccac acggccgttg cagctaccgc agccaggatc tgggcatcca ggcacggcc 179
 atg acc cct ccg agg ctc ttc tgg gtg tgg ctg ctg gtt gca gga acc 227
 Met Thr Pro Pro Arg Leu Phe Trp Val Trp Leu Leu Val Ala Gly Thr 15
 1
 5
 10
 15
 caa ggc gtg aac gat ggt gac atg cgg ctg gcc gat ggg ggc gcc acc 275
 Gln Gly Val Asn Asp Gly Asp Met Arg Leu Ala Asp Gly Gly Ala Thr 20 25 30
 aac cag ggc cgc gtg gag atc ttc tac aga ggc cag tgg ggc act gtg 323
 Asn Gln Gly Arg Val Glu Ile Phe Tyr Arg Gly Gln Trp Gly Thr Val 35 40 45
 tgt gac aac ctg tgg gac ctc act gat gcc agc gtc gtc tgc cgg gcc 371
 Cys Asp Asn Leu Trp Asp Leu Thr Asp Ala Ser Val Val Cys Arg Ala 50 55 60
 ctg ggc ttc gag aac gcc acc cag gct ctg ggc aga gct gcc ttc ggg 419
 Leu Gly Phe Glu Asn Ala Thr Gln Ala Leu Gly Arg Ala Ala Phe Gly 65 70 75 80
 caa gga tca ggc ccc atc atg ctg gac gag gtc cag tgc acg gga acc 467
 Gln Gly Ser Gly Pro Ile Met Leu Asp Glu Val Gln Cys Thr Gly Thr 85 90 95
 gag gcc tca ctg gcc gac tgc aag tcc ctg ggc tgg ctg aag agc aac 515
 Glu Ala Ser Leu Ala Asp Cys Lys Ser Leu Gly Trp Leu Lys Ser Asn 100 105 110
 tgc agg cac gag aga gac gct ggt gtg gtc tgc acc aat gaa acc agg 563
 Cys Arg His Glu Arg Asp Ala Gly Val Val Cys Thr Asn Glu Thr Arg 115 120 125
 agc acc cac acc ctg gac ctc tcc agg gag ctc tcg gag gcc ctt ggc 611
 Ser Thr His Thr Leu Asp Leu Ser Arg Glu Leu Ser Glu Ala Leu Gly 130 135 140
 cag atc ttt gac agc cag cgg ggc tgc gac ctg tcc atc agc gtg aat 659
 Gln Ile Phe Asp Ser Gln Arg Gly Cys Asp Leu Ser Ile Ser Val Asn 145 150 155 160
 gtg cag ggc gag gac gcc ctg ggc ttc tgt ggc cac acg gtc atc ctg 707
 Val Gln Gly Glu Asp Ala Leu Gly Phe Cys Gly His Thr Val Ile Leu 165 170 175
 act gcc aac ctg gag gcc cag gcc ctg tgg aag gag ccg ggc agc aat 755
 Thr Ala Asn Leu Glu Ala Gln Ala Leu Trp Lys Glu Pro Gly Ser Asn 180 185 190
 gtc acc atg agt gtg gat gct gag tgt gtg ccc atg gtc agg gac ctt 803
 Val Thr Met Ser Val Asp Ala Glu Cys Val Pro Met Val Arg Asp Leu 195 200 205
 ctc agg tac ttc tac tcc cga agg att gac atc acc ctg tcg tca gtc 851
 Leu Arg Tyr Phe Tyr Ser Arg Arg Ile Asp Ile Thr Leu Ser Ser Val 210 215 220

aag Lys 225	tgc Cys	ttc Phe	cac His	aag Lys	ctg Leu 230	gcc Ala	tct Ser	gcc Ala	tat Tyr	ggg Gly 235	gcc Ala	agg Arg	cag Gln	ctg Leu	cag Gln 240	899
ggc Gly	tac Tyr	tgc Cys	gca Ala	agc Ser 245	ctc Leu	ttt Phe	gcc Ala	atc Ile	ctc Leu 250	ctc Leu	ccc Pro	cag Gln	gac Asp	ccc Pro 255	tcg Ser	947
ttc Phe	cag Gln	atg Met	ccc Pro 260	ctg Leu	gac Asp	ctg Leu	tat Tyr	gcc Ala 265	tat Tyr	gca Ala	gtg Val	gcc Ala	aca Thr 270	ggg Gly	gac Asp	995
gcc Ala	ctg Leu	ctg Leu 275	gag Glu	aag Lys	ctc Leu	tgc Cys	cta Leu 280	cag Gln	ttc Phe	ctg Leu	gcc Ala	tgg Trp 285	aac Asn	ttc Phe	gag Glu	1043
gcc Ala 290	ttg Leu	acg Thr	cag Gln	gcc Ala	gag Glu	gcc Ala 295	tgg Trp	ccc Pro	agt Ser	gtc Val	ccc Pro 300	aca Thr	gac Asp	ctg Leu	ctc Leu	1091
caa Gln 305	ctg Leu	ctg Leu	ctg Leu	ccc Pro	agg Arg 310	agc Ser	gac Asp	ctg Leu	gcg Ala	gtg Val 315	ccc Pro	agc Ser	gag Glu	ctg Leu	gcc Ala 320	1139
cta Leu	ctg Leu	aag Lys	gcc Ala	gtg Val 325	gac Asp	acc Thr	tgg Trp	agc Ser	tgg Trp 330	ggg Gly	gag Glu	cgt Arg	gcc Ala	tcc Ser 335	cat His	1187
gag Glu	gag Glu	gtg Val	gag Glu 340	ggc Gly	ttg Leu	gtg Val	gag Glu	aag Lys 345	atc Ile	cgc Arg	ttc Phe	ccc Pro	atg Met 350	atg Met	ctc Leu	1235
cct Pro	gag Glu	gag Glu 355	ctc Leu	ttt Phe	gag Glu	ctg Leu	cag Gln 360	ttc Phe	aac Asn	ctg Leu	tcc Ser	ctg Leu 365	tac Tyr	tgg Trp	agc Ser	1283
cac His 370	gag Glu	gcc Ala	ctg Leu	ttc Phe	cag Gln	aag Lys 375	aag Lys	act Thr	ctg Leu	cag Gln	gcc Ala 380	ctg Leu	gaa Glu	ttc Phe	cac His	1331
act Thr 385	gtg Val	ccc Pro	ttc Phe	cag Gln	ttg Leu 390	ctg Leu	gcc Ala	cgg Arg	tac Tyr	aaa Lys 395	ggc Gly	ctg Leu	aac Asn	ctc Leu	acc Thr 400	1379
gag Glu	gat Asp	acc Thr	tac Tyr	aag Lys 405	ccc Pro	cgg Arg	att Ile	tac Tyr	acc Thr 410	tcg Ser	ccc Pro	acc Thr	tgg Trp	agt Ser 415	gcc Ala	1427
ttt Phe	gtg Val	aca Thr	gac Asp 420	agt Ser	tcc Ser	tgg Trp	agt Ser	gca Ala 425	cgg Arg	aag Lys	tca Ser	caa Gln	ctg Leu 430	gtc Val	tat Tyr	1475
cag Gln	tcc Ser	aga Arg 435	cgg Arg	ggg Gly	cct Pro	ttg Leu	gtc Val 440	aaa Lys	tat Tyr	tct Ser	tct Ser	gat Asp 445	tac Tyr	ttc Phe	caa Gln	1523
gcc Ala	ccc Pro 450	tct Ser	gac Asp	tac Tyr	aga Arg	tac Tyr 455	tac Tyr	ccc Pro	tac Tyr	cag Gln	tcc Ser 460	ttc Phe	cag Gln	act Thr	cca Pro	1571
caa Gln 465	cac His	ccc Pro	agc Ser	ttc Phe	ctc Leu 470	ttc Phe	cag Gln	gac Asp	aag Lys	agg Arg 475	gtg Val	tcc Ser	tgg Trp	tcc Ser	ctg Leu 480	1619
gtc Val	tac Tyr	ctc Leu	ccc Pro	acc Thr 485	atc Ile	cag Gln	agc Ser	tgc Cys	tgg Trp 490	aac Asn	tac Tyr	ggc Gly	ttc Phe	tcc Ser 495	tgc Cys	1667
tcc Ser	tcg Ser	gac Asp	gag Glu 500	ctc Leu	cct Pro	gtc Val	ctg Leu	ggc Gly 505	ctc Leu	acc Thr	aag Lys	tct Ser	ggc Gly 510	ggc Gly	tca Ser	1715
gat Asp	cgc Arg	acc Thr 515	att Ile	gcc Ala	tac Tyr	gaa Glu	aac Asn 520	aaa Lys	gcc Ala	ctg Leu	atg Met	ctc Leu 525	tgc Cys	gaa Glu	ggg Gly	1763
ctc Leu	ttc Phe 530	gtg Val	gca Ala	gac Asp	gtc Val	acc Thr 535	gat Asp	ttc Phe	gag Glu	ggc Gly	tgg Trp 540	aag Lys	gct Ala	gcg Ala	att Ile	1811

ccc agt gcc ctg gac acc aac agc tcg aag agc acc tcc tcc ttc ccc 1859
 Pro Ser Ala Leu Asp Thr Asn Ser Ser Lys Ser Thr Ser Ser Phe Pro 560
 545 550 555

tgc ccg gca ggg cac ttc aac ggc ttc cgc acg gtc atc cgc ccc ttc 1907
 Cys Pro Ala Gly His Phe Asn Gly Phe Arg Thr Val Ile Arg Pro Phe 575
 565 570

tac ctg acc aac tcc tca ggt gtg gac tag acgcgtggcc aagggtggtg 1957
 Tyr Leu Thr Asn Ser Ser Gly Val Asp 585
 580

agaaccggag aacccagga cgccctcact gcaggctccc ctccctcggct tccttcctct 2017
 ctgcaatgac cttcaacaac cggccaccag atgtcgccct actcacctga ggctcagctt 2077
 caagaaatta ctggaaggct tccactaggg tccaccagga gttctccac cacctcacca 2137
 gtttccaggt ggtaagcacc aggaggccct cgaggttgct ctggatcccc ccacagcccc 2197
 tggtcagtct gcccttgtca ctggtctgag gtcattaaaa ttacattgag gttccta 2254

<210> 42
 <211> 585
 <212> PRT
 <213> Homo sapiens

<400> 42

Met Thr Pro Pro Arg Leu Phe Trp Val Trp Leu Leu Val Ala Gly Thr
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Gln Gly Val Asn Asp Gly Asp Met Arg Leu Ala Asp Gly Gly Ala Thr
 20 25 30

Asn Gln Gly Arg Val Glu Ile Phe Tyr Arg Gly Gln Trp Gly Thr Val
 35 40 45

Cys Asp Asn Leu Trp Asp Leu Thr Asp Ala Ser Val Val Cys Arg Ala
 50 55 60

Leu Gly Phe Glu Asn Ala Thr Gln Ala Leu Gly Arg Ala Ala Phe Gly
 65 70 75 80

Gln Gly Ser Gly Pro Ile Met Leu Asp Glu Val Gln Cys Thr Gly Thr
 85 90 95

Glu Ala Ser Leu Ala Asp Cys Lys Ser Leu Gly Trp Leu Lys Ser Asn
 100 105 110

Cys Arg His Glu Arg Asp Ala Gly Val Val Cys Thr Asn Glu Thr Arg
 115 120 125

Ser Thr His Thr Leu Asp Leu Ser Arg Glu Leu Ser Glu Ala Leu Gly
 130 135 140

Gln Ile Phe Asp Ser Gln Arg Gly Cys Asp Leu Ser Ile Ser Val Asn
 145 150 155 160

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

Thr Ala Asn Leu Glu Ala Gln Ala Leu Trp Lys Glu Pro Gly Ser Asn
 180 185 190

Val Thr Met Ser Val Asp Ala Glu Cys Val Pro Met Val Arg Asp Leu
 195 200 205

Leu Arg Tyr Phe Tyr Ser Arg Arg Ile Asp Ile Thr Leu Ser Ser Val
 210 215 220
 Lys Cys Phe His Lys Leu Ala Ser Ala Tyr Gly Ala Arg Gln Leu Gln
 225 230 235 240
 Gly Tyr Cys Ala Ser Leu Phe Ala Ile Leu Leu Pro Gln Asp Pro Ser
 245 250 255
 Phe Gln Met Pro Leu Asp Leu Tyr Ala Tyr Ala Val Ala Thr Gly Asp
 260 265 270
 Ala Leu Leu Glu Lys Leu Cys Leu Gln Phe Leu Ala Trp Asn Phe Glu
 275 280 285
 Ala Leu Thr Gln Ala Glu Ala Trp Pro Ser Val Pro Thr Asp Leu Leu
 290 295 300
 Gln Leu Leu Leu Pro Arg Ser Asp Leu Ala Val Pro Ser Glu Leu Ala
 305 310 315 320
 Leu Leu Lys Ala Val Asp Thr Trp Ser Trp Gly Glu Arg Ala Ser His
 325 330 335
 Glu Glu Val Glu Gly Leu Val Glu Lys Ile Arg Phe Pro Met Met Leu
 340 345 350
 Pro Glu Glu Leu Phe Glu Leu Gln Phe Asn Leu Ser Leu Tyr Trp Ser
 355 360 365
 His Glu Ala Leu Phe Gln Lys Lys Thr Leu Gln Ala Leu Glu Phe His
 370 375 380
 Thr Val Pro Phe Gln Leu Leu Ala Arg Tyr Lys Gly Leu Asn Leu Thr
 385 390 395 400
 Glu Asp Thr Tyr Lys Pro Arg Ile Tyr Thr Ser Pro Thr Trp Ser Ala
 405 410 415
 Phe Val Thr Asp Ser Ser Trp Ser Ala Arg Lys Ser Gln Leu Val Tyr
 420 425 430
 Gln Ser Arg Arg Gly Pro Leu Val Lys Tyr Ser Ser Asp Tyr Phe Gln
 435 440 445
 Ala Pro Ser Asp Tyr Arg Tyr Tyr Pro Tyr Gln Ser Phe Gln Thr Pro
 450 455 460
 Gln His Pro Ser Phe Leu Phe Gln Asp Lys Arg Val Ser Trp Ser Leu
 465 470 475 480
 Val Tyr Leu Pro Thr Ile Gln Ser Cys Trp Asn Tyr Gly Phe Ser Cys
 485 490 495
 Ser Ser Asp Glu Leu Pro Val Leu Gly Leu Thr Lys Ser Gly Gly Ser
 500 505 510
 Asp Arg Thr Ile Ala Tyr Glu Asn Lys Ala Leu Met Leu Cys Glu Gly
 515 520 525

Leu Phe Val Ala Asp Val Thr Asp Phe Glu Gly Trp Lys Ala Ala Ile
 530 535 540

Pro Ser Ala Leu Asp Thr Asn Ser Ser Lys Ser Thr Ser Ser Phe Pro
 545 550 555 560

Cys Pro Ala Gly His Phe Asn Gly Phe Arg Thr Val Ile Arg Pro Phe
 565 570 575

Tyr Leu Thr Asn Ser Ser Gly Val Asp
 580 585

<210> 43
 <211> 1185
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (283)..(1131)
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<400> 43
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 aaggagctct acaacgtgct gcctgggtggc gagaaggagt tcgtgaacct gcagggtttt 180
 gccgccagag gcttcgaggg cttctgcctg gttggcgtct cgcacctgga catctgtgag 240
 ttcattgaca actatgcgct ctccaagaag ggtgtcaaag cc atg agc ctc aag 294
 Met Ser Leu Lys
 1

cgc tcc acc atc acg gac gca ggc ctc gag gtt atg ctt gaa cag atg 342
 Arg Ser Thr Ile Thr Asp Ala Gly Leu Glu Val Met Leu Glu Gln Met
 5 10 15 20

cag ggc gtg gtg cgt ctg gag ctg tcg ggc tgc aac gac ttc acc gag 390
 Gln Gly Val Val Arg Leu Glu Leu Ser Gly Cys Asn Asp Phe Thr Glu
 25 30 35

gcc ggg ctg tgg tcc agc ctg agc gcg cgc atc acc tcg ctg agc gtg 438
 Ala Gly Leu Trp Ser Ser Leu Ser Ala Arg Ile Thr Ser Leu Ser Val
 40 45 50

agt gac tgc atc aac gtg gcc gac gac gcc atc gcg gcc atc tcg cag 486
 Ser Asp Cys Ile Asn Val Ala Asp Asp Ala Ile Ala Ala Ile Ser Gln
 55 60 65

ctg ctg ccc aac ctg gcg gag ctg agc ctg cag gcc tac cac gtg acg 534
 Leu Leu Pro Asn Leu Ala Glu Leu Ser Leu Gln Ala Tyr His Val Thr
 70 75 80

gac acg gcg ctg gcc tac ttc acg gcg cgc cag gcc cac agc acg cac 582
 Asp Thr Ala Leu Ala Tyr Phe Thr Ala Arg Gln Gly His Ser Thr His
 85 90 95 100

acg ctg cgc ctg ctc tcc tgc tgg gag atc acc aac cac ggc gtg gtc 630
 Thr Leu Arg Leu Leu Ser Cys Trp Glu Ile Thr Asn His Gly Val Val
 105 110 115

aac gtg gtg cac agc ctg ccc aac ctc acc gcg ctc agc ctc tcg ggc 678
 Asn Val Val His Ser Leu Pro Asn Leu Thr Ala Leu Ser Leu Ser Gly
 120 125 130

tgc tcc aag gtc acc gac gac ggc gtg gag ctc gtg gcc gag aac ctg 726
 Cys Ser Lys Val Thr Asp Asp Gly Val Glu Leu Val Ala Glu Asn Leu
 135 140 145

cgc aag ctg cgc agc ctt gac ctc tcg tgg tgc cca cgc atc acc gac 774
 Arg Lys Leu Arg Ser Leu Asp Leu Ser Trp Cys Pro Arg Ile Thr Asp
 150 155 160

atg gcg ctg gag tac gtg gcc tgc gac ctg cac cgc cta gag gag ctc 822

Met Ala Leu Glu Tyr Val Ala Cys Asp Leu His Arg Leu Glu Glu Leu
 165 170 175 180
 gtg ctc gac agg tgt gta cgc atc acg gac act ggc ctc agc tat ctg 870
 Val Leu Asp Arg Cys Val Arg Ile Thr Asp Thr Gly Leu Ser Tyr Leu
 185 190 195
 tcc acc atg tcg tcc ctc cgc agc ctc tac ctg cga tgg tgc tgc cag 918
 Ser Thr Met Ser Leu Arg Ser Leu Tyr Leu Arg Trp Cys Cys Gln
 200 205 210
 gtg caa gac ttc ggg ctg aag cac ctc ctg gcc ctg ggg agt ttg cgc 966
 Val Gln Asp Phe Gly Leu Lys His Leu Ala Leu Gly Ser Leu Arg
 215 220 225
 ctc ctg tct ctg gca ggc tgc ccg ctg ctc acc acc acc ggg ctg tcg 1014
 Leu Leu Ser Leu Ala Gly Cys Pro Leu Leu Thr Thr Thr Gly Leu Ser
 230 235 240
 ggc ctg gtg cag ctg cag gag ctg gag gag ctg gag ctg acc aac tgc 1062
 Gly Leu Val Gln Leu Gln Glu Leu Glu Leu Glu Leu Thr Asn Cys
 245 250 255 260
 ccc ggg gcc acc ccc gag ctc ttc aag tat ttc tcg cag cac ctg ccc 1110
 Pro Gly Ala Thr Pro Glu Leu Phe Lys Tyr Phe Ser Gln His Leu Pro
 265 270 275
 cgc tgc ctc gtc att gag tag cgcgaggccc ccgccccggt cgcgggaacc 1161
 Arg Cys Leu Val Ile Glu
 280
 cggccatgac ctgggcgggg gcgc 1185

<210> 44
 <211> 282
 <212> PRT
 <213> Homo sapiens

<400> 44

Met Ser Leu Lys Arg Ser Thr Ile Thr Asp Ala Gly Leu Glu Val Met
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 Leu Glu Gln Met Gln Gly Val Val Arg Leu Glu Leu Ser Gly Cys Asn
 20 25 30
 Asp Phe Thr Glu Ala Gly Leu Trp Ser Ser Leu Ser Ala Arg Ile Thr
 35 40 45
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 Tyr His Val Thr Asp Thr Ala Leu Ala Tyr Phe Thr Ala Arg Gln Gly
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 His Gly Val Val Asn Val Val His Ser Leu Pro Asn Leu Thr Ala Leu
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 Ala Glu Asn Leu Arg Lys Leu Arg Ser Leu Asp Leu Ser Trp Cys Pro
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Val	Tyr	Ser	Ala	Leu	Arg	Ile	Pro	Pro	Glu	Asp						
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Phe	Ile ₃₅	Asp	Ile	Glu	Ser	Lys ₄₀	Phe	Ala	Leu	Arg	Thr ₄₅	Pro	Glu	Asp	Thr		
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Ala ₅₀	Glu	Asp	Thr	Cys	His ₅₅	Leu	Ile	Pro	Gly	Val ₆₀	Ala	Glu	Ser	Val	Ala ₆₅		
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Thr	Cys	His	Phe	Asn ₇₀	His	Ser	Ser	Lys	Thr ₇₅	Phe	Met	Val	Ile	His ₈₀	Gly		
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Trp	Thr	Val	Thr ₈₅	Gly	Met	Tyr	Glu	Ser ₉₀	Trp	Val	Pro	Lys	Leu ₉₅	Val	Ala		
gcc	ctg	tac	aag	aga	gaa	cca	gac	tcc	aat	gtc	att	gtg	gtg	gac	tgg	513	
Ala	Leu	Tyr ₁₀₀	Lys	Arg	Glu	Pro	Asp ₁₀₅	Ser	Asn	Val	Ile	Val ₁₁₀	Val	Asp	Trp		
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Leu	Phe ₂₇₅	Ile	Asp	Ser	Leu	Leu ₂₈₀	Asn	Glu	Glu	Asn	Pro ₂₈₅	Ser	Lys	Ala	Tyr		
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Tyr	Lys	Val ₃₄₀	Phe	His	Tyr	Gln	Val ₃₄₅	Lys	Ile	His	Phe	Ser ₃₅₀	Gly	Thr	Glu	
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Ser	Glu ₃₅₅	Thr	His	Thr	Asn	Gln ₃₆₀	Ala	Phe	Glu	Ile	Ser ₃₆₅	Leu	Tyr	Gly	Thr	
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Val ₃₇₀	Ala	Glu	Ser	Glu	Asn ₃₇₅	Ile	Pro	Phe	Thr	Leu ₃₈₀	Pro	Glu	Val	Ser	Thr ₃₈₅	
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Leu	Leu	Met	Leu ₄₀₅	Lys	Leu	Lys	Trp	Lys ₄₁₀	Ser	Asp	Ser	Tyr	Phe ₄₁₅	Ser	Trp	
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Gln	Asn	Val	Val	Ile	Ser	Gly	Leu	Val	Ser	Pro	Asp	Gly	Leu	Ala	Cys		
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Asp	Trp	Val	Gly	Lys	Lys	Leu	Tyr	Trp	Thr	Asp	Ser	Glu	Thr	Asn	Arg		
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Ile	Glu	Val	Ala	Asn	Leu	Asn	Gly	Thr	Ser	Arg	Lys	Val	Leu	Phe	Trp		
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Cys Thr Asp Ser Ser 1615
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<212> PRT
<213> Homo sapiens

<400> 50

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Pro Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala
35 40 45
Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly Leu Glu Asp
50 55 60
Ala Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr
65 70 75 80
Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly
85 90 95
Ala Ala Val Gln Asn Val Val Ile Ser Gly Leu Val Ser Pro Asp Gly
100 105 110
Leu Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu
115 120 125
Thr Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val
130 135 140
Leu Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro
145 150 155 160
Ala His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Thr Pro Arg Ile
165 170 175

Glu Arg Ala Gly₁₈₀ Met Asp Gly Ser Thr₁₈₅ Arg Lys Ile Ile Val₁₉₀ Asp Ser
 Asp Ile Tyr₁₉₅ Trp Pro Asn Gly Leu₂₀₀ Thr Ile Asp Leu Glu₂₀₅ Glu Gln Lys
 Leu Tyr₂₁₀ Trp Ala Asp Ala Lys₂₁₅ Leu Ser Phe Ile His₂₂₀ Arg Ala Asn Leu
 Asp Gly₂₂₅ Ser Phe Arg Gln₂₃₀ Lys Val Val Glu Gly₂₃₅ Ser Leu Thr His Pro₂₄₀
 Phe Ala Leu Thr Leu₂₄₅ Ser Gly Asp Thr Leu₂₅₀ Tyr Trp Thr Asp Trp₂₅₅ Gln
 Thr Arg Ser Ile₂₆₀ His Ala Cys Asn Lys₂₆₅ Arg Thr Gly Gly Lys₂₇₀ Arg Lys
 Glu Ile Leu₂₇₅ Ser Ala Leu Tyr Ser₂₈₀ Pro Met Asp Ile Gln₂₈₅ Val Leu Ser
 Gln Glu₂₉₀ Arg Gln Pro Phe Phe₂₉₅ His Thr Arg Cys Glu₃₀₀ Glu Asp Asn Gly
 Gly₃₀₅ Cys Ser His Leu Cys₃₁₀ Leu Leu Ser Pro Ser₃₁₅ Glu Pro Phe Tyr Thr₃₂₀
 Cys Ala Cys Pro Thr₃₂₅ Gly Val Gln Leu Gln₃₃₀ Asp Asn Gly Arg Thr₃₃₅ Cys
 Lys Ala Gly Ala₃₄₀ Glu Glu Val Leu Leu₃₄₅ Leu Ala Arg Arg Thr₃₅₀ Asp Leu
 Arg Arg Ile₃₅₅ Ser Leu Asp Thr Pro₃₆₀ Asp Phe Thr Asp Ile₃₆₅ Val Leu Gln
 Val Asp₃₇₀ Asp Ile Arg His Ala₃₇₅ Ile Ala Ile Asp Tyr₃₈₀ Asp Pro Leu Glu
 Gly₃₈₅ Tyr Val Tyr Trp Thr₃₉₀ Asp Asp Glu Val Arg₃₉₅ Ala Ile Arg Arg Ala₄₀₀
 Tyr Leu Asp Gly₄₀₅ Ser Gly Ala Gln Thr Leu₄₁₀ Val Asn Thr Glu Ile₄₁₅ Asn
 Asp Pro Asp Gly₄₂₀ Ile Ala Val Asp Trp₄₂₅ Val Ala Arg Asn Leu₄₃₀ Tyr Trp
 Thr Asp Thr₄₃₅ Gly Thr Asp Arg Ile₄₄₀ Glu Val Thr Arg Leu₄₄₅ Asn Gly Thr
 Ser Arg₄₅₀ Lys Ile Leu Val Ser₄₅₅ Glu Asp Leu Asp Glu₄₆₀ Pro Arg Ala Ile
 Ala₄₆₅ Leu His Pro Val Met₄₇₀ Gly Leu Met Tyr Trp₄₇₅ Thr Asp Trp Gly Glu₄₈₀
 Asn Pro Lys Ile Glu₄₈₅ Cys Ala Asn Leu Asp₄₉₀ Gly Gln Glu Arg Arg₄₉₅ Val

Leu Val Asn Ala Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu
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 Gln Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu
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 Val Ile Asn Val Asp Gly Thr Lys Arg Arg Thr Leu Leu Glu Asp Lys
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 Leu Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp
 545 550 555 560
 Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala
 565 570 575
 Ser Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys
 580 585 590
 Ala Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Arg
 595 600 605
 Asn Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro His Ala Thr Arg
 610 615 620
 Cys Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys
 625 630 635 640
 Ile Val Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Ala Ile His
 645 650 655
 Arg Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr
 660 665 670
 Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His
 675 680 685
 Ile Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met
 690 695 700
 Asn Gly Ser Ser Val Glu His Val Val Glu Phe Gly Leu Asp Tyr Pro
 705 710 715 720
 Glu Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp
 725 730 735
 Thr Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg
 740 745 750
 Gln Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu
 755 760 765
 Asp Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro
 770 775 780
 Arg Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val
 785 790 795 800
 Asp Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln
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Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn
 820 825 830
 Met Leu Gly Gln Glu Arg Val Val Ile Ala Asp Asp Leu Pro His Pro
 835 840 845
 Phe Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn
 850 855 860
 Leu His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr
 865 870 875 880
 Leu Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His
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 Ser Ser Arg Gln Asp Gly Leu Asn Asp Cys Met His Asn Asn Gly Gln
 900 905 910
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 915 920 925
 Ala Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro
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 Thr Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile Ser Arg Met Ile
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 Pro Asp Asp Gln His Ser Pro Asp Leu Ile Leu Pro Leu His Gly Leu
 965 970 975
 Arg Asn Val Lys Ala Ile Asp Tyr Asp Pro Leu Asp Lys Phe Ile Tyr
 980 985 990
 Trp Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr
 995 1000 1005
 Gln Pro Phe Val Leu Thr Ser Leu Ser Gln Gly Gln Asn Pro Asp
 1010 1015 1020
 Arg Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu
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 Phe Trp Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu
 1040 1045 1050
 Ser Gly Glu Ala Met Gly Val Val Leu Arg Gly Asp Arg Asp Lys
 1055 1060 1065
 Pro Arg Ala Ile Val Val Asn Ala Glu Arg Gly Tyr Leu Tyr Phe
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 Thr Asn Met Gln Asp Arg Ala Ala Lys Ile Glu Arg Ala Ala Leu
 1085 1090 1095
 Asp Gly Thr Glu Arg Glu Val Leu Phe Thr Thr Gly Leu Ile Arg
 1100 1105 1110
 Pro Val Ala Leu Val Val Asp Asn Thr Leu Gly Lys Leu Phe Trp
 1115 1120 1125

Val₁₁₃₀ Asp Ala Asp Leu Lys Arg₁₁₃₅ Ile Glu Ser Cys Asp₁₁₄₀ Leu Ser Gly
 Ala Asn₁₁₄₅ Arg Leu Thr Leu Glu₁₁₅₀ Asp Ala Asn Ile Val₁₁₅₅ Gln Pro Leu
 Gly Leu₁₁₆₀ Thr Ile Leu Gly Lys₁₁₆₅ His Leu Tyr Trp Ile₁₁₇₀ Asp Arg Gln
 Gln Gln₁₁₇₅ Met Ile Glu Arg Val₁₁₈₀ Glu Lys Thr Thr Gly₁₁₈₅ Asp Lys Arg
 Thr Arg₁₁₉₀ Ile Gln Gly Arg Val₁₁₉₅ Ala His Leu Thr Gly₁₂₀₀ Ile His Ala
 Val₁₂₀₅ Glu Glu Val Ser Leu Glu₁₂₁₀ Glu Phe Ser Ala His₁₂₁₅ Pro Cys Ala
 Arg Asp₁₂₂₀ Asn Gly Gly Cys Ser₁₂₂₅ His Ile Cys Ile Ala₁₂₃₀ Lys Gly Asp
 Gly Thr₁₂₃₅ Pro Arg Cys Ser Cys₁₂₄₀ Pro Val His Leu Val₁₂₄₅ Leu Leu Gln
 Asn Leu₁₂₅₀ Leu Thr Cys Gly Glu₁₂₅₅ Pro Pro Thr Cys Ser₁₂₆₀ Pro Asp Gln
 Phe Ala₁₂₆₅ Cys Ala Thr Gly Glu₁₂₇₀ Ile Asp Cys Ile Pro₁₂₇₅ Gly Ala Trp
 Arg Cys₁₂₈₀ Asp Gly Phe Pro Glu₁₂₈₅ Cys Asp Asp Gln Ser₁₂₉₀ Asp Glu Glu
 Gly Cys₁₂₉₅ Pro Val Cys Ser Ala₁₃₀₀ Ala Gln Phe Pro Cys₁₃₀₅ Ala Arg Gly
 Gln Cys₁₃₁₀ Val Asp Leu Arg Leu₁₃₁₅ Arg Cys Asp Gly Glu₁₃₂₀ Ala Asp Cys
 Gln Asp₁₃₂₅ Arg Ser Asp Glu Ala₁₃₃₀ Asp Cys Asp Ala Ile₁₃₃₅ Cys Leu Pro
 Asn Gln₁₃₄₀ Phe Arg Cys Ala Ser₁₃₄₅ Gly Gln Cys Val Leu₁₃₅₀ Ile Lys Gln
 Gln Cys₁₃₅₅ Asp Ser Phe Pro Asp₁₃₆₀ Cys Ile Asp Gly Ser₁₃₆₅ Asp Glu Leu
 Met Cys₁₃₇₀ Glu Ile Thr Lys Pro₁₃₇₅ Pro Ser Asp Asp Ser₁₃₈₀ Pro Ala His
 Ser Ser₁₃₈₅ Ala Ile Gly Pro Val₁₃₉₀ Ile Gly Ile Ile Leu₁₃₉₅ Ser Leu Phe
 Val₁₄₀₀ Met Gly Gly Val Tyr Phe₁₄₀₅ Val Cys Gln Arg Val₁₄₁₀ Val Cys Gln
 Arg Tyr₁₄₁₅ Ala Gly Ala Asn Gly₁₄₂₀ Pro Phe Pro His Glu₁₄₂₅ Tyr Val Ser

Gly Thr Pro His Val Pro Leu Asn Phe Ile Ala Pro Gly Gly Ser
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 Gln His Gly Pro Phe Thr Gly Ile Ala Cys Gly Lys Ser Met Met
 1445 1450 1455
 Ser Ser Val Ser Leu Met Gly Gly Arg Gly Gly Val Pro Leu Tyr
 1460 1465 1470
 Asp Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser
 1475 1480 1485
 Thr Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser
 1490 1495 1500
 Pro Ala Thr Asp Pro Ser Leu Tyr Asn Met Asp Met Phe Tyr Ser
 1505 1510 1515
 Ser Asn Ile Pro Ala Thr Val Arg Pro Tyr Arg Pro Tyr Ile Ile
 1520 1525 1530
 Arg Gly Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys
 1535 1540 1545
 Asp Ser Asp Tyr Ser Ala Ser Arg Trp Lys Ala Ser Lys Tyr Tyr
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 Leu Asp Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr
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 Pro His Ser Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser
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 Leu Leu Leu Leu Ala Val Leu Leu Ala Ala His Pro Asp Ala Gln Ala
 20 25 30
 gag gtg cgc ttg tct gta ccc ccg ctg gtg gag gtg atg cga gga aag 146
 Glu Val Arg Leu Ser Val Pro Pro Leu Val Glu Val Met Arg Gly Lys
 35 40 45
 tct gtc att ctg gac tgc acc cct acg gga acc cac gac cat tat atg 194
 Ser Val Ile Leu Asp Cys Thr Pro Thr Gly Thr His Asp His Tyr Met
 50 55 60
 ctg gaa tgg ttc ctt acc gac cgc tcg gga gct cgc ccc cgc cta gcc 242

Leu	Glu 65	Trp	Phe	Leu	Thr	Asp 70	Arg	Ser	Gly	Ala	Arg 75	Pro	Arg	Leu	Ala	
tct Ser 80	gct Ala	gag Glu	atg Met	cag Gln	ggc Gly 85	tct Ser	gag Glu	ctc Leu	cag Gln	gtc Val 90	aca Thr	atg Met	cac His	gac Asp	acc Thr 95	290
cgg Arg	ggc Gly	cgc Arg	agt Ser	ccc Pro 100	cca Pro	tac Tyr	cag Gln	ctg Leu	gac Asp 105	tcc Ser	cag Gln	ggg Gly	cgc Arg	ctg Leu 110	gtg Val	338
ctg Leu	gct Ala	gag Glu	gcc Ala 115	cag Gln	gtg Val	ggc Gly	gac Asp	gag Glu 120	cga Arg	gac Asp	tac Tyr	gtg Val	tgc Cys 125	gtg Val	gtg Val	386
agg Arg	gca Ala	ggg Lys 130	gcg Ala	gca Ala	ggc Gly	act Thr	gct Ala 135	gag Glu	gcc Ala	act Thr	gcg Ala	cgg Arg 140	ctc Leu	aac Asn	gtg Val	434
ttt Phe	gca Ala 145	aag Lys	cca Pro	gag Glu	gcc Ala	act Thr 150	gag Glu	gtc Val	tcc Ser	ccc Pro	aac Asn 155	aaa Lys	ggg Gly	aca Thr	ctg Leu	482
tct Ser 160	gtg Val	atg Met	gag Glu	gac Asp	tct Ser 165	gcc Ala	cag Gln	gag Glu	atc Ile	gcc Ala 170	acc Thr	tgc Cys	aac Asn	agc Ser	cgg Arg 175	530
aac Asn	ggg Gly	aac Asn	ccg Pro	gcc Ala 180	ccc Pro	aag Lys	atc Ile	acg Thr	tgg Trp 185	tat Tyr	cgc Arg	aac Asn	ggg Gly	cag Gln 190	cgc Arg	578
ctg Leu	gag Glu	gtg Val	ccc Pro 195	gta Val	gag Glu	atg Met	aac Asn	cca Pro 200	gag Glu	ggc Gly	tac Tyr	atg Met	acc Thr 205	agc Ser	cgc Arg	626
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ctg Leu	cgg Arg 225	ctc Leu	cgc Arg	aag Lys	gat Asp	gac Asp 230	cga Arg	gac Asp	gcc Ala	agc Ser	ttc Phe 235	cac His	tgc Cys	gcc Ala	gcc Ala	722
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ttc Phe	cac His	ctc Leu	acc Thr	ctg Leu 260	cac His	tat Tyr	ccc Pro	acg Thr	gag Glu 265	cac His	gtg Val	cag Gln	ttc Phe	tgg Trp 270	gtg Val	818
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ggg Gly 320	aac Asn	ttg Leu	acc Thr	ctg Leu	gag Glu 325	gga Gly	gtg Val	acc Thr	cgg Arg	ggc Gly 330	cag Gln	agc Ser	ggg Gly	acc Thr	tat Tyr 335	1010
ggc Gly	tgc Cys	aga Arg	gtg Val	gag Glu 340	gat Asp	tac Tyr	gac Asp	gcg Ala	gca Ala 345	gat Asp	gac Asp	gtg Val	cag Gln	ctc Leu 350	tcc Ser	1058
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gag Glu	ggg Gly	aag Lys 370	gtg Val	ctt Leu	tcc Ser	tta Leu	cct Pro 375	cta Leu	aac Asn	agc Ser	agt Ser	gca Ala 380	gtc Val	gtg Val	aac Asn	1154
tgc	tcc	gtg	cac	ggc	ctg	ccc	acc	cct	gcc	cta	cgc	tgg	acc	aag	gac	1202

Cys 385	Ser	Val	His	Gly	Leu	Pro 390	Thr	Pro	Ala	Leu	Arg 395	Trp	Thr	Lys	Asp	
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ccg Pro	gtc Val	ctc Leu	agc Ser 435	cgc Arg	acc Thr	cag Gln	aac Asn	ttc Phe 440	acg Thr	ctg Leu	ctg Leu	gtc Val	caa Gln 445	ggc Gly	tcg Ser	1346
cca Pro	gag Glu	cta Leu 450	aag Lys	aca Thr	gcg Ala	gaa Glu	ata Ile 455	gag Glu	ccc Pro	aag Lys	gca Ala	gat Asp 460	ggc Gly	agc Ser	tgg Trp	1394
agg Arg	gaa Glu 465	gga Gly	gac Asp	gaa Glu	gtc Val	aca Thr 470	ctc Leu	atc Ile	tgc Cys	tct Ser	gcc Ala 475	cgc Arg	ggc Gly	cat His	cca Pro	1442
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ctc Leu 560	ctg Leu	ctc Leu	ctc Leu	gtc Val	gtt Val 565	gct Ala	gtc Val	ttc Phe	tac Tyr	tgc Cys 570	gtg Val	aga Arg	cgc Arg	aaa Lys	ggg Gly 575	1730
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cccctcacc	cgcccctggt	ccactcctg	ccccgcct	acctccgcc	caccccatca											2342
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2479

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 35 40 45
 Val Ile Leu Asp Cys Thr Pro Thr Gly Thr His Asp His Tyr Met Leu
 50 55 60
 Glu Trp Phe Leu Thr Asp Arg Ser Gly Ala Arg Pro Arg Leu Ala Ser
 65 70 75 80
 Ala Glu Met Gln Gly Ser Glu Leu Gln Val Thr Met His Asp Thr Arg
 85 90 95
 Gly Arg Ser Pro Pro Tyr Gln Leu Asp Ser Gln Gly Arg Leu Val Leu
 100 105 110
 Ala Glu Ala Gln Val Gly Asp Glu Arg Asp Tyr Val Cys Val Val Arg
 115 120 125
 Ala Gly Ala Ala Gly Thr Ala Glu Ala Thr Ala Arg Leu Asn Val Phe
 130 135 140
 Ala Lys Pro Glu Ala Thr Glu Val Ser Pro Asn Lys Gly Thr Leu Ser
 145 150 155 160
 Val Met Glu Asp Ser Ala Gln Glu Ile Ala Thr Cys Asn Ser Arg Asn
 165 170 175
 Gly Asn Pro Ala Pro Lys Ile Thr Trp Tyr Arg Asn Gly Gln Arg Leu
 180 185 190
 Glu Val Pro Val Glu Met Asn Pro Glu Gly Tyr Met Thr Ser Arg Thr
 195 200 205
 Val Arg Glu Ala Ser Gly Leu Leu Ser Leu Thr Ser Thr Leu Tyr Leu
 210 215 220
 Arg Leu Arg Lys Asp Asp Arg Asp Ala Ser Phe His Cys Ala Ala His
 225 230 235 240
 Tyr Ser Leu Pro Glu Gly Arg His Gly Arg Leu Asp Ser Pro Thr Phe
 245 250 255
 His Leu Thr Leu His Tyr Pro Thr Glu His Val Gln Phe Trp Val Gly
 260 265 270
 Ser Pro Ser Thr Pro Ala Gly Trp Val Arg Glu Gly Asp Thr Val Gln
 275 280 285

Leu Leu Cys Arg Gly Asp Gly Ser Pro Ser Pro Glu Tyr Thr Leu Phe
 290 295 300
 Arg Leu Gln Asp Glu Gln Glu Glu Val Leu Asn Val Asn Leu Glu Gly
 305 310 315 320
 Asn Leu Thr Leu Glu Gly Val Thr Arg Gly Gln Ser Gly Thr Tyr Gly
 325 330 335
 Cys Arg Val Glu Asp Tyr Asp Ala Ala Asp Asp Val Gln Leu Ser Lys
 340 345 350
 Thr Leu Glu Leu Arg Val Ala Tyr Leu Asp Pro Leu Glu Leu Ser Glu
 355 360 365
 Gly Lys Val Leu Ser Leu Pro Leu Asn Ser Ser Ala Val Val Asn Cys
 370 375 380
 Ser Val His Gly Leu Pro Thr Pro Ala Leu Arg Trp Thr Lys Asp Ser
 385 390 395 400
 Thr Pro Leu Gly Asp Gly Pro Met Leu Ser Leu Ser Ser Ile Thr Phe
 405 410 415
 Asp Ser Asn Gly Thr Tyr Val Cys Glu Ala Ser Leu Pro Thr Val Pro
 420 425 430
 Val Leu Ser Arg Thr Gln Asn Phe Thr Leu Leu Val Gln Gly Ser Pro
 435 440 445
 Glu Leu Lys Thr Ala Glu Ile Glu Pro Lys Ala Asp Gly Ser Trp Arg
 450 455 460
 Glu Gly Asp Glu Val Thr Leu Ile Cys Ser Ala Arg Gly His Pro Asp
 465 470 475 480
 Pro Lys Leu Ser Trp Ser Gln Leu Gly Gly Ser Pro Ala Glu Pro Ile
 485 490 495
 Pro Gly Arg Gln Gly Trp Val Ser Ser Ser Leu Thr Leu Lys Val Thr
 500 505 510
 Ser Ala Leu Ser Arg Asp Gly Ile Ser Cys Glu Ala Ser Asn Pro His
 515 520 525
 Gly Asn Lys Arg His Val Phe His Phe Gly Thr Val Ser Pro Gln Thr
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 565 570 575
 Pro Cys Cys Arg Gln Arg Arg Glu Lys Gly Ala Pro Pro Pro Gly Glu
 580 585 590
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Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser
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Gly Ala Gly Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr
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ggc gct gtc cag acc gag gcc atg aag cag att ctc ggg gtg atc gac 434
Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp
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Lys Lys Leu Arg Asn Leu Glu Lys Lys Gly Lys Leu Asp Asp Tyr
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Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp
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gcc gtt tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca aaa 578
Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys
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Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr
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Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu
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Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys
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Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Asp Glu Phe Tyr
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Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln
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Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys
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Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln Glu
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Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val
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Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu
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Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys
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Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys
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Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly Val Pro
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Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu
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Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu
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His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro
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Val Cys Gly Thr Thr Tyr Lys Val Leu Lys Glu Ile Val Glu Arg Val
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Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu
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Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp Gln Val
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 Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln
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 Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr
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 Met Asp Met Pro Gln Leu Val Cys Pro Pro Val His Ser Glu Ser Arg
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 Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu
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 Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Ile
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 Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly
 485 490 495
 Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro
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 Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro
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 Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln Ala Ser
 530 535 540
 Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu
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 Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser
 565 570 575
 Pro Asp Gln Ser His Gln Val Thr Gly Asn His Gln Gln Pro Pro Gln
 580 585 590

Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn Ser Arg
 595 600 605

Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly
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Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg
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Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Thr Gln Ser Gln Phe
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Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln
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Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg
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 Met Pro Gly Pro Gln Gly Gly Arg Gly Ala Ala Thr
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 Met Ser Leu Gly Lys Leu Ser Pro Val Gly Trp Val Ser Ser Ser Gln
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 Gly Lys Arg Arg Leu Thr Ala Asp Met Ile Ser His Pro Leu Gly Asp
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 Phe Arg His Thr Met His Val Gly Arg Gly Gly Asp Val Phe Gly Asp
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 Thr Ser Phe Leu Ser Asn His Gly Gly Ser Ser Gly Ser Thr His Arg
 65 70 75

tca ccc cgc agc ttc ctg gcc aag aag ctg cag ctg gtg cgg agg gtg 649
 Ser Pro Arg Ser Phe Leu Ala Lys Lys Leu Gln Leu Val Arg Arg Val
 80 85 90

ggg gcg ccc ccc cgg agg atg gca tct ccc cct gca ccc tcc ccg gct 697

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Pro	Pro	Ala	Ile	Ser	Pro	Ile	Ile	Lys	Asn	Ala	Ile	Ser	Leu	Pro	Gln	
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Leu	Asn	Gln	Ala	Ala	Tyr	Asp	Ser	Leu	Val	Val	Gly	Lys	Leu	Ser	Phe	
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Ser Asn His Gly Gly Ser Ser Gly Ser Thr His Arg Ser Pro Arg Ser
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Phe Leu Ala Lys Lys Leu Gln Leu Val Arg Arg Val Gly Ala Pro Pro
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Arg Arg Met Ala Ser Pro Pro Ala Pro Ser Pro Ala Pro Pro Ala Ile
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Ala Tyr Asp Ser Leu Val Val Gly Lys Leu Ser Phe Asp Ser Ser Pro
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Thr Ser Ser Thr Asp Gly His Ser Ser Tyr Gly Leu Asp Ser Gly Phe
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Cys Thr Ile Ser Arg Leu Pro Arg Ser Glu Lys Pro His Asp Arg Asp
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Arg Asp Gly Ser Phe Pro Ser Glu Pro Gly Leu Arg Arg Ser Asp Ser
180    185    190
Leu Leu Ser Phe Arg Leu Asp Leu Asp Leu Gly Pro Ser Leu Leu Ser
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Glu Leu Leu Gly Val Met Ser Leu Pro Glu Ala Pro Ala Ala Glu Thr
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Pro Ala Pro Ala Ala Asn Pro Pro Ala Pro Thr Ala Asn Pro Thr Gly
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 260 265 270
 Ser Thr Pro His Gly His Cys Pro Asn Gly Val Thr Ala Gly Leu Gly
 275 280 285
 Pro Val Ala Glu Val Lys Ser Ser Pro Val Gly Gly Gly Pro Arg Gly
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 Gly His His Tyr Pro Glu Met Asp Ala Arg Gln Glu Arg Val Glu Val
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 Lys Glu Pro Pro Pro Ala Val Leu Glu Ala Asp Leu Thr Glu Gly Asp
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 Arg His Met Val Phe Gln Arg Leu Gly Gln Gly Asp Tyr Val Phe Arg
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 Pro Gly Gln Pro Asp Ala Ser Ile Tyr Val Val Gln Asp Gly Leu Leu
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 Lys Ser Asp Phe Tyr Glu Ile Met Arg Ala Gln Pro Ser Val Val Leu
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Met Asp Phe Ala Ile Asp Trp Thr Ala Val Glu Ala Gly Arg Ala Leu
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 Tyr Arg Gln Gly Asp Arg Ser Asp Cys Thr Tyr Ile Val Leu Asn Gly
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 Gly Glu Tyr Gly Arg Gly Asp Leu Ile Gly Val Val Glu Ala Leu Thr
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 Thr Trp Lys Ser Asn Cys Leu Pro Leu Arg Phe Trp Val Asn Val Ile
 355 360 365
 Lys Asn Pro Gln Phe Val Phe Asp Ile His Lys Asn Ser Thr Thr Asp
 370 375 380
 Ala Cys Leu Ser Val Val Ala Gln Thr Phe Met Asp Ser Cys Ser Thr
 385 390 395 400
 Ser Glu His Lys Leu Gly Lys Asp Ser Pro Ser Asn Lys Leu Leu Tyr
 405 410 415
 Ala Lys Asp Ile Pro Asn Tyr Lys Ser Trp Val Glu Arg Tyr Tyr Ala
 420 425 430
 Asp Ile Ala Lys Met Pro Ala Ile Ser Asp Gln Asp Met Ser Ala Tyr
 435 440 445
 Leu Ala Glu Gln Ser Arg Leu His Leu Ser Gln Phe Asn Ser Met Ser
 450 455 460
 Ala Leu His Glu Ile Tyr Ser Tyr Ile Thr Lys Tyr Lys Asp Glu Ile
 465 470 475 480
 Leu Ala Ala Leu Glu Lys Asp Glu Gln Ala Arg Arg Gln Arg Leu Arg
 485 490 495

Ser Lys Leu Glu Gln Val Val Asp Thr Met Ala Leu Ser Ser
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Asp Ser Leu His Lys Ala Pro Lys Lys Lys Ser Ile Lys Ser Ser Ile
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ggc cgt ctg ttt ggc aag aaa gag aag gga cga atg gga ccc cca ggc 96
Gly Arg Leu Phe Gly Lys Lys Glu Lys Gly Arg Met Gly Pro Pro Gly
20 25 30
cgg gac agc tct tct ctg gct gga aca ccc tca gat gag aca ctg gcc 144
Arg Asp Ser Ser Ser Leu Ala Gly Thr Pro Ser Asp Glu Thr Leu Ala
35 40 45
act gac cct ctg ggg cta gcc aag ctg aca ggc cca gga gac aag gac 192
Thr Asp Pro Leu Gly Leu Ala Lys Leu Thr Gly Pro Gly Asp Lys Asp
50 55 60
cga agg aac aag agg aag cat gaa ctc ctg gag gag gcc tgc cgc cag 240
Arg Arg Asn Lys Arg Lys His Glu Leu Leu Glu Glu Ala Cys Arg Gln
65 70 75
ggc cta cct ttt gct gcc tgg gac ggg ccc acc gtg gtg tcc tgg ctg 288
Gly Leu Pro Phe Ala Trp Asp Gly Pro Thr Val Val Ser Trp Leu
85 90
gag ctg tgg gtg ggc atg cct gcc tgg tat gtg gcc gcc tgc cgg gcc 336
Glu Leu Trp Val Gly Met Pro Ala Trp Tyr Val Ala Ala Cys Arg Ala
100 105 110
aat gtc aag agc ggt gcc atc atg gcc aac ctg tca gac acg aag atc 384
Asn Val Lys Ser Gly Ala Ile Met Ala Asn Leu Ser Asp Thr Lys Ile
115 120 125
cag cgc gag atc ggc atc agc aac ccg ctg cac cga ctc aag cta cgc 432
Gln Arg Glu Ile Gly Ile Ser Asn Pro Leu His Arg Leu Lys Leu Arg
130 135 140
ctc gcc atc cag gag atg gtc tcg ctc acc tcg ccc tca gcc ccc gcc 480
Leu Ala Ile Gln Glu Met Val Ser Leu Thr Ser Pro Ser Ala Pro Ala
145 150 155 160
tcc tcc cgc act tcc aca gga aac gtg tgg atg aca cac gag gag atg 528
Ser Ser Arg Thr Ser Thr Gly Asn Val Trp Met Thr His Glu Glu Met
165 170 175
gag tcc ctt acg gcc acg acc aag ccc gag acc aag gag atc agc tgg 576
Glu Ser Leu Thr Ala Thr Thr Lys Pro Glu Thr Lys Glu Ile Ser Trp
180 185 190
gag cag atc ctg gca tat ggc gac atg aac cac gag tgg gtg ggg aac 624
Glu Gln Ile Leu Ala Tyr Gly Asp Met Asn His Glu Trp Val Gly Asn
195 200 205
gac tgg ctg ccc agc ctg ggg ctg ccc caa tac cgc agc tac ttc atg 672
Asp Trp Leu Pro Ser Leu Gly Leu Pro Gln Tyr Arg Ser Tyr Phe Met
210 215 220
gag tcg ctg gtg gac gct cga atg tta gat cac ctt aac aag aag gag 720
Glu Ser Leu Val Asp Ala Arg Met Leu Asp His Leu Asn Lys Lys Glu
225 230 235 240
ctc cgg ggc caa ctc aag atg gtg gac agc ttt cac agg gtg agt cta 768
Leu Arg Gly Gln Leu Lys Met Val Asp Ser Phe His Arg Val Ser Leu
245 250 255
cat tat gga gtt atg tgc ctg aaa cgg ctc aac tat gac cgg aag gac 816

His Tyr Gly Val Met Cys Leu Lys Arg Leu Asn Tyr Asp Arg Lys Asp	
260 265 270	
ctg gag cgg agg cgg gaa gaa agt cag acc cag atc cga gac gtg atg	864
Leu Glu Arg Arg Arg Glu Glu Ser Gln Thr Gln Ile Arg Asp Val Met	
275 280 285	
gtg tgg tcc aat gag cgg gtc atg ggt tgg gtg tcc ggg ctg ggc ctg	912
Val Trp Ser Asn Glu Arg Val Met Gly Trp Val Ser Gly Leu Gly Leu	
290 295 300	
aag gaa ttt gcc acg aac ctc acg gag agc ggg gta cac ggg gca ctg	960
Lys Glu Phe Ala Thr Asn Leu Thr Glu Ser Gly Val His Gly Ala Leu	
305 310 315 320	
ctc gcc ctg gac gag acc ttc gac tac tcc gac ctg gcc ttg ctc ctg	1008
Leu Ala Leu Asp Glu Thr Phe Asp Tyr Ser Asp Leu Ala Leu Leu Leu	
325 330 335	
cag atc ccc acg cag aat gca cag gcc cgg cag ctt ctg gag aag gaa	1056
Gln Ile Pro Thr Gln Asn Ala Gln Ala Arg Gln Leu Leu Glu Lys Glu	
340 345 350	
ttc agc aac ctt atc tcc tta ggc aca gac agg cgg ctg gac gag gac	1104
Phe Ser Asn Leu Ile Ser Leu Gly Thr Asp Arg Arg Leu Asp Glu Asp	
355 360 365	
agc gcc aag tct ttc agc cgc tcc cca tcc tgg cgg aag atg ttc cgg	1152
Ser Ala Lys Ser Phe Ser Arg Ser Pro Ser Trp Arg Lys Met Phe Arg	
370 375 380	
gag aag gac ctc cga ggc gta act ccc gac tca gct gag atg ttg ccc	1200
Glu Lys Asp Leu Arg Gly Val Thr Pro Asp Ser Ala Glu Met Leu Pro	
385 390 395 400	
ccc aac ttt cgt tcg gct gca gcg gga gcc ctg ggc tct ccg ggg ctc	1248
Pro Asn Phe Arg Ser Ala Ala Ala Gly Ala Leu Gly Ser Pro Gly Leu	
405 410 415	
cct ctc cgc aag ctg cag cca gaa ggc cag act tct ggg agt tcc cgg	1296
Pro Leu Arg Lys Leu Gln Pro Glu Gly Gln Thr Ser Gly Ser Ser Arg	
420 425 430	
gca gac ggc gtt tcg gtc cgg acc tat tcc tgc tag tgcaggcctc	1342
Ala Asp Gly Val Ser Val Arg Thr Tyr Ser Cys	
435 440	
caggtgacct cactcggacg gaagaatctt cccgaggctg ggctgttccc tctcctgccc	1402
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 Arg Asp Ser Ser Ser Leu Ala Gly Thr Pro Ser Asp Glu Thr Leu Ala
 35 40 45
 Thr Asp Pro Leu Gly Leu Ala Lys Leu Thr Gly Pro Gly Asp Lys Asp
 50 55 60
 Arg Arg Asn Lys Arg Lys His Glu Leu Leu Glu Glu Ala Cys Arg Gln
 65 70 75 80
 Gly Leu Pro Phe Ala Ala Trp Asp Gly Pro Thr Val Val Ser Trp Leu

85										90					95				
Glu	Leu	Trp	Val ₁₀₀	Gly	Met	Pro	Ala	Trp ₁₀₅	Tyr	Val	Ala	Ala	Cys ₁₁₀	Arg	Ala				
Asn	Val	Lys ₁₁₅	Ser	Gly	Ala	Ile	Met ₁₂₀	Ala	Asn	Leu	Ser	Asp ₁₂₅	Thr	Lys	Ile				
Gln	Arg ₁₃₀	Glu	Ile	Gly	Ile	Ser ₁₃₅	Asn	Pro	Leu	His	Arg ₁₄₀	Leu	Lys	Leu	Arg				
Leu ₁₄₅	Ala	Ile	Gln	Glu	Met ₁₅₀	Val	Ser	Leu	Thr	Ser ₁₅₅	Pro	Ser	Ala	Pro	Ala ₁₆₀				
Ser	Ser	Arg	Thr	Ser ₁₆₅	Thr	Gly	Asn	Val	Trp ₁₇₀	Met	Thr	His	Glu	Glu ₁₇₅	Met				
Glu	Ser	Leu	Thr ₁₈₀	Ala	Thr	Thr	Lys	Pro ₁₈₅	Glu	Thr	Lys	Glu	Ile ₁₉₀	Ser	Trp				
Glu	Gln	Ile ₁₉₅	Leu	Ala	Tyr	Gly	Asp ₂₀₀	Met	Asn	His	Glu	Trp ₂₀₅	Val	Gly	Asn				
Asp	Trp ₂₁₀	Leu	Pro	Ser	Leu	Gly ₂₁₅	Leu	Pro	Gln	Tyr	Arg ₂₂₀	Ser	Tyr	Phe	Met				
Glu ₂₂₅	Ser	Leu	Val	Asp	Ala ₂₃₀	Arg	Met	Leu	Asp	His ₂₃₅	Leu	Asn	Lys	Lys	Glu ₂₄₀				
Leu	Arg	Gly	Gln	Leu ₂₄₅	Lys	Met	Val	Asp	Ser ₂₅₀	Phe	His	Arg	Val	Ser ₂₅₅	Leu				
His	Tyr	Gly	Val ₂₆₀	Met	Cys	Leu	Lys	Arg ₂₆₅	Leu	Asn	Tyr	Asp	Arg ₂₇₀	Lys	Asp				
Leu	Glu	Arg ₂₇₅	Arg	Arg	Glu	Glu	Ser ₂₈₀	Gln	Thr	Gln	Ile	Arg ₂₈₅	Asp	Val	Met				
Val	Trp ₂₉₀	Ser	Asn	Glu	Arg	Val ₂₉₅	Met	Gly	Trp	Val	Ser ₃₀₀	Gly	Leu	Gly	Leu				
Lys ₃₀₅	Glu	Phe	Ala	Thr	Asn ₃₁₀	Leu	Thr	Glu	Ser	Gly ₃₁₅	Val	His	Gly	Ala	Leu ₃₂₀				
Leu	Ala	Leu	Asp	Glu ₃₂₅	Thr	Phe	Asp	Tyr	Ser ₃₃₀	Asp	Leu	Ala	Leu	Leu ₃₃₅	Leu				
Gln	Ile	Pro	Thr ₃₄₀	Gln	Asn	Ala	Gln	Ala ₃₄₅	Arg	Gln	Leu	Leu	Glu ₃₅₀	Lys	Glu				
Phe	Ser	Asn ₃₅₅	Leu	Ile	Ser	Leu	Gly ₃₆₀	Thr	Asp	Arg	Arg	Leu ₃₆₅	Asp	Glu	Asp				
Ser	Ala ₃₇₀	Lys	Ser	Phe	Ser	Arg ₃₇₅	Ser	Pro	Ser	Trp	Arg ₃₈₀	Lys	Met	Phe	Arg				
Glu ₃₈₅	Lys	Asp	Leu	Arg	Gly ₃₉₀	Val	Thr	Pro	Asp	Ser ₃₉₅	Ala	Glu	Met	Leu	Pro ₄₀₀				
Pro	Asn	Phe	Arg	Ser	Ala	Ala	Ala	Gly	Ala	Leu	Gly	Ser	Pro	Gly	Leu				

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410

415

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Ala Asp Gly Val Ser Val Arg Thr Tyr Ser Cys
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 Met Glu Gly Ser 5 Gly Ala Gly Glu Arg Ala Pro Leu 15 Gly
 gcg cgg cgg gcg gcg gcg gcc gcg gcg gcg gct ggg gcg ttc gcg ggc 154
 Ala Arg Arg Ala Ala Ala Ala Ala Ala Ala Ala Gly Ala Phe Ala Gly
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 cgg cgc gcg gcg tgc ggg gcc gtg ctg ctg acg gag ctg ctg gag cgc 202
 Arg Arg Ala Ala Cys Gly Ala Val Leu Leu Thr Glu Leu Leu Glu Arg
 35 40 45
 gcc gct ttc tac ggc atc acg tcc aac ctg gtg cta ttc ctg aac ggc 250
 Ala Ala Phe Tyr Gly Ile Thr Ser Asn Leu Val Leu Phe Leu Asn Gly
 50 55 60
 gcg ccg ttc tgc tgg gag ggc gcg cag gcc agc gag gcg ctg ctg ctc 298
 Ala Pro Phe Cys Trp Glu Gly Ala Gln Ala Ser Glu Ala Leu Leu Leu
 65 70 75 80
 ttc atg ggc ctc acc tac ctg ggc tcc ccg ttc gga ggc tgg ctg gcc 346
 Phe Met Gly Leu Thr Tyr Leu Gly Ser Pro Phe Gly Gly Trp Leu Ala
 85 90 95
 gac gcg cgg ctg ggc cgg gcg cgc gcc atc ctg ctg agc ctg gcg ctc 394
 Asp Ala Arg Leu 100 Gly Arg Ala Arg Ala Ile Leu Leu Ser Leu Ala Leu
 105 110
 tac ctg ctg ggc atg ctg gcc ttc ccg ctg ctg gcc gcg ccc gcc acg 442
 Tyr Leu Leu 115 Gly Met Leu Ala Phe 120 Pro Leu Leu Ala Ala Pro Ala Thr
 125
 cga gcc gcg ctc tgc ggt tcc gcg cgc ctg ctc aac tgc acg gcg cct 490
 Arg Ala Ala Leu Cys Gly Ser 135 Ala Arg Leu Leu Asn Cys Thr Ala Pro
 130 140
 ggt ccc gac gcc gcc gcc cgc tgc tgc tca ccg gcc acc ttc gcg ggg 538
 Gly Pro Asp Ala Ala Ala Arg Cys Cys Ser Pro 155 Ala Thr Phe Ala Gly
 145 150 160
 ctg gtg ctg gtg ggc ctg ggc gtg gcc acc gtc aag gcc aac atc acg 586
 Leu Val Leu Val Gly Leu Gly Val Ala Thr Val Lys Ala Asn Ile Thr
 165 170 175
 ccc ttc ggc gcc gac cag gtt aaa gat cga ggt ccg gaa gcc act agg 634
 Pro Phe Gly Ala Asp Gln Val Lys Asp Arg Gly Pro Glu Ala Thr Arg
 180 185 190
 aga ttt ttt aat tgg ttt tat tgg agc att aac ctg gga gcg atc ctg 682
 Arg Phe Phe Asn Trp Phe Tyr Trp Ser Ile Asn Leu Gly Ala Ile Leu
 195 200 205
 tcg tta ggt ggc att gcc tat att cag cag aac gtc agc ttt gtc act 730
 Ser Leu Gly Gly Ile Ala Tyr Ile Gln Gln Asn Val Ser Phe Val Thr
 210 215 220

ggt Gly 225	tat Tyr	gcg Ala	atc Ile	ccc Pro	act Thr 230	gtc Val	tgc Cys	gtc Val	ggc Gly	ctt Leu 235	gct Ala	ttt Phe	gtg Val	gtc Val	ttc Phe 240	778
ctc Leu	tgt Cys	ggc Gly	cag Gln	agc Ser 245	gtt Val	ttc Phe	atc Ile	acc Thr	aag Lys 250	cct Pro	cct Pro	gat Asp	ggc Gly	agt Ser 255	gcc Ala	826
ttc Phe	acc Thr	gac Asp	atg Met 260	ttc Phe	aag Lys	ata Ile	ctg Leu	acg Thr 265	tat Tyr	tcc Ser	tgc Cys	tgt Cys	tcc Ser 270	cag Gln	aag Lys	874
cga Arg	agt Ser	gga Gly 275	gag Glu	cgc Arg	cag Gln	agt Ser	aat Asn 280	ggt Gly	gaa Glu	ggc Gly	att Ile	gga Gly 285	gtc Val	ttt Phe	cag Gln	922
caa Gln	tct Ser 290	tct Ser	aaa Lys	caa Gln	agt Ser	ctg Leu 295	ttt Phe	gat Asp	tca Ser	tgt Cys	aag Lys 300	atg Met	tct Ser	cat His	ggt Gly	970
ggg Gly 305	cca Pro	ttt Phe	aca Thr	gaa Glu	gag Glu 310	aaa Lys	gtg Val	gaa Glu	gat Asp	gtg Val 315	aaa Lys	gct Ala	ctg Leu	gtc Val	aag Lys 320	1018
att Ile	gtc Val	cct Pro	gtt Val	ttc Phe 325	ttg Leu	gct Ala	ttg Leu	ata Ile	cct Pro 330	tac Tyr	tgg Trp	aca Thr	gtg Val	tat Tyr 335	ttc Phe	1066
caa Gln	atg Met	cag Gln	aca Thr 340	aca Thr	tat Tyr	gtt Val	tta Leu	cag Gln 345	agt Ser	ctt Leu	cat His	ttg Leu	agg Arg 350	att Ile	cca Pro	1114
gaa Glu	att Ile	tca Ser 355	aat Asn	att Ile	aca Thr	acc Thr	act Thr 360	cct Pro	cac His	acg Thr	ctc Leu	cct Pro 365	gca Ala	gcc Ala	tgg Trp	1162
ctg Leu	acc Thr 370	atg Met	ttt Phe	gat Asp	gct Ala	gtg Val 375	ctc Leu	atc Ile	ctc Leu	ctg Leu	ctc Leu 380	atc Ile	cct Pro	ctg Leu	aag Lys	1210
gac Asp 385	aaa Lys	ctg Leu	gtc Val	gat Asp	ccc Pro 390	att Ile	ttg Leu	aga Arg	aga Arg	cat His 395	ggc Gly	ctg Leu	ctc Leu	cca Pro	tcc Ser 400	1258
tcc Ser	ctg Leu	aag Lys	agg Arg	atc Ile 405	gcc Ala	gtg Val	ggc Gly	atg Met	ttc Phe 410	ttt Phe	gtc Val	atg Met	tgc Cys	tcg Ser 415	gcc Ala	1306
ttt Phe	gct Ala	gca Ala	gga Gly 420	att Ile	ttg Leu	gag Glu	agt Ser	aaa Lys 425	agg Arg	ctg Leu	aac Asn	ctt Leu	gtt Val 430	aaa Lys	gag Glu	1354
aaa Lys	acc Thr	att Ile 435	aat Asn	cag Gln	acc Thr	atc Ile	ggc Gly 440	aac Asn	gtc Val	gtc Val	tac Tyr	cat His 445	gct Ala	gcc Ala	gat Asp	1402
ctg Leu	tgc Ser 450	ctg Leu	tgg Trp	tgg Trp	cag Gln	gtg Val 455	ccg Pro	cag Gln	tac Tyr	ttg Leu	ctg Leu 460	att Ile	ggg Gly	atc Ile	agc Ser	1450
gag Glu 465	atc Ile	ttt Phe	gca Ala	agt Ser	atc Ile 470	gca Ala	ggc Gly	ctg Leu	gaa Glu	ttt Phe 475	gca Ala	tac Tyr	tca Ser	gct Ala	gcc Ala 480	1498
ccc Pro	aag Lys	tcc Ser	atg Met	cag Gln 485	agt Ser	gcc Ala	ata Ile	atg Met	ggc Gly 490	ttg Leu	ttc Phe	ttt Phe	ttc Phe	ttc Phe 495	tct Ser	1546
ggc Gly	gtc Val	ggg Gly	tgc Ser 500	ttc Phe	gtg Val	ggt Gly	tct Ser	gga Gly 505	ctg Leu	ctg Leu	gca Ala	ctg Leu	gtg Val 510	tct Ser	atc Ile	1594
aaa Lys	gcc Ala	atc Ile 515	gga Gly	tgg Trp	atg Met	agc Ser	agt Ser 520	cac His	aca Thr	gac Asp	ttt Phe	ggt Gly 525	aat Asn	att Ile	aac Asn	1642
ggc Gly	tgc Cys 530	tat Tyr	ttg Leu	aac Asn	tat Tyr	tac Tyr 535	ttt Phe	ttt Phe	ctt Leu	ctg Leu	gct Ala 540	gct Ala	att Ile	caa Gln	gga Gly	1690

gct acc ctc ctg ctt ttc ctc att att tct gtg aaa tat gac cat cat 1738
 Ala Thr Leu Leu Leu Phe Leu Ile Ile Ser Val Lys Tyr Asp His His 560
 545 550
 cga gac cat cag cga tca aga gcc aat ggc gtg ccc acc agc agg agg 1786
 Arg Asp His Gln Arg Ser Arg Ala Asn Gly Val Pro Thr Ser Arg Arg 575
 565 570
 gcc tga ccttcctgag gccatgtgcg gtttctgagg ctgacatgtc agtaactgac 1842
 Ala
 tgggggtgcac tgagaacagg caagacttta aattcccata aaatgtctga cttcactgaa 1902
 acttgcattgt tgcctggatt gatttcttct ttccctctat ccaaaggagc ttggtaagtgt 1962
 ccttactgca gcgtgtctcc tggcacgctg ggccctccgg gaggagagct gcagatttctg 2022
 agtatgtcgc ttgtcattca aggtctctgt gaatcctcta gctgggttcc cttttttaca 2082
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 aaaaaa 2807

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Arg Arg Ala Ala Cys Gly Ala Val Leu Leu Thr Glu Leu Leu Glu Arg
35 40 45

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

Ala Pro Phe Cys Trp Glu Gly Ala Gln Ala Ser Glu Ala Leu Leu Leu
65 70 75 80

Phe Met Gly Leu Thr Tyr Leu Gly Ser Pro Phe Gly Gly Trp Leu Ala
85 90 95

Asp Ala Arg Leu Gly Arg Ala Arg Ala Ile Leu Leu Ser Leu Ala Leu
100 105 110

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

Lys Thr Ile Asn Gln Thr Ile Gly Asn Val Val Tyr His Ala Ala Asp
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 Leu Ser Leu Trp Trp Gln Val Pro Gln Tyr Leu Leu Ile Gly Ile Ser
 450 455 460
 Glu Ile Phe Ala Ser Ile Ala Gly Leu Glu Phe Ala Tyr Ser Ala Ala
 465 470 475 480
 Pro Lys Ser Met Gln Ser Ala Ile Met Gly Leu Phe Phe Phe Phe Ser
 485 490 495
 Gly Val Gly Ser Phe Val Gly Ser Gly Leu Leu Ala Leu Val Ser Ile
 500 505 510
 Lys Ala Ile Gly Trp Met Ser Ser His Thr Asp Phe Gly Asn Ile Asn
 515 520 525
 Gly Cys Tyr Leu Asn Tyr Tyr Phe Phe Leu Leu Ala Ala Ile Gln Gly
 530 535 540
 Ala Thr Leu Leu Leu Phe Leu Ile Ile Ser Val Lys Tyr Asp His His
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 Arg Asp His Gln Arg Ser Arg Ala Asn Gly Val Pro Thr Ser Arg Arg
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 Ala

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 cc atg gga ggg gcc gtg gtg gac gag ggc ccc aca ggc gtc aag gcc 107
 Met Gly Gly Ala Val Val Asp Glu Gly Pro Thr Gly Val Lys Ala 15
 1 5 10
 cct gac ggc ggc tgg ggc tgg gcc gtg ctc ttc ggc tgt ttc gtc atc 155
 Pro Asp Gly Gly Trp Gly Trp Ala Val Leu Phe Gly Cys Phe Val Ile 20 25 30
 20
 act ggc ttc tcc tac gcc ttc ccc aag gcc gtc agt gtc ttc ttc aag 203
 Thr Gly Phe Ser Tyr Ala Phe Pro Lys Ala Val Ser Val Phe Phe Lys 35 40 45
 35
 gag ctc ata cag gag ttt ggg atc ggc tac agc gac aca gcc tgg atc 251
 Glu Leu Ile Gln Glu Phe Gly Ile Gly Tyr Ser Asp Thr Ala Trp Ile 50 55 60
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 tcc tcc atc ctg ctg gcc atg ctc tac ggg aca ggt ccg ctc tgc agt 299
 Ser Ser Ile Leu Leu Ala Met Leu Tyr Gly Thr Gly Pro Leu Cys Ser 65 70 75
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 gtg tgc gtg aac cgc ttt ggc tgc cgg ccc gtc atg ctt gtg ggg ggt 347
 Val Cys Val Asn Arg Phe Gly Cys Arg Pro Val Met Leu Val Gly Gly 80 85 90 95
 80
 ctc ttt gcg tcg ctg ggc atg gtg gct gcg tcc ttt tgc cgg agc atc 395
 Leu Phe Ala Ser Leu Gly Met Val Ala Ala Ser Phe Cys Arg Ser Ile 100 105 110
 100

atc Ile	cag Gln	gtc Val	tac Tyr 115	ctc Leu	acc Thr	act Thr	ggg Gly	gtc Val 120	atc Ile	acg Thr	ggg Gly	ttg Leu	ggt Gly 125	ttg Leu	gca Ala	443
ctc Leu	aac Asn	ttc Phe 130	cag Gln	ccc Pro	tcg Ser	ctc Leu	atc Ile 135	atg Met	ctg Leu	aac Asn	cgc Arg	tac Tyr 140	ttc Phe	agc Ser	aag Lys	491
cgg Arg	cgc Arg 145	ccc Pro	atg Met	gcc Ala	aac Asn	ggg Gly 150	ctg Leu	gcg Ala	gca Ala	gca Ala	ggt Gly 155	agc Ser	cct Pro	gtc Val	ttc Phe	539
ctg Leu 160	tgt Cys	gcc Ala	ctg Leu	agc Ser	ccg Pro 165	ctg Leu	ggg Gly	cag Gln	ctg Leu	ctg Leu 170	cag Gln	gac Asp	cgc Arg	tac Tyr	ggc Gly 175	587
tgg Trp	cgg Arg	ggc Gly	ggc Gly	ttc Phe 180	ctc Leu	atc Ile	ctg Leu	ggc Gly	ggc Gly 185	ctg Leu	ctg Leu	ctc Leu	aac Asn	tgc Cys 190	tgc Cys	635
gtg Val	tgt Cys	gcc Ala	gca Ala 195	ctc Leu	atg Met	agg Arg	ccc Pro	ctg Leu 200	gtg Val	gtc Val	acg Thr	gcc Ala	cag Gln 205	ccg Pro	ggc Gly	683
tcg Ser	ggg Gly	ccg Pro 210	ccg Pro	cga Arg	ccc Pro	tcc Ser	cgg Arg 215	cgc Arg	ctg Leu	cta Leu	gac Asp	ctg Leu 220	agc Ser	gtc Val	ttc Phe	731
cgg Arg	gac Asp 225	cgc Arg	ggc Gly	ttt Phe	gtg Val	ctt Leu 230	tac Tyr	gcc Ala	gtg Val	gcc Ala	gcc Ala 235	tcg Ser	gtc Val	atg Met	gtg Val	779
ctg Leu 240	ggg Gly	ctc Leu	ttc Phe	gtc Val	ccg Pro 245	ccc Pro	gtg Val	ttc Phe	gtg Val	gtg Val 250	agc Ser	tac Tyr	gcc Ala	aag Lys	gac Asp 255	827
ctg Leu	ggc Gly	gtg Val	ccc Pro	gac Asp 260	acc Thr	aag Lys	gcc Ala	gcc Ala	ttc Phe 265	ctg Leu	ctc Leu	acc Thr	atc Ile	ctg Leu 270	ggc Gly	875
ttc Phe	att Ile	gac Asp	atc Ile 275	ttc Phe	gcg Ala	cgg Arg	ccg Pro	gcc Ala 280	gcg Ala	ggc Gly	ttc Phe	gtg Val	gcg Ala 285	ggg Gly	ctt Leu	923
ggg Gly	aag Lys	gtg Val 290	cgg Arg	ccc Pro	tac Tyr	tcc Ser	gtc Val 295	tac Tyr	ctc Leu	ttc Phe	agc Ser	ttc Phe 300	tcc Ser	atg Met	ttc Phe	971
ttc Phe	aac Asn 305	ggc Gly	ctc Leu	gcg Ala	gac Asp	ctg Leu 310	gcg Ala	ggc Gly	tct Ser	acg Thr	gcg Ala 315	ggc Gly	gac Asp	tac Tyr	ggc Gly	1019
ggc Gly 320	ctc Leu	gtg Val	gtc Val	ttc Phe	tgc Cys 325	atc Ile	ttc Phe	ttt Phe	ggc Gly	atc Ile 330	tcc Ser	tac Tyr	ggc Gly	atg Met	gtg Val 335	1067
ggg Gly	gcc Ala	ctg Leu	cag Gln	ttc Phe 340	gag Glu	gtg Val	ctc Leu	atg Met	gcc Ala 345	atc Ile	gtg Val	ggc Gly	acc Thr	cac His 350	aag Lys	1115
ttc Phe	tcc Ser	agt Ser	gcc Ala 355	att Ile	ggc Gly	ctg Leu	gtg Val	ctg Leu 360	ctg Leu	atg Met	gag Glu	gcg Ala	gtg Val 365	gcc Ala	gtg Val	1163
ctc Leu	gtc Val	ggg Gly 370	ccc Pro	cct Pro	tcg Ser	gga Gly	ggc Gly 375	aaa Lys	ctc Leu	ctg Leu	gat Asp	gcg Ala 380	acc Thr	cac His	gtc Val	1211
tac Tyr	atg Met 385	tac Tyr	gtg Val	ttc Phe	atc Ile	ctg Leu 390	gcg Ala	ggg Gly	gcc Ala	gag Glu	gtg Val 395	ctc Leu	acc Thr	tcc Ser	tcc Ser	1259
ctg Leu 400	att Ile	ttg Leu	ctg Leu	ctg Leu	ggc Gly 405	aac Asn	ttc Phe	ttc Phe	tgc Cys	att Ile 410	agg Arg	aag Lys	aag Lys	ccc Pro	aaa Lys 415	1307
gag Glu	cca Pro	cag Gln	cct Pro	gag Glu 420	gtg Val	gcg Ala	gcc Ala	gcg Ala	gag Glu 425	gag Glu	gag Glu	aag Lys	ctc Leu	cac His 430	aag Lys	1355

cct cct gca gac tcg ggg gtg gac ttg cgg gag gtg gag cat ttc ctg 1403
 Pro Pro Ala Asp Ser Gly Val Asp Leu Arg Glu Val Glu His Phe Leu 445
 aag gct gag cct gag aaa aac ggg gag gtg gtt cac acc ccg gaa aca 1451
 Lys Ala Glu Pro Glu Lys Asn Gly Glu Val Val His Thr Pro Glu Thr 460
 agt gtc tga gtggctgggc ggggccggca ggcacaggga ggaggtacag 1500
 Ser Val 465
 aagccggcaa cgcttgctat ttattttaca aactggactg gctcaggcag ggccacggct 1560
 gggctccagc tgccggccca gcggatcgtc gcccgatcag tgttttgagg gggaaggtgg 1620
 cggggtggga accgtgtcat tccagagtgg atctgcggtg aagccaagcc gcaaggttac 1680
 aaggcatcct caccaggggc cccgcctgct gctcccaggt ggcctgcggc cactgctatg 1740
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 ggctcacatg gggcctgtgc ccacccctct tgagtgtctt ggggacagct ctttccaccc 1920
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 tt 1982

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 35 40 45
 Leu Ile Gln Glu Phe Gly Ile Gly Tyr Ser Asp Thr Ala Trp Ile Ser
 50 55 60
 Ser Ile Leu Leu Ala Met Leu Tyr Gly Thr Gly Pro Leu Cys Ser Val
 65 70 75 80
 Cys Val Asn Arg Phe Gly Cys Arg Pro Val Met Leu Val Gly Gly Leu
 85 90 95
 Phe Ala Ser Leu Gly Met Val Ala Ala Ser Phe Cys Arg Ser Ile Ile
 100 105 110
 Gln Val Tyr Leu Thr Thr Gly Val Ile Thr Gly Leu Gly Leu Ala Leu
 115 120 125
 Asn Phe Gln Pro Ser Leu Ile Met Leu Asn Arg Tyr Phe Ser Lys Arg
 130 135 140
 Arg Pro Met Ala Asn Gly Leu Ala Ala Ala Gly Ser Pro Val Phe Leu
 145 150 155 160
 Cys Ala Leu Ser Pro Leu Gly Gln Leu Leu Gln Asp Arg Tyr Gly Trp
 165 170 175

Arg Gly Gly Phe₁₈₀ Leu Ile Leu Gly Gly₁₈₅ Leu Leu Leu Asn Cys₁₉₀ Cys Val
 Cys Ala Ala₁₉₅ Leu Met Arg Pro Leu₂₀₀ Val Val Thr Ala Gln₂₀₅ Pro Gly Ser
 Gly Pro₂₁₀ Pro Arg Pro Ser Arg₂₁₅ Arg Leu Leu Asp Leu₂₂₀ Ser Val Phe Arg
 Asp₂₂₅ Arg Gly Phe Val Leu₂₃₀ Tyr Ala Val Ala Ala₂₃₅ Ser Val Met Val Leu₂₄₀
 Gly Leu Phe Val Pro₂₄₅ Pro Val Phe Val Val₂₅₀ Ser Tyr Ala Lys Asp₂₅₅ Leu
 Gly Val Pro Asp₂₆₀ Thr Lys Ala Ala Phe₂₆₅ Leu Leu Thr Ile Leu₂₇₀ Gly Phe
 Ile Asp Ile₂₇₅ Phe Ala Arg Pro Ala₂₈₀ Ala Gly Phe Val Ala₂₈₅ Gly Leu Gly
 Lys Val₂₉₀ Arg Pro Tyr Ser Val₂₉₅ Tyr Leu Phe Ser Phe₃₀₀ Ser Met Phe Phe
 Asn Gly Leu Ala Asp Leu₃₁₀ Ala Gly Ser Thr Ala₃₁₅ Gly Asp Tyr Gly Gly₃₂₀
 Leu Val Val Phe Cys₃₂₅ Ile Phe Phe Gly Ile₃₃₀ Ser Tyr Gly Met Val₃₃₅ Gly
 Ala Leu Gln Phe₃₄₀ Glu Val Leu Met Ala₃₄₅ Ile Val Gly Thr His₃₅₀ Lys Phe
 Ser Ser Ala₃₅₅ Ile Gly Leu Val Leu₃₆₀ Leu Met Glu Ala Val₃₆₅ Ala Val Leu
 Val Gly Pro Pro Ser Gly Gly₃₇₅ Lys Leu Leu Asp Ala₃₈₀ Thr His Val Tyr
 Met₃₈₅ Tyr Val Phe Ile Leu₃₉₀ Ala Gly Ala Glu Val₃₉₅ Leu Thr Ser Ser Leu₄₀₀
 Ile Leu Leu Leu Gly₄₀₅ Asn Phe Phe Cys Ile₄₁₀ Arg Lys Lys Pro Lys₄₁₅ Glu
 Pro Gln Pro Glu₄₂₀ Val Ala Ala Ala Glu₄₂₅ Glu Glu Lys Leu His₄₃₀ Lys Pro
 Pro Ala Asp₄₃₅ Ser Gly Val Asp Leu₄₄₀ Arg Glu Val Glu His₄₄₅ Phe Leu Lys
 Ala Glu₄₅₀ Pro Glu Lys Asn Gly₄₅₅ Glu Val Val His Thr₄₆₀ Pro Glu Thr Ser
 Val₄₆₅

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<213> Homo sapiens

<220>

<221> CDS

<222> (591)..(2216)

<223>

<400> 67

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 ttctggcatc ccagccctca gtgtccaaga ccagggcagc ccgggtcccc gcctcccgga 180
 tccaggcgtc cgggatctgc gccaccagaa cctagcctcc tgcagacctc cgccatctgg 240
 gggcactcaa cctcctggag ccaagggccc cacgtcccac ccagagaaac tctcgtattc 300
 ccagctccta gggccaagga acccgggagc tccgaactcc cagctttcgg acatctggca 360
 cacggggcag agcagagaag ctacagcggc agcctgggga atttaaacac tccagcttcc 420
 aagagccaag gaacttcagt gctgtgaact cacaactcta aggagccctc caaagttcca 480
 gtctccaggt gctgttactc aactcagtc taggaacgtc gggtcctggg aaggagccca 540
 agcgctcca gccagcttcc aggcgctaag aaaccccggt gcttcccatc atg gtg 596
 Met Val
 1

gcc gat cct cct cga gac tcc aag ggg ctc gca gcg gcg gag ccc acc 644
 Ala Asp Pro Pro Arg Asp Ser Lys Gly Leu Ala Ala Ala Glu Pro Thr
 5 10 15

gcc aac ggg ggc ctg gcg ctg gcc tcc atc gag gac caa ggc gcg gca 692
 Ala Asn Gly Gly Leu Ala Leu Ala Ser Ile Glu Asp Gln Gly Ala Ala
 20 25 30

gca ggc ggc tac tgc ggt tcc cgg gac cag gtg cgc cgc tgc ctt cga 740
 Ala Gly Gly Tyr Cys Gly Ser Arg Asp Gln Val Arg Arg Cys Leu Arg
 35 40 45 50

gcc aac ctg ctt gtg ctg ctg aca gtg gtg gcc gtg gtg gcc ggc gtg 788
 Ala Asn Leu Leu Val Leu Leu Thr Val Val Ala Val Val Ala Gly Val
 55 60 65

gcg ctg gga ctg ggg gtg tcg ggg gcc ggg ggt gcg ctg gcg ttg ggc 836
 Ala Leu Gly Leu Gly Val Ser Gly Ala Gly Gly Ala Leu Ala Leu Gly
 70 75 80

ccg gag cgc ttg agc gcc ttc gtc ttc ccg ggc gag ctg ctg ctg cgt 884
 Pro Glu Arg Leu Ser Ala Phe Val Phe Pro Gly Glu Leu Leu Leu Arg
 85 90 95

ctg ctg cgg atg atc atc ttg ccg ctg gtg gtg tgc agc ttg atc ggc 932
 Leu Leu Arg Met Ile Ile Leu Pro Leu Val Val Cys Ser Leu Ile Gly
 100 105 110

ggc gcc gcc agc ctg gac ccc ggc gcg ctc ggc cgt ctg ggc gcc tgg 980
 Gly Ala Ala Ser Leu Asp Pro Gly Ala Leu Gly Arg Leu Gly Ala Trp
 115 120 125 130

gcg ctg ctc ttt ttc ctg gtc acc acg ctg ctg gcg tcg gcg ctc gga 1028
 Ala Leu Leu Phe Phe Leu Val Thr Thr Leu Leu Ala Ser Ala Leu Gly
 135 140 145

gtg ggc ttg gcg ctg gct ctg cag ccg ggc gcc gcc tcc gcc gcc atc 1076
 Val Gly Leu Ala Leu Ala Leu Gln Pro Gly Ala Ala Ser Ala Ala Ile
 150 155 160

aac gcc tcc gtg gga gcc gcg ggc agt gcc gaa aat gcc ccc agc aag 1124
 Asn Ala Ser Val Gly Ala Ala Gly Ser Ala Glu Asn Ala Pro Ser Lys
 165 170 175

gag gtg ctc gat tcg ttc ctg gat ctt gcg aga aat atc ttc cct tcc 1172
 Glu Val Leu Asp Ser Phe Leu Asp Leu Ala Arg Asn Ile Phe Pro Ser
 180 185 190

aac ctg gtg tca gca gcc ttt cgc tca tac tct acc acc tat gaa gag 1220
 Asn Leu Val Ser Ala Ala Phe Arg Ser Tyr Ser Thr Thr Tyr Glu Glu

195					200					205					210	
agg Arg	aat Asn	atc Ile	acc Thr	gga Gly 215	acc Thr	agg Arg	gtg Val	aag Lys	gtg Val 220	ccc Pro	gtg Val	ggg Gly	cag Gln	gag Glu 225	gtg Val	1268
gag Glu	ggg Gly	atg Met	aac Asn 230	atc Ile	ctg Leu	ggc Gly	ttg Leu	gta Val 235	gtg Val	ttt Phe	gcc Ala	atc Ile	gtc Val 240	ttt Phe	ggg Gly	1316
gtg Val	gcg Ala	ctg Leu 245	cgg Arg	aag Lys	ctg Leu	ggg Gly	cct Pro 250	gaa Glu	ggg Gly	gag Glu	ctg Leu	ctt Leu 255	atc Ile	cgc Arg	ttc Phe	1364
ttc Phe	aac Asn 260	tcc Ser	ttc Phe	aat Asn	gag Glu	gcc Ala 265	acc Thr	atg Met	gtt Val	ctg Leu	gtc Val 270	tcc Ser	tgg Trp	atc Ile	atg Met	1412
tgg Trp 275	tac Tyr	gcc Ala	cct Pro	gtg Val	ggc Gly 280	atc Ile	atg Met	ttc Phe	ctg Leu	gtg Val 285	gct Ala	ggc Gly	aag Lys	atc Ile	gtg Val 290	1460
gag Glu	atg Met	gag Glu	gat Asp	gtg Val 295	ggg Gly	tta Leu	ctc Leu	ttt Phe	gcc Ala 300	cgc Arg	ctt Leu	ggc Gly	aag Lys	tac Tyr 305	att Ile	1508
ctg Leu	tgc Cys	tgc Cys	ctg Leu 310	ctg Leu	ggg Gly	cac His	gcc Ala	atc Ile 315	cat His	ggg Gly	ctc Leu	ctg Leu	gta Val 320	ctg Leu	ccc Pro	1556
ctc Leu	atc Ile	tac Tyr 325	ttc Phe	ctc Leu	ttc Phe	acc Thr	cgc Arg 330	aaa Lys	aac Asn	ccc Pro	tac Tyr	cgc Arg 335	ttc Phe	ctg Leu	tgg Trp	1604
ggc Gly	atc Ile 340	gtg Val	acg Thr	ccg Pro	ctg Leu	gcc Ala 345	act Thr	gcc Ala	ttt Phe	ggg Gly	acc Thr 350	tct Ser	tcc Ser	agt Ser	tcc Ser	1652
gcc Ala 355	acg Thr	ctg Leu	ccg Pro	ctg Leu	atg Met 360	atg Met	aag Lys	tgc Cys	gtg Val	gag Glu 365	gag Glu	aat Asn	aat Asn	ggc Gly	gtg Val 370	1700
gcc Ala	aag Lys	cac His	atc Ile	agc Ser 375	cgt Arg	ttc Phe	atc Ile	ctg Leu	ccc Pro 380	atc Ile	ggc Gly	gcc Ala	acc Thr	gtc Val 385	aac Asn	1748
atg Met	gac Asp	ggg Gly	gcc Ala 390	gcg Ala	ctc Leu	ttc Phe	cag Gln	tgc Cys 395	gtg Val	gcc Ala	gca Ala	gtg Val	ttc Phe 400	att Ile	gca Ala	1796
cag Gln	ctc Leu	agc Ser 405	cag Gln	cag Gln	tcc Ser	ttg Leu	gac Asp 410	ttc Phe	gta Val	aag Lys	atc Ile	atc Ile 415	acc Thr	atc Ile	ctg Leu	1844
gtc Val	acg Thr 420	gcc Ala	aca Thr	gcg Ala	tcc Ser	agc Ser 425	gtg Val	ggg Gly	gca Ala	gca Ala	ggc Gly 430	atc Ile	cct Pro	gct Ala	gga Gly	1892
ggg Gly 435	gtc Val	ctc Leu	act Thr	ctg Leu	gcc Ala 440	atc Ile	atc Ile	ctc Leu	gaa Glu	gca Ala 445	gtc Val	aac Asn	ctc Leu	ccg Pro	gtc Val 450	1940
gac Asp	cat His	atc Ile	tcc Ser	ttg Leu 455	atc Ile	ctg Leu	gct Ala	gtg Val	gac Asp 460	tgg Trp	cta Leu	gtc Val	gac Asp	cgg Arg 465	tcc Ser	1988
tgt Cys	acc Thr	gtc Val	ctc Leu 470	aat Asn	gta Val	gaa Glu	ggg Gly	gac Asp 475	gct Ala	ctg Leu	ggg Gly	gca Ala	gga Gly 480	ctc Leu	ctc Leu	2036
caa Gln	aat Asn	tat Tyr 485	gtg Val	gac Asp	cgt Arg	acg Thr	gag Glu 490	tcg Ser	aga Arg	agc Ser	aca Thr	gag Glu 495	cct Pro	gag Glu	ttg Leu	2084
ata Ile	caa Gln 500	gtg Val	aag Lys	agt Ser	gag Glu	ctg Leu 505	ccc Pro	ctg Leu	gat Asp	ccg Pro	ctg Leu 510	cca Pro	gtc Val	ccc Pro	act Thr	2132
gag Glu	gaa Glu	gga Gly	aac Asn	ccc Pro	ctc Leu	ctc Leu	aaa Lys	cac His	tat Tyr	cgg Arg	ggg Gly	ccc Pro	gca Ala	ggg Gly	gat Asp	2180

515	520	525	530	
gcc acg gtc gcc tct gag aag gaa tca gtc atg taa accccgggag				2226
Ala Thr Val Ala Ser Glu Lys Glu Ser Val Met				
ggaccttccc tgccctgctg ggggtgctct ttggacactg gattatgagg aatggataaa				2286
tggatgagct agggctctgg ggggtctgcct gcacactctg gggagccagg ggccccagca				2346
ccctccagga caggagatct gggatgcctg gctgctggag tacatgtgtt cacaaggggtt				2406
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tggagaaata atgttctgct gcgtccccac cgtgacctgc ctggcctccc ctgtctcagg				2526
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<400> 68

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

Leu Arg Ala Asn Leu Leu Val Leu Leu Thr Val Val Ala Val Val Ala
 50 55 60

Gly Val Ala Leu Gly Leu Gly Val Ser Gly Ala Gly Gly Ala Leu Ala
 65 70 75 80

Leu Gly Pro Glu Arg Leu Ser Ala Phe Val Phe Pro Gly Glu Leu Leu
 85 90 95

Leu Arg Leu Leu Arg Met Ile Ile Leu Pro Leu Val Val Cys Ser Leu
 100 105 110

Ile Gly Gly Ala Ala Ser Leu Asp Pro Gly Ala Leu Gly Arg Leu Gly
 115 120 125

Ala Trp Ala Leu Leu Phe Phe Leu Val Thr Thr Leu Leu Ala Ser Ala
 130 135 140

Leu Gly Val Gly Leu Ala Leu Ala Leu Gln Pro Gly Ala Ala Ser Ala
 145 150 155 160

Ala Ile Asn Ala Ser Val Gly Ala Ala Gly Ser Ala Glu Asn Ala Pro
 165 170 175

Ser Lys Glu Val₁₈₀ Leu Asp Ser Phe Leu₁₈₅ Asp Leu Ala Arg Asn Ile Phe
 Pro Ser Asn₁₉₅ Leu Val Ser Ala Ala₂₀₀ Phe Arg Ser Tyr Ser₂₀₅ Thr Thr Tyr
 Glu Glu₂₁₀ Arg Asn Ile Thr Gly₂₁₅ Thr Arg Val Lys Val₂₂₀ Pro Val Gly Gln
 Glu Val₂₂₅ Glu Gly Met Asn₂₃₀ Ile Leu Gly Leu Val₂₃₅ Val Phe Ala Ile Val₂₄₀
 Phe Gly Val Ala Leu₂₄₅ Arg Lys Leu Gly Pro₂₅₀ Glu Gly Glu Leu Leu₂₅₅ Ile
 Arg Phe Phe Asn₂₆₀ Ser Phe Asn Glu Ala₂₆₅ Thr Met Val Leu Val₂₇₀ Ser Trp
 Ile Met Trp₂₇₅ Tyr Ala Pro Val Gly₂₈₀ Ile Met Phe Leu Val₂₈₅ Ala Gly Lys
 Ile Val₂₉₀ Glu Met Glu Asp Val₂₉₅ Gly Leu Leu Phe Ala₃₀₀ Arg Leu Gly Lys
 Tyr Ile₃₀₅ Leu Cys Cys Leu₃₁₀ Leu Gly His Ala Ile₃₁₅ His Gly Leu Leu Val₃₂₀
 Leu Pro Leu Ile Tyr₃₂₅ Phe Leu Phe Thr Arg₃₃₀ Lys Asn Pro Tyr Arg₃₃₅ Phe
 Leu Trp Gly Ile₃₄₀ Val Thr Pro Leu Ala₃₄₅ Thr Ala Phe Gly Thr₃₅₀ Ser Ser
 Ser Ser Ala₃₅₅ Thr Leu Pro Leu Met₃₆₀ Met Lys Cys Val Glu₃₆₅ Glu Asn Asn
 Gly Val₃₇₀ Ala Lys His Ile Ser₃₇₅ Arg Phe Ile Leu Pro₃₈₀ Ile Gly Ala Thr
 Val₃₈₅ Asn Met Asp Gly Ala₃₉₀ Ala Leu Phe Gln Cys₃₉₅ Val Ala Ala Val Phe₄₀₀
 Ile Ala Gln Leu Ser₄₀₅ Gln Gln Ser Leu Asp₄₁₀ Phe Val Lys Ile Ile₄₁₅ Thr
 Ile Leu Val Thr₄₂₀ Ala Thr Ala Ser Ser₄₂₅ Val Gly Ala Ala Gly₄₃₀ Ile Pro
 Ala Gly Gly₄₃₅ Val Leu Thr Leu Ala₄₄₀ Ile Ile Leu Glu Ala₄₄₅ Val Asn Leu
 Pro Val₄₅₀ Asp His Ile Ser Leu₄₅₅ Ile Leu Ala Val Asp₄₆₀ Trp Leu Val Asp
 Arg Ser Cys Thr Val Leu₄₇₀ Asn Val Glu Gly Asp₄₇₅ Ala Leu Gly Ala Gly₄₈₀
 Leu Leu Gln Asn Tyr₄₈₅ Val Asp Arg Thr Glu₄₉₀ Ser Arg Ser Thr Glu₄₉₅ Pro

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

Gly Asp Ala Thr Val Ala Ser Glu Lys Glu Ser Val Met
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gcagcccccg acctcccggg ctcaggtgat tctccgcct cagcaccgag agcagctagg 180
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aagctccggg aaaccctgag cagccagggt gcctgctccg cccgctcccg ctcccgatct 360
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gcagtcgggtc gtgggtctga gagtactgg agctaccaga agcatc atg ggg ccc 475
Met Gly Pro
1
tgg gga gag cca gag ctc ctg gtg tgg cgc ccc gag gcg gta gct tca 523
Trp Gly Glu Pro Glu Leu Leu Val Trp Arg Pro Glu Ala Val Ala Ser
5 10 15
gag cct cca gtg cct gtg ggg ctg gag gtg aag ttg ggg gcc ctg gtg 571
Glu Pro Pro Val Pro Val Gly Leu Glu Val Lys Leu Gly Ala Leu Val
20 25 30 35
ctg ctg ctg gtg ctc acc ctc ctc tgc agc ctg gtg ccc atc tgt gtg 619
Leu Leu Leu Val Leu Thr Leu Leu Cys Ser Leu Val Pro Ile Cys Val
40 45 50
ctg cgc cgg cca gga gct aac cat gaa ggc tca gct tcc cgc cag aaa 667
Leu Arg Arg Pro Gly Ala Asn His Glu Gly Ser Ala Ser Arg Gln Lys
55 60 65
gcc ctg agc cta gta agc tgt ttc gcg ggg ggc gtc ttt ttg gcc act 715
Ala Leu Ser Leu Val Ser Cys Phe Ala Gly Gly Val Phe Leu Ala Thr
70 75 80
tgt ctc ctg gac ctg ctg cct gac tac ctg gct gcc ata gat gag gcc 763
Cys Leu Leu Asp Leu Leu Pro Asp Tyr Leu Ala Ala Ile Asp Glu Ala
85 90 95
ctg gca gcc ttg cac gtg acg ctc cag ttc cca ctg caa gag ttc atc 811
Leu Ala Ala Leu His Val Thr Leu Gln Phe Pro Leu Gln Glu Phe Ile
100 105 110 115
ctg gcc atg ggc ttc ttc ctg gtc ctg gtg atg gag cag atc aca ctg 859
Leu Ala Met Gly Phe Phe Leu Val Leu Val Met Glu Gln Ile Thr Leu
120 125 130
gct tac aag gag cag tca ggg ccg tca cct ctg gag gaa aca agg gct 907
Ala Tyr Lys Glu Gln Ser Gly Pro Ser Pro Leu Glu Glu Thr Arg Ala
135 140 145
ctg ctg gga aca gtg aat ggt ggg ccg cag cat tgg cat gat ggg cca 955
Leu Leu Gly Thr Val Asn Gly Gly Pro Gln His Trp His Asp Gly Pro
150 155 160

ggg gtc cca cag gcg agt gga gcc cca gca acc ccc tca gcc ttg cgt Gly Val Pro Gln Ala Ser Gly Ala Pro Ala Thr Pro Ser Ala Leu Arg 165 170 175	1003
gcc tgt gta ctg gtg ttc tcc ctg gcc ctc cac tcc gtg ttc gag ggg Ala Cys Val Leu Val Phe Ser Leu Ala Leu His Ser Val Phe Glu Gly 180 185 190 195	1051
ctg gcg gta ggg ctg cag cga gac cgg gct cgg gcc atg gag ctg tgc Leu Ala Val Gly Leu Gln Arg Asp Arg Ala Arg Ala Met Glu Leu Cys 200 205 210	1099
ctg gct ttg ctg ctc cac aag ggc atc ctg gct gtc agc ctg tcc ctg Leu Ala Leu Leu Leu His Lys Gly Ile Leu Ala Val Ser Leu Ser Leu 215 220 225	1147
cgg ctg ttg cag agc cac ctt agg gca cag gtg gtg gct ggc tgt ggg Arg Leu Leu Gln Ser His Leu Arg Ala Gln Val Val Ala Gly Cys Gly 230 235 240	1195
atc ctc ttc tca tgc atg aca cct cta ggc atc ggg ctg ggt gca gct Ile Leu Phe Ser Ser Cys Met Thr Pro Leu Gly Ile Gly Leu Gly Ala Ala 245 250 255	1243
ctg gca gag tcg gca gga cct ctg cac cag ctg gcc cag tct gtg cta Leu Ala Glu Ser Ala Gly Pro Leu His Gln Leu Ala Gln Ser Val Leu 260 265 270 275	1291
gag ggc atg gca gct ggc acc ttt ctc tat atc acc ttt ctg gaa atc Glu Gly Met Ala Ala Gly Thr Phe Leu Tyr Ile Thr Phe Leu Glu Ile 280 285 290	1339
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tcccttccct cccccagttg tggggaatag gaaggaaagg ggaagggaaa tactgaggac	1551
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caccctgcc cttggagtg acccctccta ctcttcttag cgcctaccct catacctatc	1911
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tcttctctgg cctctccagt cctgcttact cctctatctt taaagtgcc aacaaatccc	2031
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ggacatggac atggtgtccc atgcccagat gataaacact gagctgccaa aacatttttt	2271
taaatacacc cgaggagccc aagggggaag ggcaatgcct acccccagcg ttatttttgg	2331
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<212> PRT	

<213> Homo sapiens

<400> 70

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 Ala Leu Val Leu Leu Leu Val Leu Thr Leu Leu Cys Ser Leu Val Pro
 35 40 45
 Ile Cys Val Leu Arg Arg Pro Gly Ala Asn His Glu Gly Ser Ala Ser
 50 55 60
 Arg Gln Lys Ala Leu Ser Leu Val Ser Cys Phe Ala Gly Gly Val Phe
 65 70 75 80
 Leu Ala Thr Cys Leu Leu Asp Leu Leu Pro Asp Tyr Leu Ala Ala Ile
 85 90 95
 Asp Glu Ala Leu Ala Ala Leu His Val Thr Leu Gln Phe Pro Leu Gln
 100 105 110
 Glu Phe Ile Leu Ala Met Gly Phe Phe Leu Val Leu Val Met Glu Gln
 115 120 125
 Ile Thr Leu Ala Tyr Lys Glu Gln Ser Gly Pro Ser Pro Leu Glu Glu
 130 135 140
 Thr Arg Ala Leu Leu Gly Thr Val Asn Gly Gly Pro Gln His Trp His
 145 150 155 160
 Asp Gly Pro Gly Val Pro Gln Ala Ser Gly Ala Pro Ala Thr Pro Ser
 165 170 175
 Ala Leu Arg Ala Cys Val Leu Val Phe Ser Leu Ala Leu His Ser Val
 180 185 190
 Phe Glu Gly Leu Ala Val Gly Leu Gln Arg Asp Arg Ala Arg Ala Met
 195 200 205
 Glu Leu Cys Leu Ala Leu Leu Leu His Lys Gly Ile Leu Ala Val Ser
 210 215 220
 Leu Ser Leu Arg Leu Leu Gln Ser His Leu Arg Ala Gln Val Val Ala
 225 230 235 240
 Gly Cys Gly Ile Leu Phe Ser Cys Met Thr Pro Leu Gly Ile Gly Leu
 245 250 255
 Gly Ala Ala Leu Ala Glu Ser Ala Gly Pro Leu His Gln Leu Ala Gln
 260 265 270
 Ser Val Leu Glu Gly Met Ala Ala Gly Thr Phe Leu Tyr Ile Thr Phe
 275 280 285
 Leu Glu Ile Leu Pro Gln Glu Leu Ala Ser Ser Glu Gln Arg Ile Leu
 290 295 300

Lys Val Ile Leu Leu Leu Ala Gly Phe Ala Leu Leu Thr Gly Leu Leu
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Phe Ile Gln Ile

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<212> DNA
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<223>

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<222> (1358)..(1358)
<223> n = any nucleotide

<220>
<221> misc_feature
<222> (1358)..(1358)
<223> n = a, t, c, or g

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ccacactgaa ggtccggaaa ggcgacttcc gggggctttg gcacctggcg gaccctcccg 180
gagcgctcggc acctgaacgc gaggcgctcc attgcgcgtg cgcgttgagg ggcttccgc 240
acctgatcgc gagaccccaa cggctggtgg cgtcgcctgc gcgtctcggc tgagctggcc 300
atg gcg cag ctg tgc ggg ctg agg cgg agc cgg gcg ttt ctc gcc ctg 348
Met Ala Gln Leu Cys Gly Leu Arg Arg Ser Arg Ala Phe Leu Ala Leu
1 5 10 15
ctg gga tcg ctg ctc ctc tct ggg gtc ctg gcg gcc gac cga gaa cgc 396
Leu Gly Ser Leu Leu Ser Gly Val Leu Ala Ala Asp Arg Glu Arg
20 25 30
agc atc cac gac ttc tgc ctg gtg tcg aag gtg gtg ggc aga tgc cgg 444
Ser Ile His Asp Phe Cys Leu Val Ser Lys Val Val Gly Arg Cys Arg
35 40 45
gcc tcc atg cct agg tgg tgg tac aat gtc act gac gga tcc tgc cag 492
Ala Ser Met Pro Arg Trp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln
50 55 60
ctg ttt gtg tat ggg ggc tgt gac gga aac agc aat aat tac ctg acc 540
Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr
65 70 75 80
aag gag gag tgc ctc aag aaa tgt gcc act gtc aca gag aat gcc acg 588
Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr
85 90 95
ggt gac ctg gcc acc agc agg aat gca gcg gat tcc tct gtc cca agt 636
Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser
100 105 110
gct ccc aga agg cag gat tct gaa gac cac tcc agc gat atg ttc aac 684
Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser Ser Asp Met Phe Asn
115 120 125
tat gaa gaa tac tgc acc gcc aac gca gtc act ggg cct tgc cgt gca 732
Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala
130 135 140
tcc ttc cca cgc tgg tac ttt gac gtg gag agg aac tcc tgc aat aac 780
Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn
145 150 155 160

ttc atc tat gga ggc tgc cgg ggc aat aag aac agc tac cgc tct gag 828
 Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn Ser Tyr Arg Ser Ser Glu
 165 170 175
 gag gcc tgc atg ctc cgc tgc ttc cgc cag cag gag aat cct ccc ctg 876
 Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu
 180 185 190
 ccc ctt ggc tca aag gtg gtg gtt ctg gcg ggg ctg ttc gtg atg gtg 924
 Pro Leu Gly Ser Lys Val Val Val Leu Ala Gly Leu Phe Val Met Val
 195 200 205
 ttg atc ctc ttc ctg gga gcc tcc atg gtc tac ctg atc cgg gtg gca 972
 Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr Leu Ile Arg Val Ala
 210 215 220
 cgg agg aac cag gag cgt gcc ctg cgc acc gtc tgg agc tcc gga gat 1020
 Arg Arg Asn Gln Glu Arg Ala Leu Arg Thr Val Trp Ser Ser Gly Asp
 225 230 235 240
 gac aag gag cag ctg gtg aag aac aca tat gtc ctg tga ccgccctgtc 1069
 Asp Lys Glu Gln Leu Val Lys Asn Thr Tyr Val Leu
 245 250
 gccaaaggagga ctggggaagg gaggggagac tatgtgtgag ctttttttaa atagagggat 1129
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 ttttttatta gcattctgaa agaaggaaag taaaatgtac aagtttaata aaaaggggcc 1489
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<210> 72
 <211> 252
 <212> PRT
 <213> Homo sapiens

<400> 72

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 20 25 30
 Ser Ile His Asp Phe Cys Leu Val Ser Lys Val Val Gly Arg Cys Arg
 35 40 45
 Ala Ser Met Pro Arg Trp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln
 50 55 60
 Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr
 65 70 75 80
 Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr
 85 90 95
 Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser
 100 105 110
 Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser Ser Asp Met Phe Asn
 115 120 125

Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala
 130 135 140
 Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn
 145 150 155 160
 Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn Ser Tyr Arg Ser Glu
 165 170 175
 Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu
 180 185 190
 Pro Leu Gly Ser Lys Val Val Val Leu Ala Gly Leu Phe Val Met Val
 195 200 205
 Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr Leu Ile Arg Val Ala
 210 215 220
 Arg Arg Asn Gln Glu Arg Ala Leu Arg Thr Val Trp Ser Ser Gly Asp
 225 230 235 240
 Asp Lys Glu Gln Leu Val Lys Asn Thr Tyr Val Leu
 245 250

<210> 73
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 <212> DNA
 <213> Homo sapiens

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<400> 73
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 taataccaag aacc atg tgt gcc gag cgg ctg ggc cag ttc atg acc ctg 170
 Met Cys Ala Glu Arg Leu Gly Gln Phe Met Thr Leu
 1 5 10
 gct ttg gtg ttg gcc acc ttt gac ccg gcg cgg ggg acc gac gcc acc 218
 Ala Leu Val Leu Ala Thr Phe Asp Pro Ala Arg Gly Thr Asp Ala Thr
 15 20 25
 aac cca ccc gag ggt ccc caa gac agg agc tcc cag cag aaa ggc cgc 266
 Asn Pro Pro Glu Gly Pro Gln Asp Arg Ser Ser Gln Lys Gly Arg
 30 35 40
 ctg tcc ctg cag aat aca gcg gag atc cag cac tgt ttg gtc aac gct 314
 Leu Ser Leu Gln Asn Thr Ala Glu Ile Gln His Cys Leu Val Asn Ala
 45 50 55 60
 ggc gat gtg ggg tgt ggc gtg ttt gaa tgt ttc gag aac aac tct tgt 362
 Gly Asp Val Gly Cys Gly Val Phe Glu Cys Phe Glu Asn Asn Ser Cys
 65 70 75
 gag att cgg ggc tta cat ggg att tgc atg act ttt ctg cac aac gct 410
 Glu Ile Arg Gly Leu His Gly Ile Cys Met Thr Phe Leu His Asn Ala
 80 85 90
 gga aaa ttt gat gcc cag ggc aag tca ttc atc aaa gac gcc ttg aaa 458
 Gly Lys Phe Asp Ala Gln Gly Lys Ser Phe Ile Lys Asp Ala Leu Lys
 95 100 105
 tgt aag gcc cac gct ctg cgg cac agg ttc ggc tgc ata agc cgg aag 506
 Cys Lys Ala His Ala Leu Arg His Arg Phe Gly Cys Ile Ser Arg Lys
 110 115 120
 tgc ccg gcc atc agg gaa atg gtg tcc cag ttg cag cgg gaa tgc tac 554

Cys 125	Pro	Ala	Ile	Arg	Glu 130	Met	Val	Ser	Gln	Leu 135	Gln	Arg	Glu	Cys	Tyr 140			
ctc Leu	aag Lys	cac His	gac Asp	ctg Leu 145	tgc Cys	gcg Ala	gct Ala	gcc Ala	cag Gln 150	gag Glu	aac Asn	acc Thr	cgg Arg	gtg Val 155	ata Ile	602		
gtg Val	gag Glu	atg Met	atc Ile 160	cat His	ttc Phe	aag Lys	gac Asp	ttg Leu 165	ctg Leu	ctg Leu	cac His	gaa Glu	ccc Pro 170	tac Tyr	gtg Val	650		
gac Asp	ctc Leu	gtg Val 175	aac Asn	ttg Leu	ctg Leu	ctg Leu	acc Thr 180	tgt Cys	ggg Gly	gag Glu	gag Glu	gtg Val 185	aag Lys	gag Glu	gcc Ala	698		
atc Ile	acc Thr 190	cac His	agc Ser	gtg Val	cag Gln	gtt Val 195	cag Gln	tgt Cys	gag Glu	cag Gln	aac Asn 200	tgg Trp	gga Gly	agc Ser	ctg Leu	746		
tgc Cys 205	tcc Ser	atc Ile	ttg Leu	agc Ser	ttc Phe 210	tgc Cys	acc Thr	tcg Ser	gcc Ala	atc Ile 215	cag Gln	aag Lys	cct Pro	ccc Pro	acg Thr 220	794		
gcg Ala	ccc Pro	ccc Pro	gag Glu	cgc Arg 225	cag Gln	ccc Pro	cag Gln	gtg Val	gac Asp 230	aga Arg	acc Thr	aag Lys	ctc Leu	tcc Ser 235	agg Arg	842		
gcc Ala	cac His	cac His	ggg Gly 240	gaa Glu	gca Ala	gga Gly	cat His	cac His 245	ctc Leu	cca Pro	gag Glu	ccc Pro	agc Ser 250	agt Ser	agg Arg	890		
gag Glu	act Thr	ggc Gly 255	cga Arg	ggt Gly	gcc Ala	aag Lys	ggt Gly 260	gag Glu	cga Arg	ggt Gly	agc Ser	aag Lys 265	agc Ser	cac His	cca Pro	938		
aac Asn	gcc Ala 270	cat His	gcc Ala	cga Arg	ggc Gly	aga Arg 275	gtc Val	ggg Gly	ggc Gly	ctt Leu	ggg Gly 280	gct Ala	cag Gln	gga Gly	cct Pro	986		
tcc Ser 285	gga Gly	agc Ser	agc Ser	gag Glu	tgg Trp 290	gaa Glu	gac Asp	gaa Glu	cag Gln	tct Ser 295	gag Glu	tat Tyr	tct Ser	gat Asp	atc Ile 300	1034		
cgg Arg	agg Arg	tga	aatgaaaggc ctggccacga aatctttcct ccacgccgtc													1083		
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 agaggaagaa aagagagaga gaaaagagcc tcgtgcc 2380

<210> 74
 <211> 302
 <212> PRT
 <213> Homo sapiens

<400> 74

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Ala Thr Phe Asp Pro Ala Arg Gly Thr Asp Ala Thr Asn Pro Pro Glu
 20 25 30

Gly Pro Gln Asp Arg Ser Ser Gln Gln Lys Gly Arg Leu Ser Leu Gln
 35 40 45

Asn Thr Ala Glu Ile Gln His Cys Leu Val Asn Ala Gly Asp Val Gly
 50 55 60

Cys Gly Val Phe Glu Cys Phe Glu Asn Asn Ser Cys Glu Ile Arg Gly
 65 70 75 80

Leu His Gly Ile Cys Met Thr Phe Leu His Asn Ala Gly Lys Phe Asp
 85 90 95

Ala Gln Gly Lys Ser Phe Ile Lys Asp Ala Leu Lys Cys Lys Ala His
 100 105 110

Ala Leu Arg His Arg Phe Gly Cys Ile Ser Arg Lys Cys Pro Ala Ile
 115 120 125

Arg Glu Met Val Ser Gln Leu Gln Arg Glu Cys Tyr Leu Lys His Asp
 130 135 140

Leu Cys Ala Ala Ala Gln Glu Asn Thr Arg Val Ile Val Glu Met Ile
 145 150 155 160

His Phe Lys Asp Leu Leu Leu His Glu Pro Tyr Val Asp Leu Val Asn
 165 170 175

Leu Leu Leu Thr Cys Gly Glu Glu Val Lys Glu Ala Ile Thr His Ser
 180 185 190

Val Gln Val Gln Cys Glu Gln Asn Trp Gly Ser Leu Cys Ser Ile Leu
 195 200 205

Ser Phe Cys Thr Ser Ala Ile Gln Lys Pro Pro Thr Ala Pro Pro Glu
 210 215 220

Arg Gln Pro Gln Val Asp Arg Thr Lys Leu Ser Arg Ala His His Gly
 225 230 235 240

Glu Ala Gly His His Leu Pro Glu Pro Ser Ser Arg Glu Thr Gly Arg
 245 250 255

Gly Ala Lys Gly Glu Arg Gly Ser Lys Ser His Pro Asn Ala His Ala
260 265 270

Arg Gly Arg Val Gly Gly Leu Gly Ala Gln Gly Pro Ser Gly Ser Ser
275 280 285

Glu Trp Glu Asp Glu Gln Ser Glu Tyr Ser Asp Ile Arg Arg
290 295 300

<210> 75
<211> 3662
<212> DNA
<213> Homo sapiens

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<222> (434)..(2401)
<223>

<400> 75
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gctctctcgc gcccagtcct cctccctggt tctcctcagc cgctgtcggg ggagagcacc 180
cggagacgcg ggctgcagtc gcggcggtt ctccccgcct gggcgggcgc gccgctgggc 240
aggtgctgag cgcccctaga gcctcccttg ccgcctccct cctctgcccg gccgcagcag 300
tgcacatggg gtgttgagg tagatgggct cccggcccgg gagggcgcg tggatgcggc 360
gctgggcaga agcagccgcc gattccagct gccccgcgc ccccgggcgc ccctgcgagt 420
ccccggttca gcc atg ggg acc tct ccg agc agc agc acc gcc ctc gcc 469
Met Gly Thr Ser Pro Ser Ser Ser Thr Ala Leu Ala
1 5 10
tcc tgc agc cgc atc gcc cgc cga gcc aca gcc acg atg atc gcg ggc 517
Ser Cys Ser Arg Ile Ala Arg Arg Ala Thr Ala Thr Met Ile Ala Gly
15 20 25
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Leu Thr Cys Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys
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Ala Pro His Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly
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Pro Gly Thr Ala Ile Phe Pro Arg Pro Glu His Met Glu Thr His Glu
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 Gly Thr Val Pro Asp Asn Thr Ser Ser Ala Arg Gly Lys Glu Asp Val
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 Asp Ile Leu Lys Leu Val Ala Ala Gln Val Gly Ser Gln Trp Lys Asp
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 515 520 525
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Met Arg Ala Leu
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Ala Asp Asp Glu Val Asp Val Asp Gly Thr Val Glu Glu Asp Leu Gly
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aga Arg	atg Met	ctt Leu	cgc Arg	ctc Leu 745	agt Ser	ttg Leu	aac Asn	att Ile	gac Asp 750	cct Pro	gat Asp	gca Ala	aag Lys	gtg Val 755	gaa Glu	2373
gaa Glu	gag Glu	ccc Pro	gaa Glu 760	gaa Glu	gaa Glu	cct Pro	gaa Glu	gag Glu 765	aca Thr	gca Ala	gaa Glu	gac Asp	aca Thr 770	aca Thr	gaa Glu	2421
gac Asp	aca Thr	gag Glu 775	caa Gln	gac Asp	gaa Glu	gat Asp	gaa Glu 780	gaa Glu	atg Met	gat Asp	gtg Val	gga Gly 785	aca Thr	gat Asp	gaa Glu	2469
gaa Glu	gaa Glu	gaa Glu	aca Thr	gca Ala	aag Lys	gaa Glu 795	tct Ser	aca Thr	gct Ala	gaa Glu	aaa Lys 800	gat Asp	gaa Glu	ttg Leu	taa	2517
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Val Gln Arg Glu Glu Glu Ala Ile Gln Leu Asp Gly Leu Asn Ala Ser
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Gln Ile Arg Glu Leu Arg Glu Lys Ser Glu Lys Phe Ala Phe Gln Ala
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Glu Val Asn Arg Met Met Lys Leu Ile Ile Asn Ser Leu Tyr Lys Asn
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Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu
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Asp Lys Ile Arg Leu Ile Ser Leu Thr Asp Glu Asn Ala Leu Ser Gly
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Asn Glu Glu Leu Thr Val Lys Ile Lys Cys Asp Lys Glu Lys Asn Leu
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Leu His Val Thr Asp Thr Gly Val Gly Met Thr Arg Glu Glu Leu Val
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Lys Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Ser Glu Phe Leu Asn
 165 170 175

Lys Met Thr Glu Ala Gln Glu Asp Gly Gln Ser Thr Ser Glu Leu Ile
 180 185 190

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

Val Ile Val Thr Ser Lys His Asn Asn Asp Thr Gln His Ile Trp Glu
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Ser Asp Ser Asn Glu Phe Ser Val Ile Ala Asp Pro Arg Gly Asn Thr
 225 230 235 240

Leu Gly Arg Gly Thr Thr Ile Thr Leu Val Leu Lys Glu Glu Ala Ser
 245 250 255

Asp Tyr Leu Glu Leu Asp Thr Ile Lys Asn Leu Val Lys Lys Tyr Ser
 260 265 270

Gln Phe Ile Asn Phe Pro Ile Tyr Val Trp Ser Ser Lys Thr Glu Thr
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 Glu Ser Asp Asp Glu Ala Ala Val Glu Glu Glu Glu Glu Lys Lys
 305 310 315 320
 Pro Lys Thr Lys Lys Val Glu Lys Thr Val Trp Asp Trp Glu Leu Met
 325 330 335
 Asn Asp Ile Lys Pro Ile Trp Gln Arg Pro Ser Lys Glu Val Glu Glu
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 Asp Glu Tyr Lys Ala Phe Tyr Lys Ser Phe Ser Lys Glu Ser Asp Asp
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 Pro Met Ala Tyr Ile His Phe Thr Ala Glu Gly Glu Val Thr Phe Lys
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 Ser Ile Leu Phe Val Pro Thr Ser Ala Pro Arg Gly Leu Phe Asp Glu
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 Tyr Gly Ser Lys Lys Ser Asp Tyr Ile Lys Leu Tyr Val Arg Arg Val
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 Phe Ile Thr Asp Asp Phe His Asp Met Met Pro Lys Tyr Leu Asn Phe
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 Val Lys Gly Val Val Asp Ser Asp Asp Leu Pro Leu Asn Val Ser Arg
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 Glu Thr Leu Gln Gln His Lys Leu Leu Lys Val Ile Arg Lys Lys Leu
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 Val Arg Lys Thr Leu Asp Met Ile Lys Lys Ile Ala Asp Asp Lys Tyr
 465 470 475 480
 Asn Asp Thr Phe Trp Lys Glu Phe Gly Thr Asn Ile Lys Leu Gly Val
 485 490 495
 Ile Glu Asp His Ser Asn Arg Thr Arg Leu Ala Lys Leu Leu Arg Phe
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 Gln Ser Ser His His Pro Thr Asp Ile Thr Ser Leu Asp Gln Tyr Val
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 Glu Arg Met Lys Glu Lys Gln Asp Lys Ile Tyr Phe Met Ala Gly Ser
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 Ser Arg Lys Glu Ala Glu Ser Ser Pro Phe Val Glu Arg Leu Leu Lys
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 Lys Gly Tyr Glu Val Ile Tyr Leu Thr Glu Pro Val Asp Glu Tyr Cys
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 Ile Gln Ala Leu Pro Glu Phe Asp Gly Lys Arg Phe Gln Asn Val Ala
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Lys Glu Gly Val Lys Phe Asp Glu Ser Glu Lys Thr Lys Glu Ser Arg
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 Thr Glu Ser Pro Cys Ala Leu Val Ala Ser Gln Tyr Gly Trp Ser Gly
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 Asn Met Glu Arg Ile Met Lys Ala Gln Ala Tyr Gln Thr Gly Lys Asp
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 Pro Arg His Pro Leu Ile Arg Asp Met Leu Arg Arg Ile Lys Glu Asp
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 Asp Arg Ile Glu Arg Met Leu Arg Leu Ser Leu Asn Ile Asp Pro Asp
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 Ala Lys Val Glu Glu Glu Pro Glu Glu Glu Pro Glu Glu Thr Ala Glu
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 Met Val Val Pro Glu Lys Glu Gln Ser Trp Ile Pro Lys
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 Ile Phe Lys Lys Lys Thr Cys Thr Thr Phe Ile Val Asp Ser Thr Asp 25
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 Pro Gly Gly Thr Leu Cys Gln Cys Gly Arg Pro Arg Thr Ala His Pro 30 35 40 45

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 Ala His Thr Thr Glu Lys₇₀ Pro Thr Asp Ala Tyr₇₅ Gly Glu Leu Asp Phe₈₀
 Thr Gly Ala Gly Arg₈₅ Lys His Ser Asn Phe₉₀ Leu Arg Leu Ser Asp₉₅ Arg
 Thr Asp Pro Ala₁₀₀ Ala Val Tyr Ser Leu₁₀₅ Val Thr Arg Thr Trp₁₁₀ Gly Phe
 Arg Ala Pro₁₁₅ Asn Leu Val Val Ser₁₂₀ Val Leu Gly Gly Ser₁₂₅ Gly Gly Pro
 Val Leu₁₃₀ Gln Thr Trp Leu Gln₁₃₅ Asp Leu Leu Arg Arg₁₄₀ Gly Leu Val Arg
 Ala Ala Gln Ser Thr Gly₁₅₀ Ala Trp Ile Val Thr₁₅₅ Gly Gly Leu His Thr₁₆₀
 Gly Ile Gly Arg His₁₆₅ Val Gly Val Ala Val₁₇₀ Arg Asp His Gln Met₁₇₅ Ala
 Ser Thr Gly Gly₁₈₀ Thr Lys Val Val Ala₁₈₅ Met Gly Val Ala Pro₁₉₀ Trp Gly
 Val Val Arg₁₉₅ Asn Arg Asp Thr Leu₂₀₀ Ile Asn Pro Lys Gly₂₀₅ Ser Phe Pro
 Ala Arg₂₁₀ Tyr Arg Trp Arg Gly₂₁₅ Asp Pro Glu Asp Gly₂₂₀ Val Gln Phe Pro
 Leu₂₂₅ Asp Tyr Asn Tyr Ser₂₃₀ Ala Phe Phe Leu Val₂₃₅ Asp Asp Gly Thr His₂₄₀
 Gly Cys Leu Gly Gly₂₄₅ Glu Asn Arg Phe Arg₂₅₀ Leu Arg Leu Glu Ser₂₅₅ Tyr
 Ile Ser Gln Gln₂₆₀ Lys Thr Gly Val Gly₂₆₅ Gly Thr Gly Ile Asp₂₇₀ Ile Pro
 Val Leu Leu₂₇₅ Leu Leu Ile Asp Gly₂₈₀ Asp Glu Lys Met Leu₂₈₅ Thr Arg Ile
 Glu Asn₂₉₀ Ala Thr Gln Ala Gln₂₉₅ Leu Pro Cys Leu Leu₃₀₀ Val Ala Gly Ser
 Gly₃₀₅ Gly Ala Ala Asp Cys₃₁₀ Leu Ala Glu Thr Leu₃₁₅ Glu Asp Thr Leu Ala₃₂₀
 Pro Gly Ser Gly Gly₃₂₅ Ala Arg Gln Gly Glu₃₃₀ Ala Arg Asp Arg Ile₃₃₅ Arg

Arg Phe Phe Pro Lys Gly Asp Leu Glu Val Leu Gln Ala Gln Val Glu
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 Arg Ile Met Thr Arg Lys Glu Leu Leu Thr Val Tyr Ser Ser Glu Asp
 355 360 365
 Gly Ser Glu Glu Phe Glu Thr Ile Val Leu Lys Ala Leu Val Lys Ala
 370 375 380
 Cys Gly Ser Ser Glu Ala Ser Ala Tyr Leu Asp Glu Leu Arg Leu Ala
 385 390 395 400
 Val Ala Trp Asn Arg Val Asp Ile Ala Gln Ser Glu Leu Phe Arg Gly
 405 410 415
 Asp Ile Gln Trp Arg Ser Phe His Leu Glu Ala Ser Leu Met Asp Ala
 420 425 430
 Leu Leu Asn Asp Arg Pro Glu Phe Val Arg Leu Leu Ile Ser His Gly
 435 440 445
 Leu Ser Leu Gly His Phe Leu Thr Pro Met Arg Leu Ala Gln Leu Tyr
 450 455 460
 Ser Ala Ala Pro Ser Asn Ser Leu Ile Arg Asn Leu Leu Asp Gln Ala
 465 470 475 480
 Ser His Ser Ala Gly Thr Lys Ala Pro Ala Leu Lys Gly Gly Ala Ala
 485 490 495
 Glu Leu Arg Pro Pro Asp Val Gly His Val Leu Arg Met Leu Leu Gly
 500 505 510
 Lys Met Cys Ala Pro Arg Tyr Pro Ser Gly Gly Ala Trp Asp Pro His
 515 520 525
 Pro Gly Gln Gly Phe Gly Glu Ser Met Tyr Leu Leu Ser Asp Lys Ala
 530 535 540
 Thr Ser Pro Leu Ser Leu Asp Ala Gly Leu Gly Gln Ala Pro Trp Ser
 545 550 555 560
 Asp Leu Leu Leu Trp Ala Leu Leu Leu Asn Arg Ala Gln Met Ala Met
 565 570 575
 Tyr Phe Trp Glu Met Gly Ser Asn Ala Val Ser Ser Ala Leu Gly Ala
 580 585 590
 Cys Leu Leu Leu Arg Val Met Ala Arg Leu Glu Pro Asp Ala Glu Glu
 595 600 605
 Ala Ala Arg Arg Lys Asp Leu Ala Phe Lys Phe Glu Gly Met Gly Val
 610 615 620
 Asp Leu Phe Gly Glu Cys Tyr Arg Ser Ser Glu Val Arg Ala Ala Arg
 625 630 635 640
 Leu Leu Leu Arg Arg Cys Pro Leu Trp Gly Asp Ala Thr Cys Leu Gln
 645 650 655

Leu Ala Met Gln Ala Asp Ala Arg Ala Phe Phe Ala Gln Asp Gly Val
 660 665 670
 Gln Ser Leu Leu Thr Gln Lys Trp Trp Gly Asp Met Ala Ser Thr Thr
 675 680 685
 Pro Ile Trp Ala Leu Val Leu Ala Phe Phe Cys Pro Pro Leu Ile Tyr
 690 695 700
 Thr Arg Leu Ile Thr Phe Arg Lys Ser Glu Glu Glu Pro Thr Arg Glu
 705 710 715 720
 Glu Leu Glu Phe Asp Met Asp Ser Val Ile Asn Gly Glu Gly Pro Val
 725 730 735
 Gly Thr Ala Asp Pro Ala Glu Lys Thr Pro Leu Gly Val Pro Arg Gln
 740 745 750
 Ser Gly Arg Pro Gly Cys Cys Gly Gly Arg Cys Gly Gly Arg Arg Cys
 755 760 765
 Leu Arg Arg Trp Phe His Phe Trp Gly Ala Pro Val Thr Ile Phe Met
 770 775 780
 Gly Asn Val Val Ser Tyr Leu Leu Phe Leu Leu Phe Ser Arg Val
 785 790 795 800
 Leu Leu Val Asp Phe Gln Pro Ala Pro Pro Gly Ser Leu Glu Leu Leu
 805 810 815
 Leu Tyr Phe Trp Ala Phe Thr Leu Leu Cys Glu Glu Leu Arg Gln Gly
 820 825 830
 Leu Ser Gly Gly Gly Gly Ser Leu Ala Ser Gly Gly Pro Gly Pro Gly
 835 840 845
 His Ala Ser Leu Ser Gln Arg Leu Arg Leu Tyr Leu Ala Asp Ser Trp
 850 855 860
 Asn Gln Cys Asp Leu Val Ala Leu Thr Cys Phe Leu Leu Gly Val Gly
 865 870 875 880
 Cys Arg Leu Thr Pro Gly Leu Tyr His Leu Gly Arg Thr Val Leu Cys
 885 890 895
 Ile Asp Phe Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val
 900 905 910
 Asn Lys Gln Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys
 915 920 925
 Asp Val Phe Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Tyr
 930 935 940
 Gly Val Ala Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser Asp Phe Pro
 945 950 955 960
 Ser Ile Leu Arg Arg Val Phe Tyr Arg Pro Tyr Leu Gln Ile Phe Gly
 965 970 975

Gln Ile Pro Gln Glu Asp Met Asp Val Ala Leu Met Glu His Ser Asn
980 985 990

Cys Ser Ser Glu Pro Gly Phe Trp Ala His Pro Pro Gly Ala Gln Ala
995 1000 1005

Gly Thr Cys Val Ser Gln Tyr Ala Asn Trp Leu Val Val Leu Leu
1010 1015 1020

Leu Val Ile Phe Leu Leu Val Ala Asn Ile Leu Leu Val Asn Leu
1025 1030 1035

Leu Ile Ala Met Phe Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn
1040 1045 1050

Ser Asp Leu Tyr Trp Lys Ala Gln Arg Tyr Arg Leu Ile Arg Glu
1055 1060 1065

Phe His Ser Arg Pro Ala Leu Ala Pro Pro Phe Ile Val Ile Ser
1070 1075 1080

His Leu Arg Leu Leu Leu Arg Gln Leu Cys Arg Arg Pro Arg Ser
1085 1090 1095

Pro Gln Pro Ser Ser Pro Ala Leu Glu His Phe Arg Val Tyr Leu
1100 1105 1110

Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr Trp Glu Ser Val His
1115 1120 1125

Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp Lys Arg Glu Ser
1130 1135 1140

Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val Asp Leu Ala
1145 1150 1155

Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg Leu Lys
1160 1165 1170

Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly Trp
1175 1180 1185

Val Ala Glu Ala Leu Ser Arg Ser Ala Leu Leu Pro Pro Gly Gly
1190 1195 1200

Pro Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp
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27

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 ttccctgcagg gc 72

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<210> 115
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