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(54) Title: PKD LIGANDS AND POLYNUCLEOTIDES ENCODING PKD LIGANDS

(57) Abstract: The invention relates to kinase ligands and polyligands. In particular, the invention relates to ligands, homopolyligands, and heteropolyligands that modulate protein kinase D (PKD) activity. The ligands and polyligands are utilized as research tools or as therapeutics. The invention includes linkage of the ligands and polyligands to cellular localization signals, epitope tags and/or reporters. The invention also includes polynucleotides encoding the ligands and polyligands.



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PKD LIGANDS AND POLYNUCLEOTIDES ENCODING PKD LIGANDS**Inventor: Thomas D. Reed****FIELD OF INVENTION**

The invention relates to mammalian kinase ligands, substrates and modulators. In particular, the invention relates to polypeptides, polypeptide compositions and polynucleotides that encode polypeptides that are ligands, substrates, and/or modulators of PKD. The invention also relates to polyligands that are homopolyligands or heteropolyligands that modulate PKD activity. The invention also relates to ligands and polyligands tethered to a subcellular location.

This application has subject matter related to application Nos. 10/724,532 (now US 7,071,295), 10/682,764 (US2004/0185556, PCT/US2004/013517, WO2005/040336), 11/233,246, and US20040572011P (WO2005116231). Each of these patents and applications is hereby incorporated by reference.

BACKGROUND AND PRIOR ART

Kinases are enzymes that catalyze the addition of phosphate to a molecule. The addition of phosphate by a kinase is called phosphorylation. When the kinase substrate is a protein molecule, the amino acids commonly phosphorylated are serine, threonine and tyrosine. Phosphatases are enzymes that remove phosphate from a molecule. The removal of phosphate is called dephosphorylation. Kinases and phosphatases often represent competing forces within a cell to transmit, attenuate, or otherwise modulate cellular signals and cellular control mechanisms. Kinases and phosphatases have both overlapping and unique natural substrates. Cellular signals and control mechanisms, as regulated by kinases, phosphatases, and their natural substrates are a target of research tool design and drug design.

Mammalian Protein Kinase D is also known as PKD. The enzymatic activity, activation and autoregulation of PKD have been studied. Several cellular substrates of PKD have been identified. Substrates and modified substrates are generically referred to herein as ligands. Natural and synthetic peptide ligands have been studied to examine PKD substrate specificity. While peptide ligands and variants thereof have been studied as individual PKD ligands, mixed ligands linked together as polyligands have not been demonstrated before this invention.

Design and synthesis of polypeptide ligands that modulate calcium/calmodulin-dependent protein kinase and that localize to the cardiac sarco(endo)plasmic reticulum was performed by Ji et al. (J Biol Chem (2003) 278:25063-71). Ji et al. accomplished this by generating expression constructs that localized calcium/calmodulin-dependent protein kinase inhibitory polypeptide ligands to the sarcoplasmic
 5 reticulum by fusing a sarcoplasmic reticulum localization signal derived from phospholamban to a polypeptide ligand. See also US 7,071,295.

DETAILED DESCRIPTION OF POLYPEPTIDE AND POLYNUCLEOTIDE SEQUENCES

SEQ ID NOS:1-104 represent examples of monomeric peptide ligand sequences.

Specifically, SEQ ID NOS:1-52 are fragments of natural substrates of mammalian PKD, wherein each
 10 fragment contains at least one amino acid residue phosphorylatable by PKD. SEQ ID NOS:53-104 are fragments of natural PKD substrates, where the location of the PKD phosphorylatable serine or threonine in the natural polypeptide is designated as Xaa.

SEQ ID NOS:105-116 are example polyligands and polynucleotides encoding them.

Specifically, SEQ ID NO:105 is encoded by SEQ ID NO:106, SEQ ID NO:107 and by SEQ ID NO:108,
 15 wherein the the codons of SEQ ID NO:107 and SEQ ID NO:108 have been optimized for vector insertion. SEQ ID NO:108 includes flanking restriction sites. SEQ ID NO:105 is an embodiment of a polyligand of the structure X-S1-Y-S2-Z, wherein X is SEQ ID NO:53, Y is SEQ ID NO:55, Z is SEQ ID NO:58, wherein Xaa is alanine, and wherein S1 is a four amino acid spacer of the amino acid sequence AGAG and S2 is a four amino acid spacer of amino acid sequence GAGA. A polyligand of
 20 structure A-S1-B-S2-C is called herein a heteropolyligand, shown generically in FIGURE 4B.

SEQ ID NO:109 is an embodiment of a polyligand of the structure X-S1-Y-S2-Z, wherein X is SEQ ID NO:61, Y is SEQ ID NO:65, Z is SEQ ID NO:66, wherein Xaa is alanine, wherein S1 is a four amino acid spacer of amino acid sequence AGAG and S2 is a four amino acid spacer of amino acid sequence GAGA. The PKD polyligand of SEQ ID NO:109 is encoded by SEQ ID NO:110, SEQ ID NO:111 and
 25 by SEQ ID NO:112, wherein the the codons of SEQ ID NO:111 and SEQ ID NO:112 have been optimized for vector insertion. SEQ ID NO:112 includes flanking restriction sites. A polyligand of structure X-S1-Y-S2-Z is also called herein a heteropolyligand, shown generically in FIGURE 4B.

SEQ ID NO:113 is an embodiment of a polyligand of the structure X-Y-S3-Y-X, wherein X is SEQ ID NO:53, Y is SEQ ID NO:54, wherein Xaa is alanine, and wherein S3 is a five amino acid spacer with the sequence PAGAG. The PKD polyligand of SEQ ID NO:113 is encoded by SEQ ID NO:114, SEQ ID NO:115, and by SEQ ID NO:116, wherein the the codons of SEQ ID NO:115 and SEQ ID NO:116 have
 5 been optimized for vector insertion. SEQ ID NO:116 includes flanking restriction sites. A polyligand of structure X-Y-S3-Y-X is also called herein a heteropolyligand, shown generically in FIGURE 4C.

SEQ ID NOS:117-132 are full length PKD substrates. These sequences have the following public database accession numbers: AAH64840, NP000354, CAA79356, NP001015053, NP009112, NP001531, NP065789, AAH00029, AAB48596, NP_536728, AAH47282, NP004283, NP005219,
 10 CAB95729, NP_057541, NP_849231. Each of the protein sequences represented by these accession numbers is incorporated by reference herein. In SEQ ID NOS:117-132, the positions of the amino acid(s) phosphorylatable by PKD are represented by Xaa. In wild-type proteins, Xaa is serine or threonine. In the ligands of the invention, Xaa is any amino acid.

Amino acid sequences containing Xaa encompass polypeptides where Xaa is any amino acid.

15 DETAILED DESCRIPTION OF DRAWINGS

FIGURES 1A-1C show examples of homopolymeric ligands without spacers.

FIGURES 2A-2C show examples of homopolymeric ligands with spacers.

FIGURES 3A-3C show examples of heteropolymeric ligands without spacers.

FIGURES 4A-4C show examples of heteropolymeric ligands with spacers.

20 FIGURES 5A-5G show examples of ligands and polymeric ligands linked to an optional epitope tag.

FIGURES 6A-6G show examples of ligands and polymeric ligands linked to an optional reporter.

FIGURES 7A-7G show examples of ligands and polymeric ligands linked to an optional localization signal.

25 FIGURES 8A-8G show examples of ligands and polymeric ligands linked to an optional localization signal and an optional epitope tag.

FIGURES 9A-9G show examples of gene constructs where ligands and polyligands are linked to an optional localization signal, an optional epitope tag, and an optional reporter.

FIGURES 10A-10D show examples of vectors containing ligand gene constructs.

FIGURE 11 shows an example of a sequential cloning process useful for combinatorial synthesis of polyligands.

BRIEF DESCRIPTION OF THE INVENTION

The invention relates to polypeptide ligands and polyligands for PKD. Various embodiments of the PKD ligands and polyligands are represented in SEQ ID NOS:1-132. More specifically, the invention relates to ligands, homopolyligands, and heteropolyligands that comprise any one or more of SEQ ID NOS:1-104. Additionally, the invention relates to ligands and polyligands comprising one or more subsequences of SEQ ID NOS:117-132 or any portion thereof. Furthermore, the invention relates to polyligands with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% and 99% sequence identity to a polyligand comprising one or more of SEQ ID NOS:1-104 or any portion thereof. Furthermore, the invention relates to polyligands with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% and 99% sequence identity to a polyligand comprising one or more subsequences of SEQ ID NOS:117-132 or portions thereof.

Polyligands, which can be homopolyligands or heteropolyligands, are chimeric ligands composed of two or more monomeric polypeptide ligands. An example of a monomeric ligand is the polypeptide represented by SEQ ID NO:61, wherein Xaa is any amino acid. An example of a homopolyligand is a polypeptide comprising a dimer or multimer of SEQ ID NO:61, wherein Xaa is any amino acid. An example of a heteropolyligand is a polypeptide comprising SEQ ID NO:1 and one or more of SEQ ID NOS:2-104, wherein Xaa is any amino acid. There are numerous ways to combine SEQ ID NOS:1-104 into homopolymeric or heteropolymeric ligands. Furthermore, there are numerous ways to combine portions or subsequences of SEQ ID NOS:117-132 with each other and with SEQ ID NOS:1-104 to make polymeric ligands that modulate PKD.

The polyligands of the invention optionally comprise spacer amino acids before, after, or between monomers. SEQ ID NO:105 is an embodiment of a polyligand of the structure X-S1-Y-S2-Z, wherein X is SEQ ID NO:53, Y is SEQ ID NO:55, Z is SEQ ID NO:58, wherein Xaa is alanine, and wherein S1 and S2 are four amino acid spacers. This invention intends to capture all combinations of homopolyligands and heteropolyligands without limitation to the examples given above or below. In this description, use of the term "ligand(s)" encompasses monomeric ligands, polymeric ligands, homopolymeric ligands and/or heteropolymeric ligands.

A monomeric ligand is a polypeptide where at least a portion of the polypeptide is capable of being recognized by PKD. The portion of the polypeptide capable of recognition is termed the recognition motif. In the present invention, recognition motifs can be natural or synthetic. Examples of recognition motifs are well known in the art and include, but are not limited to, naturally occurring PKD substrates and pseudosubstrate motifs.

A polymeric ligand comprises two or more monomeric ligands.

A homopolymeric ligand is a polymeric ligand where each of the monomeric ligands is identical in amino acid sequence, except that a phosphorylatable residue may be substituted or modified in one or more of the monomeric ligands.

10 A heteropolymeric ligand is a polymeric ligand where some of the monomeric ligands do not have an identical amino acid sequence.

The ligands of the invention are optionally linked to additional molecules or amino acids that provide an epitope tag, a reporter, and/or a cellular localization signal. The cellular localization signal targets the ligands to a region of a cell. The epitope tag and/or reporter and/or localization signal may be the same molecule. The epitope tag and/or reporter and/or localization signal may also be different molecules.

The invention also encompasses polynucleotides comprising a nucleotide sequence encoding ligands, homopolyligands, and heteropolyligands. The nucleic acids of the invention are optionally linked to additional nucleotide sequences encoding polypeptides with additional features, such as an epitope tag, a reporter, and/or a cellular localization signal. The polynucleotides are optionally flanked by nucleotide sequences comprising restriction endonuclease sites and other nucleotides needed for restriction endonuclease activity. The flanking sequences optionally provide unique cloning sites within a vector and optionally provide directionality of subsequence cloning. Further, the nucleic acids of the invention are optionally incorporated into vector polynucleotides. The ligands, polyligands, and polynucleotides of this invention have utility as research tools and/or therapeutics.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to ligands and polyligands that are PKD modulators. Various embodiments

of ligands and polyligands are represented in SEQ ID NOS:1-132. Polyligands are chimeric ligands comprising two or more monomeric polypeptide ligands. An example of a monomeric ligand is the polypeptide represented by SEQ ID NO:54, wherein Xaa is any amino acid. Another example of a monomeric ligand is the polypeptide represented by SEQ ID NO:1. Each of SEQ ID NOS:1-104
5 represents an individual polypeptide ligand in monomeric form, wherein Xaa is any amino acid. Additional examples of monomeric ligands are subsequence portions of SEQ ID NOS:117-132 containing a PKD recognition motif. Monomeric ligand subsequences of SEQ ID NOS:117-132 may be wild-type subsequences. Additionally, monomeric ligand subsequences of SEQ ID NOS:117-132 may have the PKD phosphorylatable amino acids replaced by other amino acids. Furthermore, monomeric
10 ligands and polyligands may have at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity to a ligand comprising an amino acid sequence in one or more of SEQ ID NOS:1-104. Furthermore, monomeric ligands and polyligands may have at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% and 99% sequence identity to a subsequence of SEQ ID NOS:117-132.

An example of a homopolyligand is a polypeptide comprising a dimer or multimer of SEQ ID NO:66,
15 wherein Xaa is any amino acid. An example of a heteropolyligand is a polypeptide comprising SEQ ID NO:104 and one or more of SEQ ID NOS:1-103, wherein Xaa is any amino acid. There are numerous ways to combine SEQ ID NOS:1-104 into homopolymeric or heteropolymeric ligands. Furthermore, there are numerous ways to combine PKD recognition motif-containing portions of SEQ ID NOS:117-132 with each other and with SEQ ID NOS:1-104 to make polymeric ligands.

20 Polyligands may comprise any two or more of a sequence selected from SEQ ID NOS:1-104 and recognition motif-containing portions of SEQ ID NOS:117-132, wherein Xaa is any amino acid. A dimer or multimer of SEQ ID NO:91 is an example of a homopolyligand. An example of a heteropolyligand is a polypeptide comprising SEQ ID NO:5 and one or more of a recognition motif-containing portion of SEQ ID NOS:117-132. There are numerous ways to combine SEQ ID NOS:1-104 and portions of SEQ
25 ID NOS:117-132 into homopolymeric or heteropolymeric ligands. The instant invention is directed to all possible combinations of homopolyligands and heteropolyligands without limitation.

SEQ ID NOS:53-104 and SEQ ID NOS:117-132 show polypeptides that contain at least one serine or threonine residue phosphorylatable by PKD, the positions of which are represented by Xaa. In nature, Xaa is, generally speaking, serine or threonine. In one embodiment of the instant invention, Xaa can be

any amino acid. Ligands where Xaa is serine or threonine can be used as part of a polyligand, however in one embodiment, at least one phosphorylatable serine or threonine is replaced with another amino acid, such as one of the naturally occurring amino acids including, alanine, aspartate, asparagine, cysteine, glutamate, glutamine, phenylalanine, glycine, histidine, isoleucine, leucine, lysine, methionine, proline, arginine, valine, tryptophan, or tyrosine. The Xaa may also be a non-naturally occurring amino acid. In another embodiment, the PKD phosphorylatable serine(s) or threonine(s) are replaced by alanine. The ligands and polyligands of the invention are designed to modulate the endogenous effects of PKD.

In general, ligand monomers based on natural PKD substrates are built by isolating a putative PKD phosphorylation recognition motif in a PKD substrate. Sometimes it is desirable to modify the phosphorylatable residue to an amino acid other than serine or threonine. Additional monomers include the PKD recognition motif as well as amino acids adjacent and contiguous on either side of the PKD recognition motif. Monomeric ligands may therefore be any length provided the monomer includes the PKD recognition motif. For example, the monomer may comprise a PKD recognition motif and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30-100 or more amino acids adjacent to the recognition motif.

For example, in one embodiment, the invention comprises an inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

- a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 194-201 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 199 of SEQ ID NO:117 is an amino acid residue other than serine or threonine;
- b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 191-203 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 199 of SEQ ID NO:117 is an amino acid residue other than serine or threonine;
- c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 189-205 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 199 of SEQ ID NO:117 is an amino acid residue other than serine or threonine; and
- d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 184-207 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 199 of SEQ ID NO:117 is an amino acid residue other than serine or threonine.

As used herein, the terms “correspond(s) to” and “corresponding to,” as they relate to sequence alignment, are intended to mean enumerated positions within a reference protein, e.g., HDAC5 (SEQ ID NO:119), and those positions that align with the positions on the reference protein. Thus, when the amino acid sequence of a subject peptide is aligned with the amino acid sequence of a reference peptide, e.g.,
5 SEQ ID NO:119, the amino acids in the subject peptide sequence that “correspond to” certain enumerated positions of the reference peptide sequence are those that align with these positions of the reference peptide sequence, but are not necessarily in these exact numerical positions of the reference sequence. Methods for aligning sequences for determining corresponding amino acids between sequences are described below.

10 Additional embodiments of the invention include monomers (as described above) based on any putative or real substrate for PKD, such as substrates identified by SEQ ID NOS:1-104 and SEQ ID NOS:117-132. Furthermore, if the substrate has more than one recognition motif, then more than one monomer may be identified therein.

Another embodiment of the invention is a nucleic acid molecule comprising a polynucleotide sequence
15 encoding at least one copy of a ligand peptide.

Another embodiment of the invention is a nucleic acid molecule wherein the polynucleotide sequence encodes one or more copies of one or more peptide ligands.

Another embodiment of the invention is a nucleic acid molecule wherein the polynucleotide sequence encodes at least a number of copies of the peptide selected from the group consisting of 2, 3, 4, 5, 6, 7, 8,
20 9 or 10.

Another embodiment of the invention is a vector comprising a nucleic acid molecule encoding at least one copy of a ligand or polyligand.

Another embodiment of the invention is a recombinant host cell comprising a vector comprising a nucleic acid molecule encoding at least one copy of a ligand or polyligand.

25 Another embodiment of the invention is a method of inhibiting PKD in a cell comprising transfecting a

vector comprising a nucleic acid molecule encoding at least one copy of a ligand or polyligand into a host cell and culturing the transfected host cell under conditions suitable to produce at least one copy of the ligand or polyligand.

- The invention also relates to modified inhibitors that are at least about 80%, 85%, 90% 95%, 96%, 97%, 98% or 99% identical to a reference inhibitor. A “modified inhibitor” is used to mean a peptide that can be created by addition, deletion or substitution of one or more amino acids in the primary structure (amino acid sequence) of a inhibitor protein or polypeptide. A “modified recognition motif” is a naturally occurring PKD recognition motif that has been modified by addition, deletion, or substitution of one or more amino acids in the primary structure (amino acid sequence) of the motif. For example, a modified PKD recognition motif may be a motif where the phosphorylatable amino acid has been modified to a non-phosphorylatable amino acid. The terms “protein” and “polypeptide” are used interchangeably herein. The reference inhibitor is not necessarily a wild-type protein or a portion thereof. Thus, the reference inhibitor may be a protein or peptide whose sequence was previously modified over a wild-type protein. The reference inhibitor may or may not be the wild-type protein from a particular organism.
- 15 A polypeptide having an amino acid sequence at least, for example, about 95% “identical” to a reference amino acid sequence is understood to mean that the amino acid sequence of the polypeptide is identical to the reference sequence except that the amino acid sequence may include up to about five modifications per each 100 amino acids of the reference amino acid sequence encoding the reference peptide. In other words, to obtain a peptide having an amino acid sequence at least about 95% identical to a reference amino acid sequence, up to about 5% of the amino acid residues of the reference sequence may be deleted or substituted with another amino acid or a number of amino acids up to about 5% of the total amino acids in the reference sequence may be inserted into the reference sequence. These modifications of the reference sequence may occur at the N-terminus or C-terminus positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among amino acids in the reference sequence or in one or more contiguous groups within the reference sequence.
- 25

As used herein, “identity” is a measure of the identity of nucleotide sequences or amino acid sequences compared to a reference nucleotide or amino acid sequence. In general, the sequences are aligned so that the highest order match is obtained. “Identity” per se has an art-recognized meaning and can be

calculated using published techniques. (See, e.g., Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York (1988); Biocomputing: Informatics And Genome Projects, Smith, D.W., ed., Academic Press, New York (1993); Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey (1994); von Heinje, G., Sequence Analysis In Molecular Biology, Academic Press (1987); and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York (1991)). While there exist several methods to measure identity between two polynucleotide or polypeptide sequences, the term "identity" is well known to skilled artisans (Carillo, H. & Lipton, D., Siam J Applied Math 48:1073 (1988)). Methods commonly employed to determine identity or similarity between two sequences include, but are not limited to, those disclosed in Guide to Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego (1994) and Carillo, H. & Lipton, D., Siam J Applied Math 48:1073 (1988). Computer programs may also contain methods and algorithms that calculate identity and similarity. Examples of computer program methods to determine identity and similarity between two sequences include, but are not limited to, GCG program package (Devereux, J., et al., Nucleic Acids Research 12(i):387 (1984)), BLASTP, ExPASy, BLASTN, FASTA (Atschul, S. F., et al., J Molec Biol 215:403 (1990)) and FASTDB. Examples of methods to determine identity and similarity are discussed in Michaels, G. and Garian, R., Current Protocols in Protein Science, Vol 1, John Wiley & Sons, Inc. (2000), which is incorporated by reference. In one embodiment of the present invention, the algorithm used to determine identity between two or more polypeptides is BLASTP.

In another embodiment of the present invention, the algorithm used to determine identity between two or more polypeptides is FASTDB, which is based upon the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990), incorporated by reference). In a FASTDB sequence alignment, the query and subject sequences are amino sequences. The result of sequence alignment is in percent identity. Parameters that may be used in a FASTDB alignment of amino acid sequences to calculate percent identity include, but are not limited to: Matrix=PAM, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject amino sequence, whichever is shorter.

If the subject sequence is shorter or longer than the query sequence because of N-terminus or C-terminus additions or deletions, not because of internal additions or deletions, a manual correction can be made, because the FASTDB program does not account for N-terminus and C-terminus truncations or additions

of the subject sequence when calculating percent identity. For subject sequences truncated at both ends, relative to the query sequence, the percent identity is corrected by calculating the number of amino acids of the query sequence that are N-and C-terminus to the reference sequence that are not matched/aligned, as a percent of the total bases of the query sequence. The results of the FASTDB sequence alignment
5 determine matching/alignment. The alignment percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score can be used for the purposes of determining how alignments “correspond” to each other, as well as percentage identity. Residues of the query (subject) sequences or the reference sequence that extend past the N-or C-termini of the reference or subject sequence,
10 respectively, may be considered for the purposes of manually adjusting the percent identity score. That is, residues that are not matched/aligned with the N-or C-termini of the comparison sequence may be counted when manually adjusting the percent identity score or alignment numbering.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue reference sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and
15 therefore, the FASTDB alignment does not show a match/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N-and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is
20 compared with a 100 reference sequence. This time the deletions are internal deletions so there are no residues at the N-or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected.

The polyligands of the invention optionally comprise spacer amino acids before, after, or between monomers. The length and composition of the spacer may vary. An example of a spacer is glycine,
25 alanine, polyglycine, or polyalanine. Specific examples of spacers used between monomers in SEQ ID NO:105 are the four amino acids AGAG, and the four amino acids GAGA. Spacer amino acids may be any amino acid and are not limited to alanine and glycine. The instant invention is directed to all combinations of homopolyligands and heteropolyligands, with or without spacers, and without limitation to the examples given above or below.

The ligands and polyligands of the invention are optionally linked to additional molecules or amino acids that provide an epitope tag, a reporter, and/or localize the ligand to a region of a cell (See FIGURES 5A-5G, FIGURES 6A-6G, FIGURES 7A-7G, and FIGURES 8A-8G). Non-limiting examples of epitope tags are FLAG[™] (Kodak; Rochester, N.Y.), HA (hemagglutinin), c-Myc and His6. Additional examples of epitope tags are given in Jarvik & Telmer 1998 Annual Review of Genetics 32:601-18. Non-limiting examples of reporters are alkaline phosphatase, galactosidase, peroxidase, luciferase and green fluorescent protein (GFP). Non-limiting examples of cellular localizations are sarcoplasmic reticulum, endoplasmic reticulum, mitochondria, golgi apparatus, nucleus, plasma membrane, apical membrane, and basolateral membrane. The epitopes, reporters and localization signals are given by way of example and without limitation. The epitope tag, reporter and/or localization signal may be the same molecule. The epitope tag, reporter and/or localization signal may also be different molecules.

Ligands and polyligands and optional amino acids linked thereto can be synthesized chemically or recombinantly using techniques known in the art. Chemical synthesis techniques include but are not limited to peptide synthesis which is often performed using an automated peptide synthesizer. Peptides can also be synthesized utilizing non-automated peptide synthesis methods known in the art. Recombinant techniques include insertion of ligand-encoding nucleic acids into expression vectors, wherein nucleic acid expression products are synthesized using cellular factors and processes.

Linkage of a cellular localization signal, epitope tag, or reporter to a ligand or polyligand can include covalent or enzymatic linkage to the ligand. When the localization signal comprises material other than a polypeptide, such as a lipid or carbohydrate, a chemical reaction to link molecules may be utilized. Additionally, non-standard amino acids and amino acids modified with lipids, carbohydrates, phosphate or other molecules may be used as precursors to peptide synthesis. The ligands of the invention have therapeutic utility with or without localization signals. However, ligands linked to localization signals have utility as subcellular tools or therapeutics. For example, ligands depicted generically in FIGURES 7A-7G and FIGURES 8A-8G represent ligands with utility as subcellular tools or therapeutics. PKD ligand-containing gene constructs are also delivered via gene therapy. FIGURES 10B and 10C depict embodiments of gene therapy vectors for delivering and controlling polypeptide expression in vivo. Polynucleotide sequences linked to the gene construct in FIGURES 10B and 10C include genome integration domains to facilitate integration of the transgene into a viral genome and/or host genome.

FIGURE 10A shows a vector containing a PKD ligand gene construct, wherein the ligand gene construct is releasable from the vector as a unit useful for generating transgenic animals. For example, the ligand gene construct, or transgene, is released from the vector backbone by restriction endonuclease digestion. The released transgene is then injected into pronuclei of fertilized mouse eggs; or the transgene is used to transform embryonic stem cells. The vector containing a ligand gene construct of FIGURE 10A is also useful for transient transfection of the transgene, wherein the promoter and codons of the transgene are optimized for the host organism. The vector containing a ligand gene construct of FIGURE 10A is also useful for recombinant expression of polypeptides in fermentable organisms adaptable for small or large scale production, wherein the promoter and codons of the transgene are optimized for the fermentation host organism.

FIGURE 10D shows a vector containing a PKD ligand gene construct useful for generating stable cell lines.

The invention also encompasses polynucleotides comprising nucleotide sequences encoding ligands, homopolyligands, and heteropolyligands. The polynucleotides of the invention are optionally linked to additional nucleotide sequences encoding epitopes, reporters and/or localization signals. Further, the nucleic acids of the invention are optionally incorporated into vector polynucleotides. The polynucleotides are optionally flanked by nucleotide sequences comprising restriction endonuclease sites and other nucleotides needed for restriction endonuclease activity. The flanking sequences optionally provide cloning sites within a vector. The restriction sites can include, but are not limited to, any of the commonly used sites in most commercially available cloning vectors. Examples of such sites are those recognized by BamHI, ClaI, EcoRI, EcoRV, SpeI, AflIII, NdeI, NheI, XbaI, XhoI, SphI, NaeI, SexAI, HindIII, HpaI, and PstI restriction endonucleases. Sites for cleavage by other restriction enzymes, including homing endonucleases, are also used for this purpose. The polynucleotide flanking sequences also optionally provide directionality of subsequence cloning. It is preferred that 5' and 3' restriction endonuclease sites differ from each other so that double-stranded DNA can be directionally cloned into corresponding complementary sites of a cloning vector.

Ligands and polyligands with or without localization signals, epitopes or reporters are alternatively synthesized by recombinant techniques. Polynucleotide expression constructs are made containing desired components and inserted into an expression vector. The expression vector is then transfected into

cells and the polypeptide products are expressed and isolated. Ligands made according to recombinant DNA techniques have utility as research tools and/or therapeutics.

5 An example of how nucleotide sequences encoding ligands, homopolyligands, and heteropolyligands are produced is as follows. Complimentary oligonucleotides encoding the ligands and flanking sequences are synthesized and annealed. The resulting double-stranded DNA molecule is inserted into a cloning vector using techniques known in the art. When the ligands and polyligands are placed in-frame adjacent to sequences within a transgenic gene construct that is translated into a protein product, they form part of a fusion protein when expressed in cells or transgenic animals.

10 Another embodiment of the invention relates to selective control of transgene expression in a desired cell or organism. The promotor portion of the recombinant gene can be a constitutive promotor, a non-constitutive promotor, a tissue-specific promotor (constitutive or non-constitutive) or a selectively controlled promotor. Different selectively controlled promotors are controlled by different mechanisms. RheoSwitch^R is an inducible promotor system available from RheoGene. Temperature sensitive promotors can also be used to increase or decrease gene expression. An embodiment of the invention
15 comprises a ligand or polyligand gene construct whose expression is controlled by an inducible promotor.

Polyligands are modular in nature. An aspect of the instant invention is the combinatorial modularity of the disclosed polyligands. Another aspect of the invention are methods of making these modular polyligands easily and conveniently. In this regard, an embodiment of the invention comprises methods
20 of modular subsequence cloning of genetic expression components. When the ligands, homopolyligands, heteropolyligands and optional amino acid expression components are synthesized recombinantly, one can consider each clonable element as a module. For speed and convenience of cloning, it is desirable to make modular elements that are compatible at cohesive ends and are easy to insert and clone sequentially. This is accomplished by exploiting the natural properties of restriction endonuclease site
25 recognition and cleavage. One aspect of the invention encompasses module flanking sequences that, at one end of the module, are utilized for restriction enzyme digestion once, and at the other end, utilized for restriction enzyme digestion as many times as desired. In other words, a restriction site in one part of the module is utilized and destroyed in order to effect sequential cloning of modular elements. An example of restriction sites flanking a coding region of interest are sequences recognized by the

restriction enzymes NgoM IV and Cla I; or Xma I and Cla I. Cutting a first circular DNA with NgoM IV and Cla I to yield linear DNA with a 5' NgoM IV overhang and a 3' Cla I overhang; and cutting a second circular DNA with Xma I and Cla I to yield linear DNA with a 5' Cla I overhang and a 3' Xma I overhang generates first and second DNA fragments with compatible cohesive ends. When these first and second DNA fragments are mixed together, annealed, and ligated to form a third circular DNA fragment, the NgoM IV site that was in the first DNA and the Xma I site that was in the second DNA are destroyed in the third circular DNA. Now this vestigial region of DNA is protected from further Xma I or NgoM IV digestion, but flanking sequences remaining in the third circular DNA still contain intact 5' NgoM IV and 3' Cla I and Xma I sites. This process can be repeated numerous times to achieve directional, sequential, modular cloning events. Restriction sites recognized by NgoM IV, Xma I, and Cla I endonucleases represent a group of sites that permit sequential cloning when used as flanking sequences.

Another way to assemble coding region modules directionally and sequentially employs linear DNA in addition to circular DNA. For example, like the sequential cloning process described above, restriction sites flanking a coding region module are sequences recognized by the restriction enzymes NgoM IV and Cla I; or Xma I and Cla I. Referring to FIGURE 11, a first circular DNA is cut with Xma I and Cla I to yield linear DNA with a 5' Cla I overhang and a 3' Xma I overhang. A second linear double-stranded DNA is generated by PCR amplification followed by digestion, or by synthesizing and annealing complimentary oligonucleotides. The second linear DNA has 5' NgoM IV overhang and a 3' Cla I overhang, which are compatible cohesive ends with the first DNA linearized. When these first and second DNA fragments are mixed together, annealed, and ligated to form a third circular DNA fragment, the Xma I site that was in the first DNA and the NgoM IV site that was in the second DNA are destroyed in the third circular DNA. Flanking sequences remaining in the third circular DNA still contain intact 5' NgoM IV and 3' Cla I and Xma I sites. This process can be repeated numerous times to achieve directional, sequential, modular cloning events. Restriction sites recognized by NgoM IV, Xma I, and Cla I endonucleases represent a group of sites that permit sequential cloning when used as flanking sequences. This process is depicted in FIGURE 11.

One of ordinary skill in the art recognizes that other restriction site groups can accomplish sequential, directional cloning as described herein. Preferred criteria for restriction endonuclease selection are selecting a pair of endonucleases that generate compatible cohesive ends but whose sites are destroyed

upon ligation with each other. Another criteria is to select a third endonuclease site that does not generate sticky ends compatible with either of the first two. When such criteria are utilized as a system for sequential, directional cloning, ligands, polyligands and other coding regions or expression components can be combinatorially assembled as desired. The same sequential process can be utilized for epitope, reporter, and/or localization signals.

Polyligands and methods of making polyligands that modulate PKD activity are disclosed. Therapeutics include delivery of purified ligand or polyligand with or without a localization signal to a cell. Alternatively, ligands and polyligands with or without a localization signals are delivered via adenovirus, lentivirus, adeno-associated virus, or other viral constructs that express protein product in a cell.

10 Example 1

A polypeptide comprising a heteropolyligand, an endoplasmic reticulum cellular localization signal, and a His6 epitope is synthesized. Examples of such polypeptides are generically represented by FIGURES 8B, 8D, 8E and 8F. The polypeptide is synthesized on an automated peptide synthesizer or is recombinantly expressed and purified. Purified polypeptide is solubilized in media and added to cells. The polypeptide is endocytosed by the cells, and transported to the endoplasmic reticulum. Verification is performed by immunohistochemical staining using an anti-His6 antibody.

Example 2

A transgene is constructed using a human cytomegalovirus (CMV) promoter to direct expression of a fusion protein comprising SEQ ID NO:113 (POLYLIGAND), green fluorescent protein (REPORTER), and a nuclear localization signal (LOCALIZATION SIGNAL). Such a transgene is generically represented by FIGURE 9A-9D. The transgene is transfected into cells for transient expression. Verification of expression and location is performed by visualization of green fluorescent protein (GFP) by confocal microscopy.

Example 3

A transgene construct is built to produce a protein product with expression driven by a tissue-specific promoter. The transgene comprises a synthetic gene expression unit engineered to encode three domains. Each of these three domains is synthesized as a pair of complementary polynucleotides that are annealed in solution, ligated and inserted into a vector. Starting at the amino-terminus, the three domains in the

expression unit are nucleotide sequences that encode a PKD ligand, a FLAGTM epitope, and an endoplasmic reticulum localization signal. The PKD ligand is a monomeric ligand, homopolymeric ligand or heteropolymeric ligand as described herein. Nucleotide sequences encoding a FLAGTM epitope are placed downstream of nucleotide sequences encoding the PKD ligand. Finally, nucleotide sequences encoding the localization signal are placed downstream of those encoding the FLAGTM epitope. The assembled gene expression unit is subsequently subcloned into an expression vector, such as that shown in FIGURE 10A, and used to transiently transfect cells. Verification is performed by immunohistochemical staining using an anti-FLAGTM antibody.

Example 4

Ligand function and localization is demonstrated in vivo by making a transgene construct used to generate mice expressing a ligand fusion protein targeted to the endoplasmic reticulum. The transgene construct is shown generically in FIGURE 10B. The expression unit contains nucleotides that encode a tetramer of SEQ ID NO:33, a hemagglutinin epitope, and a mitochondrial localization signal. This expression unit is subsequently subcloned into a pBluscript-based vector (Stratagene; La Jolla, Calif.) between nucleotide sequences including a promoter and an SV40 polyadenylation signal. The completed transgene is then injected into pronuclei of fertilized mouse oocytes. The resultant pups are screened for the presence of the transgene by PCR. Transgenic founder mice are bred with wild-type mice. Heterozygous transgenic animals from at least the third generation are used for the following tests, with their non-transgenic littermates serving as controls.

Test 1: Southern blotting analysis is performed to determine the copy number. Southern blots are hybridized with a radio-labeled probe generated from a fragment of the transgene. The probe detects bands containing DNA from transgenic mice, but does not detect bands containing DNA from non-transgenic mice. Intensities of the transgenic mice bands are measured and compared with the transgene plasmid control bands to estimate copy number. This demonstrates that mice in Example 4 harbor the transgene in their genomes.

Test 2: Tissue homogenates are prepared for Western blot analysis. This experiment demonstrates the transgene is expressed in tissues of transgenic mice because hemagglutinin epitope is detected in transgenic homogenates but not in non-transgenic homogenates.

These examples demonstrate delivery of ligands to a localized region of a cell for therapeutic or experimental purposes. The purified polypeptide ligands can be formulated for oral or parenteral administration, topical administration, or in tablet, capsule, or liquid form, intranasal or inhaled aerosol, subcutaneous, intramuscular, intraperitoneal, or other injection; intravenous instillation; or any other routes of administration. Furthermore, the nucleotide sequences encoding the ligands permit incorporation into a vector designed to deliver and express a gene product in a cell. Such vectors include plasmids, cosmids, artificial chromosomes, and modified viruses. Delivery to eukaryotic cells can be accomplished in vivo or ex vivo. Ex vivo delivery methods include isolation of the intended recipient's cells or donor cells and delivery of the vector to those cells, followed by treatment of the recipient with the cells.

Disclosed are ligands and polyligands that modulate PKD activity and methods of making and using these ligands. The ligands and polyligands are synthesized chemically or recombinantly and are utilized as research tools or as therapeutics. The invention includes linking the ligands and polyligands to cellular localization signals for subcellular therapeutics.

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25 Xaa Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu
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Ser Arg Gln Leu Xaa Xaa Gly Val Ser Glu Ile Arg His Thr Ala Asp
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25 Arg Trp Arg Val Ser Leu Asp Val Asn His
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40 Val Ala Ala Pro Ala Tyr Ser Arg Ala Leu Ser Arg Gln Leu Xaa Xaa
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Gly Val Ser Glu Ile Arg His Thr Ala Asp Arg Trp Arg Val Ser Leu
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Asp Val Asn His Phe Ala Pro Asp Glu Arg Thr Val Lys Thr
 45 50 55 60

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 Asn Glu Asp Glu Pro
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 Lys Arg Thr Ala Xaa Asn Pro Lys Val Glu Asn Glu Asp Glu Pro Val
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 Arg Leu Ala Pro Glu Arg Glu Phe Ile
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 45 1 5 10 15

Thr Ala Ser Ile Ser Leu Ser Ser Asn Leu Lys Arg Thr Ala Xaa Asn
20 25 30

Pro Lys Val Glu Asn Glu Asp Glu Pro Val Arg Leu Ala Pro Glu Arg
35 40 45

5 Glu Phe Ile Lys Ser Leu Met Ala Ile Gly Lys Arg Leu
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20 Leu Arg Tyr Lys Pro
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35 Arg Lys Thr Val Xaa Glu Pro Asn Leu Lys Leu Arg Tyr Lys Pro Lys
20 25 30

Lys Ser Leu Glu Arg Arg Lys Asn Pro
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 Pro Ser Asp Pro Pro Glu His Phe Pro Leu Arg Lys Thr Val Xaa Glu
 20 25 30
 Pro Asn Leu Lys Leu Arg Tyr Lys Pro Lys Lys Ser Leu Glu Arg Arg
 35 40 45
 15 Lys Asn Pro Leu Leu Arg Lys Glu Xaa Ala Pro Pro Ser Leu Arg Arg
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 Arg Arg Arg Pro Ala
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5  Thr Leu Gly Asp Ser Ser Pro Ser Ser
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    20          25          30

Pro Pro Gly Pro Met Gln Pro Arg Leu
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 Leu Ser Gly Ser Gly Leu His Trp Pro Leu Ser Arg Thr Arg Xaa Glu
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 10 Pro Leu Pro Pro Ser Ala Thr Ala Pro Pro Pro Pro Gly Pro Met Gln
 35 40 45
 Pro Arg Leu Glu Gln Leu Lys Thr His Val Gln Val Ile
 50 55 60

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 Ala Ser Leu Ser Ala
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 20 25 30
 Glu Pro Ala Ser Gln Ala Arg Val Leu
 45 35 40

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 15 20 25 30
 Pro Ala Ala Pro Ala Ser Leu Ser Ala Pro Glu Pro Ala Ser Gln Ala
 35 40 45
 Arg Val Leu Ser Ser Ser Glu Thr Pro Ala Arg Thr Leu
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 Lys

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Leu Leu Val Thr Glu
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20 Trp Phe Ser Asp Ile Ser Pro Gln Thr
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Glu Met Thr Lys Leu Gly Ser Lys Thr Ala Leu Asn Arg Arg Asp Thr
 1 5 10 15

35 Tyr Arg Arg Arg Gln Met Gln Arg Thr Ile Thr Arg Gln Met Xaa Phe
 20 25 30

Asp Leu Thr Lys Leu Leu Val Thr Glu Asp Trp Phe Ser Asp Ile Ser
 35 40 45

40 Pro Gln Thr Met Arg Arg Leu Leu Asn Ile Val Ser Val
 50 55 60

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 1 5 10 15

10 Lys Lys Lys Phe Glu
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25 Ile Asp Ala Leu Xaa Gly Met Glu Gly Arg Lys Lys Lys Phe Glu Ser
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Met Glu Gly Arg Lys Lys Lys Phe Glu Ser
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 Thr Glu Pro His
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 20 25 30

30 Lys Lys Lys Ser Lys Ile Ser Ala Ser
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 45 20 25 30
 Pro His Ala Lys Lys Lys Ser Lys Ile Ser Ala Ser Arg Lys Leu Gln

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Leu Lys Thr Leu Leu
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Gly Ser Gly Leu Pro Thr Asp Arg Asp Leu Gly Gly Ala Cys Pro Pro
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45 Gln Asp His Asp Met Gln Gly Leu Ala Glu Arg Ile Xaa Val Leu
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Arg Ile Xaa Ile Leu
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His Glu Met Gln Gly Leu Ala Glu Arg Ile Xaa Ile Leu
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5 Ser Leu Leu Ala Pro Glu
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 20 25 30

Gln Val Gly Arg Ala Ala Ala
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25 <211> 60

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 20 25 30

40 Ala Phe Cys Ser Leu Leu Ala Pro Glu Arg Gln Val Gly Arg Ala Ala
 35 40 45

Ala Ala Leu Met Gln Asp Arg His Thr Ala Ala Gly
 50 55 60

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 Ala Tyr Ser Arg Ala Leu Ser Arg Gln Leu Ala Ser Gly Val Ser Glu
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 Ile Arg His Thr Ala Asp Gly Ala Gly Ala Ser Leu Ser Ser Asn Leu
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 15 Lys Arg Thr Ala Ala Asn Pro Lys Val Glu Asn Glu Asp Glu Pro
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 cagctggcca gcggcgtgag cgagatcagg cacaccgccg acggcgccgg cgccagcctg 180
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 cagctcgcca gcggcgtgag cgagatcagg cacaccgccg acggcgctgg agccagcctg 180
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 35 40 45
 Pro Ser Leu Arg Arg Arg Pro Ala Glu Thr Leu Gly Asp Ser Ser Pro
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 85 90

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 cccgccggcg ccggcctgag gtacaagccc aagaagagcc tggagaggag gaagaacccc 120
 ctgctgagga aggaggccgc cccccccagc ctgaggagga ggcccgcga gaccctgggc 180
 gacagcagcc ccagcagcgg cgccggcgcc ggcoctgact ggcccctgag caggaccagg 240
 40 gccgagcccc tgccccccag cgccaccgcc ccc 273

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 cccgccggag ctggcctgag gtacaagccc aagaaaagcc tggagaggag gaagaacccc 120
 10 ctgctgagga aggaggccgc cccccctagc ctgaggagga ggcccgcga gaccctgggc 180
 gacagcagcc ctacgagcgg agctggcgct ggctgcact ggcccctgag caggaccagg 240
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 15 <212> DNA
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 20 gccggccccg agcacttccc cctgaggaag accgtggcgg agcccaacct gaagctgagg 60
 tacaagcccc cggagctgg cctgaggtac aagcccaaga aaagcctgga gaggaggaag 120
 aacccccctgc tgaggaagga ggccgcccc cctagcctga ggaggaggcc cgccgagacc 180
 ctgggcgaca gcagccctag cagcggagct ggcgctggcc tgcactggcc cctgagcagg 240
 accagggccg agcccctgcc ccctagcgcc accgcccccc ccgggggagg cggaatcgat 300
 25 t 301

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 30 <220>
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 Asp Phe Gly Ile Ser Ala Gln Ile Gly Ala Thr Leu Ala Arg Arg Leu
 1 5 10 15
 35 Ala Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu Ala Ala Leu Val
 20 25 30
 Arg Gln Met Ala Val Ala Phe Phe Phe Lys Pro Ala Gly Ala Gly Ala
 35 40 45
 Ala Leu Val Arg Gln Met Ala Val Ala Phe Phe Phe Lys Asp Phe Gly

	50	55	60	
	Ile Ser Ala Gln Ile Gly Ala Thr Leu Ala Arg Arg Leu Ala Phe Ile			
	65	70	75	80
5	Gly Thr Pro Tyr Trp Met Ala Pro Glu			
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	acccctact ggatggcccc cgaggcgcc ctggtgaggc agatggccgt ggccttcttc		120	
15	ttcaagcccg ccggcgccgg cgctgctctc gtcagacaaa tggctgtcgc tttttttttt		180	
	aaagattttg gaatttccgc tcaaattgga gctacactcg ctagaagact cgcttttatt		240	
	ggaacacctt attgatggc tcctgaa		267	
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	acccctact ggatggcccc cgaggctgcc ctggtgaggc agatggccgt ggccttcttc		120	
	ttcaagcccg ccggagccgg agctgctctc gtcagacaaa tggctgtcgc tttttttttt		180	
	aaagattttg gaatttccgc tcaaattgga gctacactcg ctagaagact cgcttttatt		240	
	ggaacacctt attgatggc tcctgaa		267	
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	atcggcaccc cctactggat ggcccccgag gctgccctgg tgaggcagat ggccgtggcc		120	
	ttctttttca agcccgccgg agccggagct gctctcgtca gacaaatggc tgtogctttt		180	

ttttttaaaag attttggaat ttccgctcaa attggagcta cactcgctag aagactcgct 240
 ttatttggaac caccttattg gatggctcct gaaccggggg gaggcggaat cgatt 295

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 Ala Pro Ile Arg Arg Arg Xaa Xaa Asn Tyr Arg Ala Tyr Ala Thr Glu
 20 20 25 30
 20 Pro His Ala Lys Lys Lys Ser Lys Ile Ser Ala Ser Arg Lys Leu Gln
 35 40 45
 Leu Lys Thr Leu Leu Leu Gln Ile Ala Lys Gln Glu Leu Glu Arg Glu
 50 55 60
 25 Ala Glu Glu Arg Arg Gly Glu Lys Gly Arg Ala Leu Ser Thr Arg Cys
 65 70 75 80
 Gln Pro Leu Glu Leu Ala Gly Leu Gly Phe Ala Glu Leu Gln Asp Leu
 85 90 95
 Cys Arg Gln Leu His Ala Arg Val Asp Lys Val Asp Glu Glu Arg Tyr
 100 105 110
 30 Asp Ile Glu Ala Lys Val Thr Lys Asn Ile Thr Glu Ile Ala Asp Leu
 115 120 125
 Thr Gln Lys Ile Phe Asp Leu Arg Gly Lys Phe Lys Arg Pro Thr Leu
 130 135 140
 35 Arg Arg Val Arg Ile Ser Ala Asp Ala Met Met Gln Ala Leu Leu Gly
 145 150 155 160
 Ala Arg Ala Lys Glu Ser Leu Asp Leu Arg Ala His Leu Lys Gln Val
 165 170 175
 Lys Lys Glu Asp Thr Glu Lys Glu Asn Arg Glu Val Gly Asp Trp Arg
 180 185 190
 40 Lys Asn Ile Asp Ala Leu Xaa Gly Met Glu Gly Arg Lys Lys Lys Phe
 195 200 205

Glu Ser
210

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Val Ser Ser Trp Leu Cys Gln Glu Pro Glu Pro Cys His Pro Gly Phe
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20 Asp Ala Glu Ser Tyr Thr Phe Thr Val Pro Arg Arg His Leu Glu Arg
35 40 45

Gly Arg Val Leu Gly Arg Val Asn Phe Glu Asp Cys Thr Gly Arg Gln
50 55 60

Arg Thr Ala Tyr Phe Ser Leu Asp Thr Arg Phe Lys Val Gly Thr Asp
25 65 70 75 80

Gly Val Ile Thr Val Lys Arg Pro Leu Arg Phe His Asn Pro Gln Ile
85 90 95

His Phe Leu Val Tyr Ala Trp Asp Ser Thr Tyr Arg Lys Phe Ser Thr
100 105 110

30 Lys Val Thr Leu Asn Thr Val Gly His His His Arg Pro Pro Pro His
115 120 125

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

35 Ser Ser Pro Gly Leu Arg Arg Gln Lys Arg Asp Trp Val Ile Pro Pro
145 150 155 160

Ile Ser Cys Pro Glu Asn Glu Lys Gly Pro Phe Pro Lys Asn Leu Val
165 170 175

Gln Ile Lys Ser Asn Lys Asp Lys Glu Gly Lys Val Phe Tyr Ser Ile
180 185 190

40 Thr Gly Gln Gly Ala Asp Thr Pro Pro Val Gly Val Phe Ile Ile Glu
195 200 205

Arg Glu Thr Gly Trp Leu Lys Val Thr Glu Pro Leu Asp Arg Glu Arg

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

	Thr	Ala	Asn	Trp	Leu	Glu	Ile	Asn	Pro	Asp	Thr	Gly	Ala	Ile	Phe	Thr	
	530						535					540					
	Arg	Ala	Glu	Leu	Asp	Arg	Glu	Asp	Phe	Glu	His	Val	Lys	Asn	Ser	Thr	
	545					550					555					560	
5	Tyr	Thr	Ala	Leu	Ile	Ile	Ala	Thr	Asp	Asn	Gly	Ser	Pro	Val	Ala	Thr	
					565					570					575		
	Gly	Thr	Gly	Thr	Leu	Leu	Leu	Ile	Leu	Ser	Asp	Val	Asn	Asp	Asn	Ala	
				580					585					590			
10	Pro	Ile	Pro	Glu	Pro	Arg	Thr	Ile	Phe	Phe	Cys	Glu	Arg	Asn	Pro	Lys	
			595					600					605				
	Pro	Gln	Val	Ile	Asn	Ile	Ile	Asp	Ala	Asp	Leu	Pro	Pro	Asn	Thr	Ser	
	610					615						620					
	Pro	Phe	Thr	Ala	Glu	Leu	Thr	His	Gly	Ala	Ser	Ala	Asn	Trp	Thr	Ile	
	625					630					635					640	
15	Gln	Tyr	Asn	Asp	Pro	Thr	Gln	Glu	Ser	Ile	Ile	Leu	Lys	Pro	Lys	Met	
					645					650					655		
	Ala	Leu	Glu	Val	Gly	Asp	Tyr	Lys	Ile	Asn	Leu	Lys	Leu	Met	Asp	Asn	
				660					665					670			
20	Gln	Asn	Lys	Asp	Gln	Val	Thr	Thr	Leu	Glu	Val	Ser	Val	Cys	Asp	Cys	
			675					680						685			
	Glu	Gly	Ala	Ala	Gly	Val	Cys	Arg	Lys	Ala	Gln	Pro	Val	Glu	Ala	Gly	
		690					695					700					
	Leu	Gln	Ile	Pro	Ala	Ile	Leu	Gly	Ile	Leu	Gly	Gly	Ile	Leu	Ala	Leu	
	705					710					715					720	
25	Leu	Ile	Leu	Ile	Leu	Leu	Leu	Leu	Leu	Phe	Leu	Arg	Arg	Arg	Ala	Val	
					725					730					735		
	Val	Lys	Glu	Pro	Leu	Leu	Pro	Pro	Glu	Asp	Asp	Thr	Arg	Asp	Asn	Val	
				740					745					750			
30	Tyr	Tyr	Tyr	Asp	Glu	Glu	Gly	Gly	Gly	Glu	Glu	Asp	Gln	Asp	Phe	Asp	
			755					760					765				
	Leu	Ser	Gln	Leu	His	Arg	Gly	Leu	Asp	Ala	Arg	Pro	Glu	Val	Thr	Arg	
		770					775					780					
	Asn	Asp	Val	Ala	Pro	Thr	Leu	Met	Ser	Val	Pro	Arg	Tyr	Leu	Pro	Arg	
	785					790					795					800	
35	Pro	Ala	Asn	Pro	Asp	Glu	Ile	Gly	Asn	Phe	Ile	Asp	Glu	Asn	Leu	Lys	
					805					810					815		
	Ala	Ala	Asp	Thr	Asp	Pro	Thr	Ala	Pro	Pro	Tyr	Asp	Ser	Leu	Leu	Val	
				820					825					830			

Phe Asp Tyr Glu Gly Ser Gly Ser Glu Ala Ala Ser Leu Ser Ser Leu
 835 840 845
 Asn Xaa Ser Glu Xaa Asp Lys Asp Gln Asp Tyr Asp Tyr Leu Asn Glu
 850 855 860
 5 Trp Gly Asn Arg Phe Lys Lys Leu Ala Asp Met Tyr Gly Gly Gly Glu
 865 870 875 880
 Asp Asp

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 25 20 25 30
 Val Glu Val Lys Pro Val Leu Pro Arg Ala Met Pro Ser Ser Met Gly
 35 40 45
 Gly Gly Gly Gly Gly Ser Pro Ser Pro Val Glu Leu Arg Gly Ala Leu
 50 55 60
 30 Val Gly Ser Val Asp Pro Thr Leu Arg Glu Gln Gln Leu Gln Gln Glu
 65 70 75 80
 Leu Leu Ala Leu Lys Gln Gln Gln Gln Leu Gln Lys Gln Leu Leu Phe
 85 90 95
 Ala Glu Phe Gln Lys Gln His Asp His Leu Thr Arg Gln His Glu Val
 35 100 105 110
 Gln Leu Gln Lys His Leu Lys Gln Gln Gln Glu Met Leu Ala Ala Lys
 115 120 125
 Gln Gln Gln Glu Met Leu Ala Ala Lys Arg Gln Gln Glu Leu Glu Gln
 130 135 140
 40 Gln Arg Gln Arg Glu Gln Gln Arg Gln Glu Glu Leu Glu Lys Gln Arg
 145 150 155 160
 Leu Glu Gln Gln Leu Leu Ile Leu Arg Asn Lys Glu Lys Ser Lys Glu

				165					170					175			
	Ser	Ala	Ile	Ala	Ser	Thr	Glu	Val	Lys	Leu	Arg	Leu	Gln	Glu	Phe	Leu	
				180					185					190			
5	Leu	Ser	Lys	Ser	Lys	Glu	Pro	Thr	Pro	Gly	Gly	Leu	Asn	His	Ser	Leu	
			195					200					205				
	Pro	Gln	His	Pro	Lys	Cys	Trp	Gly	Ala	His	His	Ala	Ser	Leu	Asp	Gln	
		210					215					220					
	Ser	Ser	Pro	Pro	Gln	Ser	Gly	Pro	Pro	Gly	Thr	Pro	Pro	Ser	Tyr	Lys	
	225					230					235					240	
10	Leu	Pro	Leu	Pro	Gly	Pro	Tyr	Asp	Ser	Arg	Asp	Asp	Phe	Pro	Leu	Arg	
					245					250						255	
	Lys	Thr	Ala	Xaa	Glu	Pro	Asn	Leu	Lys	Val	Arg	Ser	Arg	Leu	Lys	Gln	
				260					265					270			
15	Lys	Val	Ala	Glu	Arg	Arg	Ser	Ser	Pro	Leu	Leu	Arg	Arg	Lys	Asp	Gly	
			275					280					285				
	Thr	Val	Ile	Ser	Thr	Phe	Lys	Lys	Arg	Ala	Val	Glu	Ile	Thr	Gly	Ala	
		290					295					300					
	Gly	Pro	Gly	Ala	Ser	Ser	Val	Cys	Asn	Ser	Ala	Pro	Gly	Ser	Gly	Pro	
	305					310					315					320	
20	Ser	Ser	Pro	Asn	Ser	Ser	His	Ser	Thr	Ile	Ala	Glu	Asn	Gly	Phe	Thr	
				325						330					335		
	Gly	Ser	Val	Pro	Asn	Ile	Pro	Thr	Glu	Met	Leu	Pro	Gln	His	Arg	Ala	
				340					345					350			
25	Leu	Pro	Leu	Asp	Ser	Ser	Pro	Asn	Gln	Phe	Ser	Leu	Tyr	Thr	Ser	Pro	
			355					360					365				
	Ser	Leu	Pro	Asn	Ile	Ser	Leu	Gly	Leu	Gln	Ala	Thr	Val	Thr	Val	Thr	
	370						375					380					
	Asn	Ser	His	Leu	Thr	Ala	Ser	Pro	Lys	Leu	Ser	Thr	Gln	Gln	Glu	Ala	
	385					390					395					400	
30	Glu	Arg	Gln	Ala	Leu	Gln	Ser	Leu	Arg	Gln	Gly	Gly	Thr	Leu	Thr	Gly	
				405						410					415		
	Lys	Phe	Met	Ser	Thr	Ser	Ser	Ile	Pro	Gly	Cys	Leu	Leu	Gly	Val	Ala	
				420					425					430			
35	Leu	Glu	Gly	Asp	Gly	Ser	Pro	His	Gly	His	Ala	Ser	Leu	Leu	Gln	His	
			435					440					445				
	Val	Leu	Leu	Leu	Glu	Gln	Ala	Arg	Gln	Gln	Ser	Thr	Leu	Ile	Ala	Val	
	450						455					460					
	Pro	Leu	His	Gly	Gln	Ser	Pro	Leu	Val	Thr	Gly	Glu	Arg	Val	Ala	Thr	
	465					470					475					480	

Ser Met Arg Thr Val Gly Lys Leu Pro Arg His Arg Pro Leu Ser Arg
 485 490 495
 Thr Gln Xaa Ser Pro Leu Pro Gln Ser Pro Gln Ala Leu Gln Gln Leu
 500 505 510
 5 Val Met Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys Gln Gln
 515 520 525
 Gln Leu Gln Leu Gly Lys Ile Leu Thr Lys Thr Gly Glu Leu Pro Arg
 530 535 540
 10 Gln Pro Thr Thr His Pro Glu Glu Thr Glu Glu Glu Leu Thr Glu Gln
 545 550 555 560
 Gln Glu Val Leu Leu Gly Glu Gly Ala Leu Thr Met Pro Arg Glu Gly
 565 570 575
 Ser Thr Glu Ser Glu Ser Thr Gln Glu Asp Leu Glu Glu Glu Asp Glu
 580 585 590
 15 Glu Asp Asp Gly Glu Glu Glu Glu Asp Cys Ile Gln Val Lys Asp Glu
 595 600 605
 Glu Gly Glu Ser Gly Ala Glu Glu Gly Pro Asp Leu Glu Glu Pro Gly
 610 615 620
 20 Ala Gly Tyr Lys Lys Leu Phe Ser Asp Ala Gln Pro Leu Gln Pro Leu
 625 630 635 640
 Gln Val Tyr Gln Ala Pro Leu Ser Leu Ala Thr Val Pro His Gln Ala
 645 650 655
 Leu Gly Arg Thr Gln Ser Ser Pro Ala Ala Pro Gly Gly Met Lys Ser
 660 665 670
 25 Pro Pro Asp Gln Pro Val Lys His Leu Phe Thr Thr Gly Val Val Tyr
 675 680 685
 Asp Thr Phe Met Leu Lys His Gln Cys Met Cys Gly Asn Thr His Val
 690 695 700
 His Pro Glu His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg Leu Gln
 30 705 710 715 720
 Glu Thr Gly Leu Leu Ser Lys Cys Glu Arg Ile Arg Gly Arg Lys Ala
 725 730 735
 Thr Leu Asp Glu Ile Gln Thr Val His Ser Glu Tyr His Thr Leu Leu
 740 745 750
 35 Tyr Gly Thr Ser Pro Leu Asn Arg Gln Lys Leu Asp Ser Lys Lys Leu
 755 760 765
 Leu Gly Pro Ile Ser Gln Lys Met Tyr Ala Val Leu Pro Cys Gly Gly
 770 775 780

Ile Gly Val Asp Ser Asp Thr Val Trp Asn Glu Met His Ser Ser Ser
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 Ala Val Arg Met Ala Val Gly Cys Leu Leu Glu Leu Ala Phe Lys Val
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 5 Ala Ala Gly Glu Leu Lys Asn Gly Phe Ala Ile Ile Arg Pro Pro Gly
 820 825 830
 His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn Ser
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 10 Val Ala Ile Thr Ala Lys Leu Leu Gln Gln Lys Leu Asn Val Gly Lys
 850 855 860
 Val Leu Ile Val Asp Trp Asp Ile His His Gly Asn Gly Thr Gln Gln
 865 870 875 880
 Ala Phe Tyr Asn Asp Pro Ser Val Leu Tyr Ile Ser Leu His Arg Tyr
 885 890 895
 15 Asp Asn Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Glu Glu Val Gly
 900 905 910
 Gly Gly Pro Gly Val Gly Tyr Asn Val Asn Val Ala Trp Thr Gly Gly
 915 920 925
 20 Val Asp Pro Pro Ile Gly Asp Val Glu Tyr Leu Thr Ala Phe Arg Thr
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 Val Val Met Pro Ile Ala His Glu Phe Ser Pro Asp Val Val Leu Val
 945 950 955 960
 Ser Ala Gly Phe Asp Ala Val Glu Gly His Leu Ser Pro Leu Gly Gly
 965 970 975
 25 Tyr Ser Val Thr Ala Arg Cys Phe Gly His Leu Thr Arg Gln Leu Met
 980 985 990
 Thr Leu Ala Gly Gly Arg Val Val Leu Ala Leu Glu Gly Gly His Asp
 995 1000 1005
 30 Leu Thr Ala Ile Cys Asp Ala Ser Glu Ala Cys Val Ser Ala Leu
 1010 1015 1020
 Leu Ser Val Glu Leu Gln Pro Leu Asp Glu Ala Val Leu Gln Gln
 1025 1030 1035
 Lys Pro Asn Ile Asn Ala Val Ala Thr Leu Glu Lys Val Ile Glu
 1040 1045 1050
 35 Ile Gln Ser Lys His Trp Ser Cys Val Gln Lys Phe Ala Ala Gly
 1055 1060 1065
 Leu Gly Arg Ser Leu Arg Glu Ala Gln Ala Gly Glu Thr Glu Glu
 1070 1075 1080
 Ala Glu Thr Val Ser Ala Met Ala Leu Leu Ser Val Gly Ala Glu

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 Glu Glu Pro Met Glu Gln Glu Pro Ala Leu
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 30 20 25 30
 Pro Gly Pro Gln Pro Gln Pro Met Asp Leu Arg Val Gly Gln Arg Pro
 35 40 45
 Pro Val Glu Pro Pro Pro Glu Pro Thr Leu Leu Ala Leu Gln Arg Pro
 50 55 60
 35 Gln Arg Leu His His His Leu Phe Leu Ala Gly Leu Gln Gln Gln Arg
 65 70 75 80
 Ser Val Glu Pro Met Arg Leu Ser Met Asp Thr Pro Met Pro Glu Leu
 85 90 95
 Gln Val Gly Pro Gln Glu Gln Glu Leu Arg Gln Leu Leu His Lys Asp
 40 100 105 110
 Lys Ser Lys Arg Ser Ala Val Ala Ser Ser Val Val Lys Gln Lys Leu
 115 120 125
 Ala Glu Val Ile Leu Lys Lys Gln Gln Ala Ala Leu Glu Arg Thr Val
 130 135 140

	His	Pro	Asn	Ser	Pro	Gly	Ile	Pro	Tyr	Arg	Thr	Leu	Glu	Pro	Leu	Glu	
	145					150					155					160	
	Thr	Glu	Gly	Ala	Thr	Arg	Ser	Met	Leu	Ser	Ser	Phe	Leu	Pro	Pro	Val	
					165					170					175		
5	Pro	Ser	Leu	Pro	Ser	Asp	Pro	Pro	Glu	His	Phe	Pro	Leu	Arg	Lys	Thr	
				180					185					190			
	Val	Xaa	Glu	Pro	Asn	Leu	Lys	Leu	Arg	Tyr	Lys	Pro	Lys	Lys	Ser	Leu	
			195					200					205				
10	Glu	Arg	Arg	Lys	Asn	Pro	Leu	Leu	Arg	Lys	Glu	Xaa	Ala	Pro	Pro	Ser	
		210					215					220					
	Leu	Arg	Arg	Arg	Pro	Ala	Glu	Thr	Leu	Gly	Asp	Ser	Ser	Pro	Ser	Ser	
	225					230					235					240	
	Ser	Ser	Thr	Pro	Ala	Ser	Gly	Cys	Ser	Ser	Pro	Asn	Asp	Ser	Glu	His	
					245					250					255		
15	Gly	Pro	Asn	Pro	Ile	Leu	Gly	Ser	Glu	Ala	Asp	Ser	Asp	Arg	Arg	Thr	
				260					265					270			
	His	Pro	Thr	Leu	Gly	Pro	Arg	Gly	Pro	Ile	Leu	Gly	Ser	Pro	His	Thr	
			275					280					285				
20	Pro	Leu	Phe	Leu	Pro	His	Gly	Leu	Glu	Pro	Glu	Ala	Gly	Gly	Thr	Leu	
		290					295					300					
	Pro	Ser	Arg	Leu	Gln	Pro	Ile	Leu	Leu	Leu	Asp	Pro	Ser	Gly	Ser	His	
	305					310					315					320	
	Ala	Pro	Leu	Leu	Thr	Val	Pro	Gly	Leu	Gly	Pro	Leu	Pro	Phe	His	Phe	
					325					330					335		
25	Ala	Gln	Ser	Leu	Met	Thr	Thr	Glu	Arg	Leu	Ser	Gly	Ser	Gly	Leu	His	
				340					345					350			
	Trp	Pro	Leu	Ser	Arg	Thr	Arg	Xaa	Glu	Pro	Leu	Pro	Pro	Ser	Ala	Thr	
			355					360					365				
30	Ala	Pro	Pro	Pro	Pro	Gly	Pro	Met	Gln	Pro	Arg	Leu	Glu	Gln	Leu	Lys	
		370				375						380					
	Thr	His	Val	Gln	Val	Ile	Lys	Arg	Ser	Ala	Lys	Pro	Ser	Glu	Lys	Pro	
	385					390					395					400	
	Arg	Leu	Arg	Gln	Ile	Pro	Ser	Ala	Glu	Asp	Leu	Glu	Thr	Asp	Gly	Gly	
					405					410					415		
35	Gly	Pro	Gly	Gln	Val	Val	Asp	Asp	Gly	Leu	Glu	His	Arg	Glu	Leu	Gly	
				420					425					430			
	His	Gly	Gln	Pro	Glu	Ala	Arg	Gly	Pro	Ala	Pro	Leu	Gln	Gln	His	Pro	
			435					440					445				
	Gln	Val	Leu	Leu	Trp	Glu	Gln	Gln	Arg	Leu	Ala	Gly	Arg	Leu	Pro	Arg	

	450		455		460												
	Gly	Ser	Thr	Gly	Asp	Thr	Val	Leu	Leu	Pro	Leu	Ala	Gln	Gly	Gly	His	
	465					470					475					480	
5	Arg	Pro	Leu	Ser	Arg	Ala	Gln	Xaa	Ser	Pro	Ala	Ala	Pro	Ala	Ser	Leu	
					485					490					495		
	Ser	Ala	Pro	Glu	Pro	Ala	Ser	Gln	Ala	Arg	Val	Leu	Ser	Ser	Ser	Glu	
				500					505					510			
	Thr	Pro	Ala	Arg	Thr	Leu	Pro	Phe	Thr	Thr	Gly	Leu	Ile	Tyr	Asp	Ser	
			515					520					525				
10	Val	Met	Leu	Lys	His	Gln	Cys	Ser	Cys	Gly	Asp	Asn	Ser	Arg	His	Pro	
		530					535					540					
	Glu	His	Ala	Gly	Arg	Ile	Gln	Ser	Ile	Trp	Ser	Arg	Leu	Gln	Glu	Arg	
	545					550					555					560	
15	Gly	Leu	Arg	Ser	Gln	Cys	Glu	Cys	Leu	Arg	Gly	Arg	Lys	Ala	Ser	Leu	
					565					570					575		
	Glu	Glu	Leu	Gln	Ser	Val	His	Ser	Glu	Arg	His	Val	Leu	Leu	Tyr	Gly	
				580					585					590			
	Thr	Asn	Pro	Leu	Ser	Arg	Leu	Lys	Leu	Asp	Asn	Gly	Lys	Leu	Ala	Gly	
			595					600					605				
20	Leu	Leu	Ala	Gln	Arg	Met	Phe	Val	Met	Leu	Pro	Cys	Gly	Gly	Val	Gly	
		610					615					620					
	Val	Asp	Thr	Asp	Thr	Ile	Trp	Asn	Glu	Leu	His	Ser	Ser	Asn	Ala	Ala	
	625					630					635					640	
25	Arg	Trp	Ala	Ala	Gly	Ser	Val	Thr	Asp	Leu	Ala	Phe	Lys	Val	Ala	Ser	
					645					650					655		
	Arg	Glu	Leu	Lys	Asn	Gly	Phe	Ala	Val	Val	Arg	Pro	Pro	Gly	His	His	
				660					665					670			
	Ala	Asp	His	Ser	Thr	Ala	Met	Gly	Phe	Cys	Phe	Phe	Asn	Ser	Val	Ala	
			675					680					685				
30	Ile	Ala	Cys	Arg	Gln	Leu	Gln	Gln	Gln	Ser	Lys	Ala	Ser	Lys	Ile	Leu	
		690					695				700						
	Ile	Val	Asp	Trp	Asp	Val	His	His	Gly	Asn	Gly	Thr	Gln	Gln	Thr	Phe	
	705					710					715					720	
35	Tyr	Gln	Asp	Pro	Ser	Val	Leu	Tyr	Ile	Ser	Leu	His	Arg	His	Asp	Asp	
					725					730					735		
	Gly	Asn	Phe	Phe	Pro	Gly	Ser	Gly	Ala	Val	Asp	Glu	Val	Gly	Ala	Gly	
				740					745					750			
	Ser	Gly	Glu	Gly	Phe	Asn	Val	Asn	Val	Ala	Trp	Ala	Gly	Gly	Leu	Asp	
			755					760					765				

Pro Pro Met Gly Asp Pro Glu Tyr Leu Ala Ala Phe Arg Ile Val Val
 770 775 780
 Met Pro Ile Ala Arg Glu Phe Ser Pro Asp Leu Val Leu Val Ser Ala
 785 790 795 800
 5 Gly Phe Asp Ala Ala Glu Gly His Pro Ala Pro Leu Gly Gly Tyr His
 805 810 815
 Val Ser Ala Lys Cys Phe Gly Tyr Met Thr Gln Gln Leu Met Asn Leu
 820 825 830
 10 Ala Gly Gly Ala Val Val Leu Ala Leu Glu Gly Gly His Asp Leu Thr
 835 840 845
 Ala Ile Cys Asp Ala Ser Glu Ala Cys Val Ala Ala Leu Leu Gly Asn
 850 855 860
 Arg Val Asp Pro Leu Ser Glu Glu Gly Trp Lys Gln Lys Pro Asn Leu
 865 870 875 880
 15 Asn Ala Ile Arg Ser Leu Glu Ala Val Ile Arg Val His Ser Lys Tyr
 885 890 895
 Trp Gly Cys Met Gln Arg Leu Ala Ser Cys Pro Asp Ser Trp Val Pro
 900 905 910
 20 Arg Val Pro Gly Ala Asp Lys Glu Glu Val Glu Ala Val Thr Ala Leu
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 Ala Ser Leu Ser Val Gly Ile Leu Ala Glu Asp Arg Pro Ser Glu Gln
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 Leu Val Glu Glu Glu Glu Pro Met Asn Leu
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 Tyr Asp Leu Leu Gln Arg Leu Gly Gly Gly Thr Tyr Gly Glu Val Phe
 20 25 30
 Lys Ala Arg Asp Lys Val Ser Gly Asp Leu Val Ala Leu Lys Met Val
 35 40 45
 40 Lys Met Glu Pro Asp Asp Asp Val Ser Thr Leu Gln Lys Glu Ile Leu

	50		55		60												
	Ile	Leu	Lys	Thr	Cys	Arg	His	Ala	Asn	Ile	Val	Ala	Tyr	His	Gly	Ser	
	65					70					75					80	
5	Tyr	Leu	Trp	Leu	Gln	Lys	Leu	Trp	Ile	Cys	Met	Glu	Phe	Cys	Gly	Ala	
					85					90					95		
	Gly	Ser	Leu	Gln	Asp	Ile	Tyr	Gln	Val	Thr	Gly	Ser	Leu	Ser	Glu	Leu	
				100					105					110			
	Gln	Ile	Ser	Tyr	Val	Cys	Arg	Glu	Val	Leu	Gln	Gly	Leu	Ala	Tyr	Leu	
				115				120					125				
10	His	Ser	Gln	Lys	Lys	Ile	His	Arg	Asp	Ile	Lys	Gly	Ala	Asn	Ile	Leu	
				130			135					140					
	Ile	Asn	Asp	Ala	Gly	Glu	Val	Arg	Leu	Ala	Asp	Phe	Gly	Ile	Ser	Ala	
	145					150					155					160	
15	Gln	Ile	Gly	Ala	Thr	Leu	Ala	Arg	Arg	Leu	Xaa	Phe	Ile	Gly	Thr	Pro	
					165					170					175		
	Tyr	Trp	Met	Ala	Pro	Glu	Val	Ala	Ala	Val	Ala	Leu	Lys	Gly	Gly	Tyr	
				180					185					190			
	Asn	Glu	Leu	Cys	Asp	Ile	Trp	Ser	Leu	Gly	Ile	Thr	Ala	Ile	Glu	Leu	
			195					200					205				
20	Ala	Glu	Leu	Gln	Pro	Pro	Leu	Phe	Asp	Val	His	Pro	Leu	Arg	Val	Leu	
				210			215					220					
	Phe	Leu	Met	Thr	Lys	Ser	Gly	Tyr	Gln	Pro	Pro	Arg	Leu	Lys	Glu	Lys	
	225					230					235					240	
25	Gly	Lys	Trp	Ser	Ala	Ala	Phe	His	Asn	Phe	Ile	Lys	Val	Thr	Leu	Thr	
					245					250					255		
	Lys	Ser	Pro	Lys	Lys	Arg	Pro	Ser	Ala	Thr	Lys	Met	Leu	Ser	His	Gln	
				260					265					270			
	Leu	Val	Ser	Gln	Pro	Gly	Leu	Asn	Arg	Gly	Leu	Ile	Leu	Asp	Leu	Leu	
			275					280					285				
30	Asp	Lys	Leu	Lys	Asn	Pro	Gly	Lys	Gly	Pro	Ser	Ile	Gly	Asp	Ile	Glu	
		290					295					300					
	Asp	Glu	Glu	Pro	Glu	Leu	Pro	Pro	Ala	Ile	Pro	Arg	Arg	Ile	Arg	Ser	
	305					310					315					320	
35	Thr	His	Arg	Ser	Ser	Ser	Leu	Gly	Ile	Pro	Asp	Ala	Asp	Cys	Cys	Arg	
					325					330					335		
	Arg	His	Met	Glu	Phe	Arg	Lys	Leu	Arg	Gly	Met	Glu	Thr	Arg	Pro	Pro	
				340					345					350			
	Ala	Asn	Thr	Ala	Arg	Leu	Gln	Pro	Pro	Arg	Asp	Leu	Arg	Ser	Ser	Ser	
			355					360					365				

	Pro	Arg	Lys	Gln	Leu	Ser	Glu	Ser	Ser	Asp	Asp	Asp	Tyr	Asp	Asp	Val	
	370						375					380					
	Asp	Ile	Pro	Thr	Pro	Ala	Glu	Asp	Thr	Pro	Pro	Pro	Leu	Pro	Pro	Lys	
	385					390					395					400	
5	Pro	Lys	Phe	Arg	Ser	Pro	Ser	Asp	Glu	Gly	Pro	Gly	Ser	Met	Gly	Asp	
					405					410					415		
	Asp	Gly	Gln	Leu	Ser	Pro	Gly	Val	Leu	Val	Arg	Cys	Ala	Ser	Gly	Pro	
				420					425						430		
10	Pro	Pro	Asn	Ser	Pro	Arg	Pro	Gly	Pro	Pro	Pro	Ser	Thr	Ser	Ser	Pro	
			435					440						445			
	His	Leu	Thr	Ala	His	Ser	Glu	Pro	Ser	Leu	Trp	Asn	Pro	Pro	Ser	Arg	
	450						455					460					
	Glu	Leu	Asp	Lys	Pro	Pro	Leu	Leu	Pro	Pro	Lys	Lys	Glu	Lys	Met	Lys	
	465					470					475					480	
15	Arg	Lys	Gly	Cys	Ala	Leu	Leu	Val	Lys	Leu	Phe	Asn	Gly	Cys	Pro	Leu	
					485					490					495		
	Arg	Ile	His	Ser	Thr	Ala	Ala	Trp	Thr	His	Pro	Ser	Thr	Lys	Asp	Gln	
				500					505					510			
20	His	Leu	Leu	Leu	Gly	Ala	Glu	Glu	Gly	Ile	Phe	Ile	Leu	Asn	Arg	Asn	
		515					520						525				
	Asp	Gln	Glu	Ala	Thr	Leu	Glu	Met	Leu	Phe	Pro	Ser	Arg	Thr	Thr	Trp	
	530						535					540					
	Val	Tyr	Ser	Ile	Asn	Asn	Val	Leu	Met	Ser	Leu	Ser	Gly	Lys	Thr	Pro	
	545				550					555						560	
25	His	Leu	Tyr	Ser	His	Ser	Ile	Leu	Gly	Leu	Leu	Glu	Arg	Lys	Glu	Thr	
					565				570						575		
	Arg	Ala	Gly	Asn	Pro	Ile	Ala	His	Ile	Ser	Pro	His	Arg	Leu	Leu	Ala	
				580				585						590			
30	Arg	Lys	Asn	Met	Val	Ser	Thr	Lys	Ile	Gln	Asp	Thr	Lys	Gly	Cys	Arg	
			595					600					605				
	Ala	Cys	Cys	Val	Ala	Glu	Gly	Ala	Ser	Ser	Gly	Gly	Pro	Phe	Leu	Cys	
	610						615					620					
	Gly	Ala	Leu	Glu	Thr	Ser	Val	Val	Leu	Leu	Gln	Trp	Tyr	Gln	Pro	Met	
	625				630						635					640	
35	Asn	Lys	Phe	Leu	Leu	Val	Arg	Gln	Val	Leu	Phe	Pro	Leu	Pro	Thr	Pro	
					645					650					655		
	Leu	Ser	Val	Phe	Ala	Leu	Leu	Thr	Gly	Pro	Gly	Ser	Glu	Leu	Pro	Ala	
				660				665						670			

Val Cys Ile Gly Val Ser Pro Gly Arg Pro Gly Lys Ser Val Leu Phe
675 680 685

His Thr Val Arg Phe Gly Ala Leu Ser Cys Trp Leu Gly Glu Met Ser
690 695 700

5 Thr Glu His Arg Gly Pro Val Gln Val Thr Gln Val Glu Glu Asp Met
705 710 715 720

Val Met Val Leu Met Asp Gly Ser Val Lys Leu Val Thr Pro Glu Gly
725 730 735

10 Ser Pro Val Arg Gly Leu Arg Thr Pro Glu Ile Pro Met Thr Glu Ala
740 745 750

Val Glu Ala Val Ala Met Val Gly Gly Gln Leu Gln Ala Phe Trp Lys
755 760 765

His Gly Val Gln Val Trp Ala Leu Gly Ser Asp Gln Leu Leu Gln Glu
770 775 780

15 Leu Arg Asp Pro Thr Leu Thr Phe Arg Leu Leu Gly Ser Pro Arg Leu
785 790 795 800

Glu Cys Ser Gly Thr Ile Ser Pro His Cys Asn Leu Leu Leu Pro Gly
805 810 815

20 Ser Ser Asn Ser Pro Ala Ser Ala Ser Arg Val Ala Gly Ile Thr Gly
820 825 830

Leu

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 30 <223> Xaa can be any naturally occurring amino acid
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Met Thr Glu Arg Arg Val Pro Phe Ser Leu Leu Arg Gly Pro Ser Trp
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Asp Pro Phe Arg Asp Trp Tyr Pro His Ser Arg Leu Phe Asp Gln Ala
35 20 25 30

Phe Gly Leu Pro Arg Leu Pro Glu Glu Trp Ser Gln Trp Leu Gly Gly
35 40 45

Ser Ser Trp Pro Gly Tyr Val Arg Pro Leu Pro Pro Ala Ala Ile Glu
50 55 60

40 Ser Pro Ala Val Ala Ala Pro Ala Tyr Ser Arg Ala Leu Ser Arg Gln
65 70 75 80

Leu Xaa Ser Gly Val Ser Glu Ile Arg His Thr Ala Asp Arg Trp Arg
 85 90 95
 Val Ser Leu Asp Val Asn His Phe Ala Pro Asp Glu Leu Thr Val Lys
 100 105 110
 5 Thr Lys Asp Gly Val Val Glu Ile Thr Gly Lys His Glu Glu Arg Gln
 115 120 125
 Asp Glu His Gly Tyr Ile Ser Arg Cys Phe Thr Arg Lys Tyr Thr Leu
 130 135 140
 10 Pro Pro Gly Val Asp Pro Thr Gln Val Ser Ser Ser Leu Ser Pro Glu
 145 150 155 160
 Gly Thr Leu Thr Val Glu Ala Pro Met Pro Lys Leu Ala Thr Gln Ser
 165 170 175
 Asn Glu Ile Thr Ile Pro Val Thr Phe Glu Ser Arg Ala Gln Leu Gly
 180 185 190
 15 Gly Pro Glu Ala Ala Lys Ser Asp Glu Thr Ala Ala Lys
 195 200 205

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

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

	Thr	Asp	Gly	Asp	Met	Leu	Gly	Tyr	Asp	Leu	Tyr	Ser	Ser	Ala	Leu	Ala	
			435					440					445				
	Asp	Ile	Leu	Ser	Glu	Pro	Thr	Met	Gln	Pro	Pro	Ile	Cys	Val	Gly	Leu	
		450					455					460					
5	Tyr	Ala	Gln	Trp	Gly	Ser	Gly	Lys	Ser	Phe	Leu	Leu	Lys	Lys	Leu	Glu	
	465					470					475					480	
	Asp	Glu	Met	Lys	Thr	Phe	Ala	Gly	Gln	Gln	Ile	Glu	Pro	Leu	Phe	Gln	
					485					490					495		
10	Phe	Ser	Trp	Leu	Ile	Val	Phe	Leu	Thr	Leu	Leu	Leu	Cys	Gly	Gly	Leu	
				500					505					510			
	Gly	Leu	Leu	Phe	Ala	Phe	Thr	Val	His	Pro	Asn	Leu	Gly	Ile	Ala	Val	
			515						520				525				
	Ser	Leu	Ser	Phe	Leu	Ala	Leu	Leu	Tyr	Ile	Phe	Phe	Ile	Val	Ile	Tyr	
		530					535					540					
15	Phe	Gly	Gly	Arg	Arg	Glu	Gly	Glu	Ser	Trp	Asn	Trp	Ala	Trp	Val	Leu	
	545					550					555					560	
	Ser	Thr	Arg	Leu	Ala	Arg	His	Ile	Gly	Tyr	Leu	Glu	Leu	Leu	Leu	Lys	
				565						570					575		
20	Leu	Met	Phe	Val	Asn	Pro	Pro	Glu	Leu	Pro	Glu	Gln	Thr	Thr	Lys	Ala	
				580					585					590			
	Leu	Pro	Val	Arg	Phe	Leu	Phe	Thr	Asp	Tyr	Asn	Arg	Leu	Ser	Ser	Val	
			595					600					605				
	Gly	Gly	Glu	Thr	Ser	Leu	Ala	Glu	Met	Ile	Ala	Thr	Leu	Ser	Asp	Ala	
		610					615					620					
25	Cys	Glu	Arg	Glu	Phe	Gly	Phe	Leu	Ala	Thr	Arg	Leu	Phe	Arg	Val	Phe	
	625					630					635					640	
	Lys	Thr	Glu	Asp	Thr	Gln	Gly	Lys	Lys	Lys	Trp	Lys	Lys	Thr	Cys	Cys	
				645						650					655		
30	Leu	Pro	Ser	Phe	Val	Ile	Phe	Leu	Phe	Ile	Ile	Gly	Cys	Ile	Ile	Ser	
				660					665					670			
	Gly	Ile	Thr	Leu	Leu	Ala	Ile	Phe	Arg	Val	Asp	Pro	Lys	His	Leu	Thr	
			675					680					685				
	Val	Asn	Ala	Val	Leu	Ile	Ser	Ile	Ala	Ser	Val	Val	Gly	Leu	Ala	Phe	
		690					695					700					
35	Val	Leu	Asn	Cys	Arg	Thr	Trp	Trp	Gln	Val	Leu	Asp	Ser	Leu	Leu	Asn	
	705					710					715					720	
	Ser	Gln	Arg	Lys	Arg	Leu	His	Asn	Ala	Ala	Ser	Lys	Leu	His	Lys	Leu	
					725					730					735		

Lys Ser Glu Gly Phe Met Lys Val Leu Lys Cys Glu Val Glu Leu Met
 740 745 750
 Ala Arg Met Ala Lys Thr Ile Asp Ser Phe Thr Gln Asn Gln Thr Arg
 755 760 765
 5 Leu Val Val Ile Ile Asp Gly Leu Asp Ala Cys Glu Gln Asp Lys Val
 770 775 780
 Leu Gln Met Leu Asp Thr Val Arg Val Leu Phe Ser Lys Gly Pro Phe
 785 790 795 800
 10 Ile Ala Ile Phe Ala Ser Asp Pro His Ile Ile Ile Lys Ala Ile Asn
 805 810 815
 Gln Asn Leu Asn Ser Val Leu Arg Asp Ser Asn Ile Asn Gly His Asp
 820 825 830
 Tyr Met Arg Asn Ile Val His Leu Pro Val Phe Leu Asn Ser Arg Gly
 835 840 845
 15 Leu Ser Asn Ala Arg Lys Phe Leu Val Thr Ser Ala Thr Asn Gly Asp
 850 855 860
 Val Pro Cys Ser Asp Thr Thr Gly Ile Gln Glu Asp Ala Asp Arg Arg
 865 870 875 880
 20 Val Ser Gln Asn Ser Leu Gly Glu Met Thr Lys Leu Gly Ser Lys Thr
 885 890 895
 Ala Leu Asn Arg Arg Asp Thr Tyr Arg Arg Arg Gln Met Gln Arg Thr
 900 905 910
 Ile Thr Arg Gln Met Xaa Phe Asp Leu Thr Lys Leu Leu Val Thr Glu
 915 920 925
 25 Asp Trp Phe Ser Asp Ile Ser Pro Gln Thr Met Arg Arg Leu Leu Asn
 930 935 940
 Ile Val Ser Val Thr Gly Arg Leu Leu Arg Ala Asn Gln Ile Ser Phe
 945 950 955 960
 30 Asn Trp Asp Arg Leu Ala Ser Trp Ile Asn Leu Thr Glu Gln Trp Pro
 965 970 975
 Tyr Arg Thr Ser Trp Leu Ile Leu Tyr Leu Glu Glu Thr Glu Gly Ile
 980 985 990
 Pro Asp Gln Met Thr Leu Lys Thr Ile Tyr Glu Arg Ile Ser Lys Asn
 995 1000 1005
 35 Ile Pro Thr Thr Lys Asp Val Glu Pro Leu Leu Glu Ile Asp Gly
 1010 1015 1020
 Asp Ile Arg Asn Phe Glu Val Phe Leu Ser Ser Arg Thr Pro Val
 1025 1030 1035
 Leu Val Ala Arg Asp Val Lys Val Phe Leu Pro Cys Thr Val Asn

	1040		1045		1050	
	Leu Asp Pro Lys Leu Arg Glu Ile Ile Ala Asp Val Arg Ala Ala					
	1055		1060		1065	
5	Arg Glu Gln Ile Ser Ile Gly Gly Leu Ala Tyr Pro Pro Leu Pro					
	1070		1075		1080	
	Leu His Glu Gly Pro Pro Arg Ala Pro Ser Gly Tyr Ser Gln Pro					
	1085		1090		1095	
	Pro Ser Val Cys Ser Ser Thr Ser Phe Asn Gly Pro Phe Ala Gly					
	1100		1105		1110	
10	Gly Val Val Ser Pro Gln Pro His Ser Ser Tyr Tyr Ser Gly Met					
	1115		1120		1125	
	Thr Gly Pro Gln His Pro Phe Tyr Asn Arg Pro Phe Phe Ala Pro					
	1130		1135		1140	
15	Tyr Leu Tyr Thr Pro Arg Tyr Tyr Pro Gly Gly Ser Gln His Leu					
	1145		1150		1155	
	Ile Ser Arg Pro Ser Val Lys Thr Ser Leu Pro Arg Asp Gln Asn					
	1160		1165		1170	
	Asn Gly Leu Glu Val Ile Lys Glu Asp Ala Ala Glu Gly Leu Ser					
	1175		1180		1185	
20	Ser Pro Thr Asp Ser Ser Arg Gly Ser Gly Pro Ala Pro Gly Pro					
	1190		1195		1200	
	Val Val Leu Leu Asn Ser Leu Asn Val Asp Ala Val Cys Glu Lys					
	1205		1210		1215	
25	Leu Lys Gln Ile Glu Gly Leu Asp Gln Ser Met Leu Pro Gln Tyr					
	1220		1225		1230	
	Cys Thr Thr Ile Lys Lys Ala Asn Ile Asn Gly Arg Val Leu Ala					
	1235		1240		1245	
	Gln Cys Asn Ile Asp Glu Leu Lys Lys Glu Met Asn Met Asn Phe					
	1250		1255		1260	
30	Gly Asp Trp His Leu Phe Arg Ser Thr Val Leu Glu Met Arg Asn					
	1265		1270		1275	
	Ala Glu Ser His Val Val Pro Glu Asp Pro Arg Phe Leu Ser Glu					
	1280		1285		1290	
35	Ser Ser Ser Gly Pro Ala Pro His Gly Glu Pro Ala Arg Arg Ala					
	1295		1300		1305	
	Ser His Asn Glu Leu Pro His Thr Glu Leu Ser Ser Gln Thr Pro					
	1310		1315		1320	
	Tyr Thr Leu Asn Phe Ser Phe Glu Glu Leu Asn Thr Leu Gly Leu					
	1325		1330		1335	

	Asp	Glu	Gly	Ala	Pro	Arg	His	Ser	Asn	Leu	Ser	Trp	Gln	Ser	Gln
	1340						1345					1350			
	Thr	Arg	Arg	Thr	Pro	Ser	Leu	Ser	Ser	Leu	Asn	Ser	Gln	Asp	Ser
	1355						1360					1365			
5	Ser	Ile	Glu	Ile	Ser	Lys	Leu	Thr	Asp	Lys	Val	Gln	Ala	Glu	Tyr
	1370						1375					1380			
	Arg	Asp	Ala	Tyr	Arg	Glu	Tyr	Ile	Ala	Gln	Met	Ser	Gln	Leu	Glu
	1385						1390					1395			
10	Gly	Gly	Pro	Gly	Ser	Thr	Thr	Ile	Ser	Gly	Arg	Ser	Ser	Pro	His
	1400						1405					1410			
	Ser	Thr	Tyr	Tyr	Met	Gly	Gln	Ser	Ser	Ser	Gly	Gly	Ser	Ile	His
	1415						1420					1425			
	Ser	Asn	Leu	Glu	Gln	Glu	Lys	Gly	Lys	Asp	Ser	Glu	Pro	Lys	Pro
	1430						1435					1440			
15	Asp	Asp	Gly	Arg	Lys	Ser	Phe	Leu	Met	Lys	Arg	Gly	Asp	Val	Ile
	1445						1450					1455			
	Asp	Tyr	Ser	Ser	Ser	Gly	Val	Ser	Thr	Asn	Asp	Ala	Ser	Pro	Leu
	1460						1465					1470			
20	Asp	Pro	Ile	Thr	Glu	Glu	Asp	Glu	Lys	Ser	Asp	Gln	Ser	Gly	Ser
	1475						1480					1485			
	Lys	Leu	Leu	Pro	Gly	Lys	Lys	Ser	Ser	Glu	Arg	Ser	Ser	Leu	Phe
	1490						1495					1500			
	Gln	Thr	Asp	Leu	Lys	Leu	Lys	Gly	Ser	Gly	Leu	Arg	Tyr	Gln	Lys
	1505						1510					1515			
25	Leu	Pro	Ser	Asp	Glu	Asp	Glu	Ser	Gly	Thr	Glu	Glu	Ser	Asp	Asn
	1520						1525					1530			
	Thr	Pro	Leu	Leu	Lys	Asp	Asp	Lys	Asp	Arg	Lys	Ala	Glu	Gly	Lys
	1535						1540					1545			
30	Val	Glu	Arg	Val	Pro	Lys	Ser	Pro	Glu	His	Ser	Ala	Glu	Pro	Ile
	1550						1555					1560			
	Arg	Thr	Phe	Ile	Lys	Ala	Lys	Glu	Tyr	Leu	Ser	Asp	Ala	Leu	Leu
	1565						1570					1575			
	Asp	Lys	Lys	Asp	Ser	Ser	Asp	Ser	Gly	Val	Arg	Ser	Ser	Glu	Ser
	1580						1585					1590			
35	Ser	Pro	Asn	His	Ser	Leu	His	Asn	Glu	Val	Ala	Asp	Asp	Ser	Gln
	1595						1600					1605			
	Leu	Glu	Lys	Ala	Asn	Leu	Ile	Glu	Leu	Glu	Asp	Asp	Ser	His	Ser
	1610						1615					1620			

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Gly Lys  Arg Gly Ile Pro His  Ser Leu Ser Gly Leu  Gln Asp Pro
1625                                1630                    1635

Ile Ile  Ala Arg Met Ser  Ile  Cys Ser Glu Asp Lys  Lys Ser Pro
1640                                1645                    1650

5  Ser Glu  Cys Ser Leu Ile  Ala  Ser Ser Pro Glu Glu  Asn Trp Pro
1655                                1660                    1665

Ala Cys  Gln Lys Ala Tyr  Asn  Leu Asn Arg Thr  Pro  Ser Thr Val
1670                                1675                    1680

10 Thr Leu  Asn Asn Asn Ser  Ala  Pro Ala Asn Arg Ala  Asn Gln Asn
1685                                1690                    1695

Phe Asp  Glu Met Glu Gly  Ile  Arg Glu Thr Ser  Gln  Val Ile Leu
1700                                1705                    1710

Arg Pro  Ser Ser Ser Pro  Asn  Pro Thr Thr Ile  Gln  Asn Glu Asn
1715                                1720                    1725

15 Leu Lys  Ser Met Thr His  Lys  Arg Ser Gln Arg  Ser  Ser Tyr Thr
1730                                1735                    1740

Arg Leu  Ser Lys Asp Pro  Pro  Glu Leu His Ala  Ala  Ala Ser Ser
1745                                1750                    1755

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

Ile Thr Glu Gly Val Gly Glu Leu Ser Val Ile Asp Pro Glu Val Ala
35 35 40 45

Gln Lys Ala Cys Gln Glu Val Leu Glu Lys Val Lys Leu Leu His Gly
50 55 60

Gly Val Ala Val Ser Ser Arg Gly Thr Pro Leu Glu Leu Val Asn Gly
65 70 75 80

40 Asp Gly Val Asp Ser Glu Ile Arg Cys Leu Asp Asp Pro Pro Ala Gln
85 90 95

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

	Ala	Arg	Ile	Pro	Glu	Asn	Arg	Ile	Arg	Ser	Thr	Arg	Ser	Val	Glu	Asn
					405					410					415	
	Leu	Pro	Glu	Cys	Gly	Ile	Thr	His	Glu	Gln	Arg	Ala	Gly	Ser	Phe	Ser
				420					425					430		
5	Thr	Val	Pro	Asn	Tyr	Asp	Asn	Asp	Asp	Glu	Ala	Trp	Ser	Val	Asp	Asp
			435				440						445			
	Ile	Gly	Glu	Leu	Gln	Val	Glu	Leu	Pro	Glu	Val	His	Thr	Asn	Ser	Cys
		450					455					460				
10	Asp	Asn	Ile	Ser	Gln	Phe	Ser	Val	Asp	Ser	Ile	Thr	Ser	Gln	Glu	Ser
	465					470					475				480	
	Lys	Glu	Pro	Val	Phe	Ile	Ala	Ala	Gly	Asp	Ile	Arg	Arg	Arg	Leu	Ser
					485					490					495	
	Glu	Gln	Leu	Ala	His	Thr	Pro	Thr	Ala	Phe	Lys	Arg	Asp	Pro	Glu	Asp
				500					505					510		
15	Pro	Ser	Ala	Val	Ala	Leu	Lys	Glu	Pro	Trp	Gln	Glu	Lys	Val	Arg	Arg
			515					520					525			
	Ile	Arg	Glu	Gly	Ser	Pro	Tyr	Gly	His	Leu	Pro	Asn	Trp	Arg	Leu	Leu
		530					535					540				
20	Ser	Val	Ile	Val	Lys	Cys	Gly	Asp	Asp	Leu	Arg	Gln	Glu	Leu	Leu	Ala
	545					550					555					560
	Phe	Gln	Val	Leu	Lys	Gln	Leu	Gln	Ser	Ile	Trp	Glu	Gln	Glu	Arg	Val
					565					570					575	
	Pro	Leu	Trp	Ile	Lys	Pro	Tyr	Lys	Ile	Leu	Val	Ile	Ser	Ala	Asp	Ser
				580					585					590		
25	Gly	Met	Ile	Glu	Pro	Val	Val	Asn	Ala	Val	Ser	Ile	His	Gln	Val	Lys
		595						600					605			
	Lys	Gln	Ser	Gln	Leu	Ser	Leu	Leu	Asp	Tyr	Phe	Leu	Gln	Glu	His	Gly
		610					615					620				
30	Ser	Tyr	Thr	Thr	Glu	Ala	Phe	Leu	Ser	Ala	Gln	Arg	Asn	Phe	Val	Gln
	625					630					635					640
	Ser	Cys	Ala	Gly	Tyr	Cys	Leu	Val	Cys	Tyr	Leu	Leu	Gln	Val	Lys	Asp
					645					650					655	
	Arg	His	Asn	Gly	Asn	Ile	Leu	Leu	Asp	Ala	Glu	Gly	His	Ile	Ile	His
				660					665					670		
35	Ile	Asp	Phe	Gly	Phe	Ile	Leu	Ser	Ser	Ser	Pro	Arg	Asn	Leu	Gly	Phe
		675						680					685			
	Glu	Thr	Ser	Ala	Phe	Lys	Leu	Thr	Thr	Glu	Phe	Val	Asp	Val	Met	Gly
		690					695					700				
	Gly	Leu	Asp	Gly	Asp	Met	Phe	Asn	Tyr	Tyr	Lys	Met	Leu	Met	Leu	Gln

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705              710              715              720
Gly Leu Ile Ala Ala Arg Lys His Met Asp Lys Val Val Gln Ile Val
              725              730              735
5  Glu Ile Met Gln Gln Gly Ser Gln Leu Pro Cys Phe His Gly Ser Ser
              740              745              750
Thr Ile Arg Asn Leu Lys Glu Arg Phe His Met Ser Met Thr Glu Glu
              755              760              765
Gln Leu Gln Leu Leu Val Glu Gln Met Val Asp Gly Ser Met Arg Ser
              770              775              780
10 Ile Thr Thr Lys Leu Tyr Asp Gly Phe Gln Tyr Leu Thr Asn Gly Ile
    785              790              795              800
Met

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Met Ser Ser Asn Cys Thr Ser Thr Thr Ala Val Ala Val Ala Pro Leu
1      5      10      15
25 Ser Ala Ser Lys Thr Lys Thr Lys Lys Lys His Phe Val Cys Gln Lys
    20      25      30
Val Lys Leu Phe Arg Ala Ser Glu Pro Ile Leu Ser Val Leu Met Trp
    35      40      45
30 Gly Val Asn His Thr Ile Asn Glu Leu Ser Asn Val Pro Val Pro Val
    50      55      60
Met Leu Met Pro Asp Asp Phe Lys Ala Tyr Ser Lys Ile Lys Val Asp
65      70      75      80
Asn His Leu Phe Asn Lys Glu Asn Leu Pro Ser Arg Phe Lys Phe Lys
    85      90      95
35 Glu Tyr Cys Pro Met Val Phe Arg Asn Leu Arg Glu Arg Phe Gly Ile
    100     105     110
Asp Asp Gln Asp Tyr Gln Asn Ser Val Thr Arg Ser Ala Pro Ile Asn
    115     120     125
40 Ser Asp Ser Gln Gly Arg Cys Gly Thr Arg Phe Leu Thr Thr Tyr Asp
    130     135     140

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Arg Arg Phe Val Ile Lys Thr Val Ser Ser Glu Asp Val Ala Glu Met
145          150          155          160

His Asn Ile Leu Lys Lys Tyr His Gln Phe Ile Val Glu Cys His Gly
          165          170          175

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

Gly Val Glu Thr Tyr Met Val Val Thr Arg Asn Val Phe Ser His Arg
          195          200          205

10 Leu Thr Val His Arg Lys Tyr Asp Leu Lys Gly Ser Thr Val Ala Arg
    210          215          220

Glu Ala Ser Asp Lys Glu Lys Ala Lys Asp Leu Pro Thr Phe Lys Asp
225          230          235          240

Asn Asp Phe Leu Asn Glu Gly Gln Lys Leu His Val Gly Glu Glu Ser
          245          250          255

15 Lys Lys Asn Phe Leu Glu Lys Leu Lys Arg Asp Val Glu Phe Leu Ala
    260          265          270

Gln Leu Lys Ile Met Asp Tyr Ser Leu Leu Val Gly Ile His Asp Val
    275          280          285

20 Asp Arg Ala Glu Gln Glu Glu Met Glu Val Glu Glu Arg Ala Glu Asp
    290          295          300

Glu Glu Cys Glu Asn Asp Gly Val Gly Gly Asn Leu Leu Cys Ser Tyr
305          310          315          320

Gly Thr Pro Pro Asp Ser Pro Gly Asn Leu Leu Ser Phe Pro Arg Phe
          325          330          335

25 Phe Gly Pro Gly Glu Phe Asp Pro Ser Val Asp Val Tyr Ala Met Lys
    340          345          350

Ser His Glu Ser Ser Pro Lys Lys Glu Val Tyr Phe Met Ala Ile Ile
    355          360          365

30 Asp Ile Leu Thr Pro Tyr Asp Thr Lys Lys Lys Ala Ala His Ala Ala
    370          375          380

Lys Xaa Val Lys His Gly Ala Gly Ala Glu Ile Ser Thr Val Asn Pro
385          390          395          400

Glu Gln Tyr Ser Lys Arg Phe Asn Glu Phe Met Ser Asn Ile Leu
          405          410          415

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<400> 126

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   Ser Ala Ser Lys Thr Lys Thr Lys Lys Lys His Phe Val Cys Gln Lys
      20          25          30

   Val Lys Leu Phe Arg Ala Ser Glu Pro Ile Leu Ser Val Leu Met Trp
      35          40          45

10  Gly Val Asn His Thr Ile Asn Glu Leu Ser Asn Val Pro Val Pro Val
   50          55          60

   Met Leu Met Pro Asp Asp Phe Lys Ala Tyr Ser Lys Ile Lys Val Asp
   65          70          75          80

   Asn His Leu Phe Asn Lys Glu Asn Leu Pro Ser Arg Phe Lys Phe Lys
15          85          90          95

   Glu Tyr Cys Pro Met Val Phe Arg Asn Leu Arg Glu Arg Phe Gly Ile
      100          105          110

   Asp Asp Gln Asp Tyr Gln Asn Ser Val Thr Arg Ser Ala Pro Ile Asn
      115          120          125

20  Ser Asp Ser Gln Gly Arg Cys Gly Thr Arg Phe Leu Thr Thr Tyr Asp
   130          135          140

   Arg Arg Phe Val Ile Lys Thr Val Ser Ser Glu Asp Val Ala Glu Met
   145          150          155          160

   His Asn Ile Leu Lys Lys Tyr His Gln Phe Ile Val Glu Cys His Gly
25          165          170          175

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

   Gly Val Glu Thr Tyr Met Val Val Thr Arg Asn Val Phe Ser His Arg
      195          200          205

30  Leu Thr Val His Arg Lys Tyr Asp Leu Lys Gly Ser Thr Val Ala Arg
   210          215          220

   Glu Ala Ser Asp Lys Glu Lys Ala Lys Asp Leu Pro Thr Phe Lys Asp
   225          230          235          240

   Asn Asp Phe Leu Asn Glu Gly Gln Lys Leu His Val Gly Glu Glu Ser
35          245          250          255

   Lys Lys Asn Phe Leu Glu Lys Leu Lys Arg Asp Val Glu Phe Leu Ala
      260          265          270

   Gln Leu Lys Ile Met Asp Tyr Ser Leu Leu Val Gly Ile His Asp Val
      275          280          285

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Asp Arg Ala Glu Gln Glu Glu Met Glu Val Glu Glu Arg Ala Glu Glu
 290 295 300
 Glu Glu Cys Glu Asn Asp Gly Val Gly Gly Ser Leu Leu Cys Ser Tyr
 305 310 315 320
 5 Gly Thr Pro Pro Asp Ser Pro Gly Asn Leu Leu Ser Phe Pro Arg Phe
 325 330 335
 Phe Gly Pro Gly Glu Phe Asp Pro Ser Val Asp Val Tyr Ala Met Lys
 340 345 350
 10 Ser His Glu Ser Ala Pro Lys Lys Glu Val Tyr Phe Met Ala Ile Ile
 355 360 365
 Asp Ile Leu Thr Pro Tyr Asp Ala Lys Lys Lys Ala Ala His Ala Ala
 370 375 380
 Lys Xaa Val Lys His Gly Ala Gly Ala Glu Ile Ser Thr Val Asn Pro
 385 390 395 400
 15 Glu Gln Tyr Ser Lys Arg Phe Asn Glu Phe Met Ser Asn Ile Leu Thr
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 30 Phe Val Gln Gln Lys Val Lys Val Phe Arg Ala Ala Asp Pro Leu Val
 35 40 45
 Gly Val Phe Leu Trp Gly Val Ala His Ser Ile Asn Glu Leu Ser Gln
 50 55 60
 Val Pro Pro Pro Val Met Leu Leu Pro Asp Asp Phe Lys Ala Ser Ser
 35 65 70 75 80
 Lys Ile Lys Val Asn Asn His Leu Phe His Arg Glu Asn Leu Pro Ser
 85 90 95
 His Phe Lys Phe Lys Glu Tyr Cys Pro Gln Val Phe Arg Asn Leu Arg
 100 105 110
 40 Asp Arg Phe Ala Ile Asp Asp His Asp Tyr Leu Val Ser Leu Thr Arg
 115 120 125

Ser Pro Pro Ser Glu Thr Glu Gly Ser Asp Gly Arg Phe Leu Ile Ser
 130 135 140
 Tyr Asp Arg Thr Leu Val Ile Lys Glu Val Ser Ser Glu Asp Ile Ala
 145 150 155 160
 5 Asp Met His Ser Asn Leu Ser Asn Tyr His Gln Tyr Ile Val Lys Cys
 165 170 175
 His Gly Asn Thr Leu Leu Pro Gln Phe Leu Gly Met Tyr Arg Val Ser
 180 185 190
 10 Val Glu Asn Glu Asp Ser Tyr Met Leu Val Met Arg Asn Met Phe Ser
 195 200 205
 His Arg Leu Pro Val His Arg Lys Tyr Asp Leu Lys Gly Ser Leu Val
 210 215 220
 Ser Arg Glu Ala Ser Asp Lys Glu Lys Val Lys Glu Leu Pro Thr Leu
 225 230 235 240
 15 Lys Asp Met Asp Phe Leu Asn Lys Asn Gln Lys Val Tyr Ile Gly Glu
 245 250 255
 Glu Glu Lys Lys Val Phe Leu Glu Lys Leu Lys Arg Asp Val Glu Phe
 260 265 270
 20 Leu Val Gln Leu Lys Ile Met Asp Tyr Ser Leu Leu Leu Gly Ile His
 275 280 285
 Asp Ile Ile Arg Gly Ser Glu Pro Glu Glu Glu Gly Pro Val Arg Glu
 290 295 300
 Glu Glu Ser Glu Trp Asp Gly Asp Cys Asn Leu Thr Gly Pro Pro Ala
 305 310 315 320
 25 Leu Val Gly Ser Tyr Gly Thr Ser Pro Glu Gly Ile Gly Gly Tyr Ile
 325 330 335
 His Ser His Arg Pro Leu Gly Pro Gly Glu Phe Glu Ser Phe Ile Asp
 340 345 350
 30 Val Tyr Ala Ile Arg Ser Ala Glu Gly Ala Pro Glu Gly Gly Val Phe
 355 360 365
 His Gly Leu Ile Asp Ile Leu Thr Gln Tyr Asp Ala Lys Lys Lys Ala
 370 375 380
 Ala His Ala Ala Lys Xaa Val Lys His Gly Ala Gly Ala Glu Ile Ser
 385 390 395 400
 35 Thr Val His Pro Glu Gln Tyr Ala Lys Arg Phe Leu Asp Phe Ile Ser
 405 410 415
 Asn Ile Phe Ala
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 Pro Ser Ser Phe Thr Thr Gly His Leu Ala Arg Glu Lys Pro Ala Gln
 20 25 30
 15 Asp Pro Leu Tyr Asp Val Pro Asn Ala Ser Gly Gly Gln Ala Gly Gly
 35 40 45
 Pro Gln Arg Pro Gly Arg Val Val Ser Leu Arg Glu Arg Leu Leu Leu
 50 55 60
 Thr Arg Pro Val Trp Leu Gln Leu Gln Ala Asn Ala Ala Ala Ala Leu
 65 70 75 80
 20 His Met Leu Arg Thr Glu Pro Pro Gly Thr Phe Leu Val Arg Lys Ser
 85 90 95
 Asn Thr Arg Gln Cys Gln Ala Leu Cys Met Arg Leu Pro Glu Ala Ser
 100 105 110
 25 Gly Pro Ser Phe Val Ser Ser His Tyr Ile Leu Glu Ser Pro Gly Gly
 115 120 125
 Val Ser Leu Glu Gly Ser Glu Leu Met Phe Pro Asp Leu Val Gln Leu
 130 135 140
 Ile Cys Ala Tyr Cys His Thr Arg Asp Ile Leu Leu Leu Pro Leu Gln
 145 150 155 160
 30 Leu Pro Arg Ala Ile His His Ala Ala Thr His Lys Glu Leu Glu Ala
 165 170 175
 Ile Ser His Leu Gly Ile Glu Phe Trp Ser Ser Ser Leu Asn Ile Lys
 180 185 190
 35 Ala Gln Arg Gly Pro Ala Gly Gly Pro Val Leu Pro Gln Leu Lys Ala
 195 200 205
 Arg Ser Pro Gln Glu Leu Asp Gln Gly Thr Gly Ala Ala Leu Cys Phe
 210 215 220
 Phe Asn Pro Leu Phe Pro Gly Asp Leu Gly Pro Thr Lys Arg Glu Lys
 225 230 235 240
 40 Phe Lys Arg Ser Phe Lys Val Arg Val Ser Thr Glu Thr Ser Ser Pro
 245 250 255

	Leu	Ser	Pro	Pro	Ala	Val	Pro	Pro	Pro	Pro	Val	Pro	Val	Leu	Pro	Gly
				260					265					270		
	Ala	Val	Pro	Ser	Gln	Thr	Glu	Arg	Leu	Pro	Pro	Cys	Gln	Leu	Leu	Arg
			275					280					285			
5	Arg	Glu	Ser	Ser	Val	Gly	Tyr	Arg	Val	Pro	Ala	Gly	Ser	Gly	Pro	Ser
		290					295					300				
	Leu	Pro	Pro	Met	Pro	Ser	Leu	Gln	Glu	Val	Asp	Cys	Gly	Ser	Pro	Ser
	305					310					315					320
10	Ser	Ser	Glu	Glu	Glu	Gly	Val	Pro	Gly	Ser	Arg	Gly	Ser	Pro	Ala	Thr
					325					330					335	
	Ser	Pro	His	Leu	Gly	Arg	Arg	Arg	Pro	Leu	Leu	Arg	Ser	Met	Xaa	Ala
				340					345					350		
	Ala	Phe	Cys	Ser	Leu	Leu	Ala	Pro	Glu	Arg	Gln	Val	Gly	Arg	Ala	Ala
			355					360					365			
15	Ala	Ala	Leu	Met	Gln	Asp	Arg	His	Thr	Ala	Ala	Gly	Gln	Leu	Val	Gln
		370					375					380				
	Asp	Leu	Leu	Thr	Gln	Val	Arg	Ala	Gly	Pro	Glu	Pro	Gln	Glu	Leu	Gln
	385					390					395					400
20	Gly	Ile	Arg	Gln	Ala	Leu	Ser	Arg	Ala	Arg	Ala	Met	Leu	Ser	Ala	Glu
				405						410					415	
	Leu	Gly	Pro	Glu	Lys	Leu	Leu	Ser	Pro	Lys	Arg	Leu	Glu	His	Val	Leu
				420					425					430		
	Glu	Lys	Ser	Leu	His	Cys	Ser	Val	Leu	Lys	Pro	Leu	Arg	Pro	Ile	Leu
			435					440					445			
25	Ala	Ala	Arg	Leu	Arg	Arg	Arg	Leu	Ala	Ala	Asp	Gly	Ser	Leu	Gly	Arg
		450					455					460				
	Leu	Ala	Glu	Gly	Leu	Arg	Leu	Ala	Arg	Ala	Gln	Gly	Pro	Gly	Ala	Phe
	465					470					475					480
30	Gly	Ser	His	Leu	Ser	Leu	Pro	Ser	Pro	Val	Glu	Leu	Glu	Gln	Val	Arg
				485					490					495		
	Gln	Lys	Leu	Leu	Gln	Leu	Leu	Arg	Thr	Tyr	Ser	Pro	Ser	Ala	Gln	Val
				500					505					510		
	Lys	Arg	Leu	Leu	Gln	Ala	Cys	Lys	Leu	Leu	Tyr	Met	Ala	Leu	Arg	Thr
			515					520					525			
35	Gln	Glu	Gly	Glu	Gly	Ala	Gly	Ala	Asp	Glu	Phe	Leu	Pro	Leu	Leu	Ser
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	Leu	Val	Leu	Ala	His	Cys	Asp	Leu	Pro	Glu	Leu	Leu	Leu	Glu	Ala	Glu
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Tyr Met Ser Glu Leu Leu Glu Pro Ser Leu Leu Thr Gly Glu Gly Gly
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 Tyr Tyr Leu Thr Ser Leu Ser Ala Ser Leu Ala Leu Leu Ser Gly Leu
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 5 Gly Gln Ala His Thr Leu Pro Leu Ser Pro Val Gln Glu Leu Arg Arg
 595 600 605
 Ser Leu Ser Leu Trp Glu Gln Arg Arg Leu Pro Ala Thr His Cys Phe
 610 615 620
 10 Gln His Leu Leu Arg Val Ala Tyr Gln Asp Pro Ser Ser Gly Cys Thr
 625 630 635 640
 Ser Lys Thr Leu Ala Val Pro Pro Glu Ala Ser Ile Ala Thr Leu Asn
 645 650 655
 Gln Leu Cys Ala Thr Lys Phe Arg Val Thr Gln Pro Asn Thr Phe Gly
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 15 Leu Phe Leu Tyr Lys Glu Gln Gly Tyr His Arg Leu Pro Pro Gly Ala
 675 680 685
 Leu Ala His Arg Leu Pro Thr Thr Gly Tyr Leu Val Tyr Arg Arg Ala
 690 695 700
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 705 710 715 720
 Gln Ser Glu Ala Arg Ser Arg Gly Glu Glu Gln Gly Cys Gln Gly Asp
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 Gly Asp Ala Gly Val Lys Ala Ser Pro Arg Asp Ile Arg Glu Gln Ser
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5	Gly Thr Ser Asn Lys Leu Thr	Gln Leu Gly Thr Phe	Glu Asp His Phe
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	Leu Ser Leu Gln Arg Met Phe Asn Asn Cys	Glu Val Val Leu Gly Asn	
	50	55	60
	Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr	Asp Leu Ser Phe Leu Lys	
	65	70	75
10	Thr Ile Gln Glu Val Ala Gly Tyr Val	Leu Ile Ala Leu Asn Thr Val	
	85	90	95
	Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg	Gly Asn Met Tyr	
	100	105	110
15	Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn	Tyr Asp Ala Asn	
	115	120	125
	Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn	Leu Gln Glu Ile Leu	
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	His Gly Ala Val Arg Phe Ser Asn Asn Pro	Ala Leu Cys Asn Val Glu	
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20	Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp	Phe Leu Ser Asn Met	
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	Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln	Lys Cys Asp Pro	
	180	185	190
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	Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser	Gly Arg Cys Arg	
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	Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys	Ala Ala Gly Cys	
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30	Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg	Lys Phe Arg Asp	
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	Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met	Leu Tyr Asn Pro	
	260	265	270
35	Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr	Ser Phe Gly	
	275	280	285
	Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val	Thr Asp His	
	290	295	300
	Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met	Glu Glu	
	305	310	315
			320

	Asp	Gly	Val	Arg	Lys	Cys	Lys	Lys	Cys	Glu	Gly	Pro	Cys	Arg	Lys	Val	
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	Cys	Asn	Gly	Ile	Gly	Ile	Gly	Glu	Phe	Lys	Asp	Ser	Leu	Ser	Ile	Asn	
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	Leu	His	Ile	Leu	Pro	Val	Ala	Phe	Arg	Gly	Asp	Ser	Phe	Thr	His	Thr	
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10	Pro	Pro	Leu	Asp	Pro	Gln	Glu	Leu	Asp	Ile	Leu	Lys	Thr	Val	Lys	Glu	
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	Ile	Thr	Gly	Phe	Leu	Leu	Ile	Gln	Ala	Trp	Pro	Glu	Asn	Arg	Thr	Asp	
				405						410					415		
	Leu	His	Ala	Phe	Glu	Asn	Leu	Glu	Ile	Ile	Arg	Gly	Arg	Thr	Lys	Gln	
				420					425					430			
15	His	Gly	Gln	Phe	Ser	Leu	Ala	Val	Val	Ser	Leu	Asn	Ile	Thr	Ser	Leu	
			435					440					445				
	Gly	Leu	Arg	Ser	Leu	Lys	Glu	Ile	Ser	Asp	Gly	Asp	Val	Ile	Ile	Ser	
		450					455					460					
20	Gly	Asn	Lys	Asn	Leu	Cys	Tyr	Ala	Asn	Thr	Ile	Asn	Trp	Lys	Lys	Leu	
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	Phe	Gly	Thr	Ser	Gly	Gln	Lys	Thr	Lys	Ile	Ile	Ser	Asn	Arg	Gly	Glu	
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	Asn	Ser	Cys	Lys	Ala	Thr	Gly	Gln	Val	Cys	His	Ala	Leu	Cys	Ser	Pro	
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25	Glu	Gly	Cys	Trp	Gly	Pro	Glu	Pro	Arg	Asp	Cys	Val	Ser	Cys	Arg	Asn	
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	Glu	Cys	Leu	Pro	Gln	Ala	Met	Asn	Ile	Thr	Cys	Thr	Gly	Arg	Gly	Pro	
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	Asp	Asn	Cys	Ile	Gln	Cys	Ala	His	Tyr	Ile	Asp	Gly	Pro	His	Cys	Val	
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	Lys	Tyr	Ala	Asp	Ala	Gly	His	Val	Cys	His	Leu	Cys	His	Pro	Asn	Cys	
		610					615					620					

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 Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu
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 5 Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His
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 Ile Val Arg Lys Arg Xaa Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu
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 10 Val Glu Pro Leu Xaa Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu
 690 695 700
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 740 745 750
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 755 760 765
 20 Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser
 770 775 780
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 Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp
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 Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp
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 35 Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser
 900 905 910
 Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu
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 Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr

930 935 940
 Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys
 945 950 955 960
 Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln
 5 965 970 975
 Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro
 980 985 990
 Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp
 995 1000 1005
 10 Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe
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 Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu
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 15 Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn
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 Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg
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 Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp
 1070 1075 1080
 20 Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val Pro
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 Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln
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 25 Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro
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15 Leu Phe Gly Lys Gly Asp Ser Glu Glu Ala Phe Pro Val Asp Cys Pro
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His Glu Glu Gly Glu Leu Asp Ser Cys Pro Thr Ile Thr Val Ser Pro
65 65 70 75 80

Val Ile Thr Ile Gln Arg Pro Gly Asp Gly Pro Thr Gly Ala Arg Leu
20 85 90 95

Leu Ser Gln Asp Ser Val Ala Ala Ser Thr Glu Lys Thr Leu Arg Leu
100 100 105 110

Tyr Asp Arg Arg Xaa Ile Phe Glu Ala Val Ala Gln Asn Asn Cys Gln
115 115 120 125

25 Asp Leu Glu Ser Leu Leu Leu Phe Leu Gln Lys Ser Lys Lys His Leu
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Thr Asp Asn Glu Phe Lys Asp Pro Glu Thr Gly Lys Thr Cys Leu Leu
145 145 150 155 160

Lys Ala Met Leu Asn Leu His Asp Gly Gln Asn Thr Thr Ile Pro Leu
30 165 170 175

Leu Leu Glu Ile Ala Arg Gln Thr Asp Ser Leu Lys Glu Leu Val Asn
180 180 185 190

Ala Ser Tyr Thr Asp Ser Tyr Tyr Lys Gly Gln Thr Ala Leu His Ile
195 195 200 205

35 Ala Ile Glu Arg Arg Asn Met Ala Leu Val Thr Leu Leu Val Glu Asn
210 210 215 220

Gly Ala Asp Val Gln Ala Ala Ala His Gly Asp Phe Phe Lys Lys Thr
225 225 230 235 240

Lys Gly Arg Pro Gly Phe Tyr Phe Gly Glu Leu Pro Leu Ser Leu Ala
40 245 250 255

Ala Cys Thr Asn Gln Leu Gly Ile Val Lys Phe Leu Leu Gln Asn Ser

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		290					295					300				
	Phe	Val	Thr	Ser	Met	Tyr	Asn	Glu	Ile	Leu	Met	Leu	Gly	Ala	Lys	Leu
	305					310					315					320
	His	Pro	Thr	Leu	Lys	Leu	Glu	Glu	Leu	Thr	Asn	Lys	Lys	Gly	Met	Thr
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	Ile	Leu	Gln	Arg	Glu	Ile	Gln	Glu	Pro	Glu	Cys	Arg	His	Leu	Ser	Arg
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	Leu	Ser	Cys	Ile	Asp	Thr	Cys	Glu	Lys	Asn	Ser	Val	Leu	Glu	Val	Ile
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	Ala	Tyr	Ser	Ser	Ser	Glu	Thr	Pro	Asn	Arg	His	Asp	Met	Leu	Leu	Val
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20	Glu	Pro	Leu	Asn	Arg	Leu	Leu	Gln	Asp	Lys	Trp	Asp	Arg	Phe	Val	Lys
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	Arg	Ile	Phe	Tyr	Phe	Asn	Phe	Leu	Val	Tyr	Cys	Leu	Tyr	Met	Ile	Ile
			435					440					445			
25	Phe	Thr	Met	Ala	Ala	Tyr	Tyr	Arg	Pro	Val	Asp	Gly	Leu	Pro	Pro	Phe
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	Lys	Met	Glu	Lys	Thr	Gly	Asp	Tyr	Phe	Arg	Val	Thr	Gly	Glu	Ile	Leu
	465					470					475					480
	Ser	Val	Leu	Gly	Gly	Val	Tyr	Phe	Phe	Phe	Arg	Gly	Ile	Gln	Tyr	Phe
				485						490					495	
30	Leu	Gln	Arg	Arg	Pro	Ser	Met	Lys	Thr	Leu	Phe	Val	Asp	Ser	Tyr	Ser
				500					505					510		
	Glu	Met	Leu	Phe	Phe	Leu	Gln	Ser	Leu	Phe	Met	Leu	Ala	Thr	Val	Val
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	Leu	Ala	Leu	Gly	Trp	Thr	Asn	Met	Leu	Tyr	Tyr	Thr	Arg	Gly	Phe	Gln
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 Asp Ser Ser Tyr Asn Ser Leu Tyr Ser Thr Cys Leu Glu Leu Phe Lys
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 10 Phe Thr Ile Gly Met Gly Asp Leu Glu Phe Thr Glu Asn Tyr Asp Phe
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 Lys Ala Val Phe Ile Ile Leu Leu Leu Ala Tyr Val Ile Leu Thr Tyr
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 Ile Leu Leu Leu Asn Met Leu Ile Ala Leu Met Gly Glu Thr Val Asn
 675 680 685
 15 Lys Ile Ala Gln Glu Ser Lys Asn Ile Trp Lys Leu Gln Arg Ala Ile
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 Thr Ile Leu Asp Thr Glu Lys Ser Phe Leu Lys Cys Met Arg Lys Ala
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 Asp Asp Tyr Arg Trp Cys Phe Arg Val Asp Glu Val Asn Trp Thr Thr
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 Trp Asn Thr Asn Val Gly Ile Ile Asn Glu Asp Pro Gly Asn Cys Glu
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 25 Gly Val Lys Arg Thr Leu Ser Phe Ser Leu Arg Ser Ser Arg Val Ser
 770 775 780
 Gly Arg His Trp Lys Asn Phe Ala Leu Val Pro Leu Leu Arg Glu Ala
 785 790 795 800
 Ser Ala Arg Asp Arg Gln Ser Ala Gln Pro Glu Glu Val Tyr Leu Arg
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Pro Leu Leu Pro Gln Ile Pro Ala Pro Gly Ser Gly Val Ser Phe His
10 35           40           45

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

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

15 Phe Pro Glu Cys Gly Phe Tyr Gly Leu Tyr Asp Lys Ile Leu Leu Phe
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Lys His Asp Pro Thr Ser Ala Asn Leu Leu Gln Leu Val Arg Ser Ser
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Gly Asp Ile Gln Glu Gly Asp Leu Val Glu Val Val Leu Ser Ala Ser
20 115          120          125

Ala Thr Phe Glu Asp Phe Gln Ile Arg Pro His Ala Leu Thr Val His
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Ser Tyr Arg Ala Pro Ala Phe Cys Asp His Cys Gly Glu Met Leu Phe
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25 Gly Leu Val Arg Gln Gly Leu Lys Cys Asp Gly Cys Gly Leu Asn Tyr
  165          170          175

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

35 Ser Ser Ala Ser Ser Tyr Thr Gly Arg Pro Ile Glu Leu Asp Lys Met
  245          250          255

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

Thr Arg Pro Thr Val Cys Gln Ala Cys Lys Lys Leu Leu Lys Gly Leu
40 275          280          285

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	Lys	Ser	Ala	Leu	Met	Asp	Glu	Ser	Glu	Asp	Ser	Gly	Val	Ile	Pro	Gly
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			355					360					365			
	Gly	Gly	Lys	Ala	Gln	Ser	Ser	Leu	Gly	Tyr	Ile	Pro	Leu	Met	Arg	Val
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15	Glu	Gly	Trp	Val	Val	His	Tyr	Ser	Asn	Lys	Asp	Thr	Leu	Arg	Lys	Arg
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	His	Tyr	Trp	Arg	Leu	Asp	Cys	Lys	Cys	Ile	Thr	Leu	Phe	Gln	Asn	Asn
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	Val	Glu	Ser	Ala	Gln	Asn	Phe	Ser	Leu	Val	Pro	Pro	Gly	Thr	Asn	Pro
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	His	Cys	Phe	Glu	Ile	Val	Thr	Ala	Asn	Ala	Thr	Tyr	Phe	Val	Gly	Glu
		465				470					475					480
25	Met	Pro	Gly	Gly	Thr	Pro	Gly	Gly	Pro	Ser	Gly	Gln	Gly	Ala	Glu	Ala
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	Ala	Arg	Gly	Trp	Glu	Thr	Ala	Ile	Arg	Gln	Ala	Leu	Met	Pro	Val	Ile
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	Ser	Leu	Ser	Ile	Ser	Val	Ser	Asn	Ser	Gln	Ile	Gln	Glu	Asn	Val	Asp
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35	Gln	Phe	Gly	Val	Val	Tyr	Gly	Gly	Lys	His	Arg	Lys	Thr	Gly	Arg	Asp
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	Val	Ala	Val	Lys	Val	Ile	Asp	Lys	Leu	Arg	Phe	Pro	Thr	Lys	Gln	Glu
				580					585					590		

Ser Gln Leu Arg Asn Glu Val Ala Ile Leu Gln Ser Leu Arg His Pro
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 Gly Ile Val Asn Leu Glu Cys Met Phe Glu Thr Pro Glu Lys Val Phe
 610 615 620
 5 Val Val Met Glu Lys Leu His Gly Asp Met Leu Glu Met Ile Leu Ser
 625 630 635 640
 Ser Glu Lys Gly Arg Leu Pro Glu Arg Leu Thr Lys Phe Leu Ile Thr
 645 650 655
 10 Gln Ile Leu Val Ala Leu Arg His Leu His Phe Lys Asn Ile Val His
 660 665 670
 Cys Asp Leu Lys Pro Glu Asn Val Leu Leu Ala Ser Ala Asp Pro Phe
 675 680 685
 Pro Gln Val Lys Leu Cys Asp Phe Gly Phe Ala Arg Ile Ile Gly Glu
 690 695 700
 15 Lys Ser Phe Arg Arg Ser Val Val Gly Thr Pro Ala Tyr Leu Ala Pro
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 20 Val Gly Val Ile Met Tyr Val Ser Leu Ser Gly Thr Phe Pro Phe Asn
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 Pro Ala Ser Pro Trp Ser His Ile Ser Ala Gly Ala Ile Asp Leu Ile
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 Ser Leu Ser His Pro Trp Leu Gln Glu Tyr Gln Thr Trp Leu Asp Leu
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 Ile Gln Ile Gly Leu Thr Arg Glu Phe Val Leu Leu Pro Ala Ala Ser
 50 55 60
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 65 70 75 80
 Phe Pro Glu Cys Gly Phe Tyr Gly Leu Tyr Asp Lys Ile Leu Leu Phe
 85 90 95
 20 Lys His Asp Pro Thr Ser Ala Asn Leu Leu Gln Leu Val Arg Ser Ala
 100 105 110
 Ala Asp Ile Gln Glu Gly Asp Leu Val Glu Val Val Leu Ser Ala Ser
 115 120 125
 Ala Thr Phe Glu Asp Phe Gln Ile Arg Pro His Ala Leu Thr Val His
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 25 Ser Tyr Arg Ala Pro Ala Phe Cys Asp His Cys Gly Glu Met Leu Phe
 145 150 155 160
 Gly Leu Val Arg Gln Gly Leu Lys Cys Asp Gly Cys Gly Leu Asn Tyr
 165 170 175
 30 His Lys Arg Cys Ala Phe Ser Ile Pro Asn Asn Cys Ser Gly Ala Arg
 180 185 190
 Lys Arg Arg Leu Ser Ser Thr Ser Leu Ala Ser Gly His Ser Val Arg
 195 200 205
 Leu Gly Ser Ser Glu Ser Leu Pro Cys Thr Ala Glu Glu Leu Ser Arg
 210 215 220
 35 Ser Thr Thr Asp Leu Leu Pro Arg Arg Pro Pro Ser Ser Ser Ser Ser
 225 230 235 240
 Ser Ser Ser Ser Ser Phe Tyr Thr Gly Arg Pro Ile Glu Leu Asp Lys
 245 250 255
 40 Met Leu Met Ser Lys Val Lys Val Pro His Thr Phe Leu Ile His Ser
 260 265 270

Tyr Thr Arg Pro Thr Val Cys Gln Ala Cys Lys Lys Leu Leu Lys Gly
 275 280 285
 Leu Phe Arg Gln Gly Leu Gln Cys Lys Asp Cys Lys Phe Asn Cys His
 290 295 300
 5 Lys Arg Cys Ala Thr Arg Val Pro Asn Asp Cys Leu Gly Glu Ala Leu
 305 310 315 320
 Ile Asn Gly Asp Val Pro Met Glu Glu Ala Ala Asp Tyr Ser Glu Ala
 325 330 335
 10 Asp Lys Ser Ser Ile Ser Asp Glu Leu Glu Asp Ser Gly Val Ile Pro
 340 345 350
 Gly Ser His Ser Glu Ser Ala Leu His Ala Ser Glu Glu Glu Glu Gly
 355 360 365
 Glu Gly His Lys Ala Gln Ser Ser Leu Gly Tyr Ile Pro Leu Met Arg
 370 375 380
 15 Val Val Gln Ser Val Arg His Thr Thr Arg Lys Ser Ser Thr Thr Leu
 385 390 395 400
 Arg Glu Gly Trp Val Val His Tyr Ser Asn Lys Asp Thr Leu Arg Lys
 405 410 415
 20 Arg His Tyr Trp Arg Leu Asp Cys Lys Cys Ile Thr Leu Phe Gln Asn
 420 425 430
 Asn Thr Thr Asn Arg Tyr Tyr Lys Glu Ile Pro Leu Ser Glu Ile Leu
 435 440 445
 Ala Val Glu Pro Ala Gln Asn Phe Ser Leu Val Pro Pro Gly Thr Asn
 450 455 460
 25 Pro His Cys Phe Glu Ile Ile Thr Ala Asn Val Thr Tyr Phe Val Gly
 465 470 475 480
 Glu Thr Pro Gly Gly Ala Pro Gly Gly Pro Ser Gly Gln Gly Thr Glu
 485 490 495
 30 Ala Val Arg Gly Trp Glu Thr Ala Ile Arg Gln Ala Leu Met Pro Val
 500 505 510
 Ile Leu Gln Asp Ala Pro Ser Ala Pro Gly His Thr Pro His Arg Gln
 515 520 525
 Ala Ser Leu Ser Ile Ser Val Ser Asn Ser Gln Ile Gln Glu Asn Val
 530 535 540
 35 Asp Ile Ala Thr Val Tyr Gln Ile Phe Pro Asp Glu Val Leu Gly Ser
 545 550 555 560
 Gly Gln Phe Gly Val Val Tyr Gly Gly Lys His Arg Lys Thr Gly Arg
 565 570 575
 Asp Val Ala Val Lys Val Ile Asp Lys Leu Arg Phe Pro Thr Lys Gln

	580		585		590
	Glu Ser Gln Leu Arg Asn Glu Val Ala Ile Leu Gln Ser Leu Arg His				
	595		600		605
5	Pro Gly Ile Val Asn Leu Glu Cys Met Phe Glu Thr Pro Glu Lys Val				
	610		615		620
	Phe Val Val Met Glu Lys Leu His Gly Asp Met Leu Glu Met Ile Leu				
	625		630		635
	Ser Ser Glu Lys Gly Arg Leu Pro Glu Arg Leu Thr Lys Phe Leu Ile				
			645		650
10	Thr Gln Ile Leu Val Ala Leu Arg His Leu His Phe Lys Asn Ile Val				
			660		665
	His Cys Asp Leu Lys Pro Glu Asn Val Leu Leu Ala Ser Ala Asp Pro				
			675		680
15	Phe Pro Gln Val Lys Leu Cys Asp Phe Gly Phe Ala Arg Ile Ile Gly				
	690		695		700
	Glu Lys Ser Phe Arg Arg Ser Val Val Gly Thr Pro Ala Tyr Leu Ala				
	705		710		715
	Pro Glu Val Leu Leu Asn Gln Gly Tyr Asn Arg Ser Leu Asp Met Trp				
			725		730
20	Ser Val Gly Val Ile Met Tyr Val Ser Leu Ser Gly Thr Phe Pro Phe				
			740		745
	Asn Glu Asp Glu Asp Ile Asn Asp Gln Ile Gln Asn Ala Ala Phe Met				
			755		760
25	Tyr Pro Ala Ser Pro Trp Ser His Ile Ser Ser Gly Ala Ile Asp Leu				
	770		775		780
	Ile Asn Asn Leu Leu Gln Val Lys Met Arg Lys Arg Tyr Ser Val Asp				
	785		790		795
	Lys Ser Leu Ser His Pro Trp Leu Gln Glu Tyr Gln Thr Trp Leu Asp				
			805		810
30	Leu Arg Glu Leu Glu Gly Lys Met Gly Glu Arg Tyr Ile Thr His Glu				
			820		825
	Ser Asp Asp Ala Arg Trp Asp Gln Phe Val Ala Glu Arg His Gly Thr				
			835		840
35	Pro Ala Glu Gly Asp Leu Gly Gly Ala Cys Leu Pro Gln Asp His Glu				
	850		855		860
	Met Gln Gly Leu Ala Glu Arg Ile Xaa Ile Leu				
	865		870		875

WHAT IS CLAIMED IS:

1. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:
 - a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 19-29 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 23 of SEQ ID NO:117 is an amino acid residue other than serine or threonine;
 - b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 18-30 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 23 of SEQ ID NO:117 is an amino acid residue other than serine or threonine;
 - c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 15-32 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 23 of SEQ ID NO:117 is an amino acid residue other than serine or threonine; and
 - d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 9-35 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 23 of SEQ ID NO:117 is an amino acid residue other than serine or threonine.

2. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:
 - a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 19-29 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 24 of SEQ ID NO:117 is an amino acid residue other than serine or threonine;
 - b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 18-30 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 24 of SEQ ID NO:117 is an amino acid residue other than serine or threonine;
 - c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 15-32 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 24 of SEQ ID NO:117 is an amino acid residue other than serine or threonine; and
 - d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 9-35 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 24 of SEQ ID NO:117 is an amino acid residue other than serine or threonine.

3. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:
 - a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 194-201 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 199 of SEQ ID NO:117 is an amino acid residue other than serine or threonine;

- b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 191-203 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 199 of SEQ ID NO:117 is an amino acid residue other than serine or threonine;
- c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 189-205 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 199 of SEQ ID NO:117 is an amino acid residue other than serine or threonine; and
- d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 184-207 of SEQ ID NO:117, wherein the amino acid residue corresponding to amino acid residue 199 of SEQ ID NO:117 is an amino acid residue other than serine or threonine.

4. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

- a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 847-855 of the amino acid sequence of SEQ ID NO:118, wherein the amino acid residue corresponding to amino acid residue 850 of SEQ ID NO:118 is an amino acid residue other than serine or threonine;
- b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 843-852 of the amino acid sequence of SEQ ID NO:118, wherein the amino acid residue corresponding to amino acid residue 850 of SEQ ID NO:118 is an amino acid residue other than serine or threonine;
- c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 842-859 of the amino acid sequence of SEQ ID NO:118, wherein the amino acid residue corresponding to amino acid residue 850 of SEQ ID NO:118 is an amino acid residue other than serine or threonine; and
- d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 839-862 of the amino acid sequence of SEQ ID NO:118, wherein the amino acid residue corresponding to amino acid residue 850 of SEQ ID NO:118 is an amino acid residue other than serine or threonine.

5. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

- a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 848-857 of the amino acid sequence of SEQ ID NO:118, wherein the amino acid residue corresponding to amino acid residue 853 of SEQ ID NO:118 is an amino acid residue other than serine or threonine;
- b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino

acid residues 843-859 of the amino acid sequence of SEQ ID NO:118, wherein the amino acid residue corresponding to amino acid residue 853 of SEQ ID NO:118 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 841-861 of the amino acid sequence of SEQ ID NO:118, wherein the amino acid residue corresponding to amino acid residue 853 of SEQ ID NO:118 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 851-862 of the amino acid sequence of SEQ ID NO:118, wherein the amino acid residue corresponding to amino acid residue 853 of SEQ ID NO:118 is an amino acid residue other than serine or threonine.

6. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 255-264 of the amino acid sequence of SEQ ID NO:119, wherein the amino acid residue corresponding to amino acid residue 260 of SEQ ID NO:119 is an amino acid residue other than serine or threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 253-266 of the amino acid sequence of SEQ ID NO:119, wherein the amino acid residue corresponding to amino acid residue 260 of SEQ ID NO:119 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 250-270 of the amino acid sequence of SEQ ID NO:119, wherein the amino acid residue corresponding to amino acid residue 260 of SEQ ID NO:119 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 245-275 of the amino acid sequence of SEQ ID NO:119 wherein the amino acid residue corresponding to amino acid residue 260 of SEQ ID NO:119 is an amino acid residue other than serine or threonine.

7. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 494-502 of the amino acid sequence of SEQ ID NO:119, wherein the amino acid residue corresponding to amino acid residue 499 of SEQ ID NO:119 is an amino acid residue other than serine or

threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 491-506 of the amino acid sequence of SEQ ID NO:119, wherein the amino acid residue corresponding to amino acid residue 499 of SEQ ID NO:119 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 488-509 of the amino acid sequence of SEQ ID NO:119, wherein the amino acid residue corresponding to amino acid residue 499 of SEQ ID NO:119 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 485-514 of the amino acid sequence of SEQ ID NO:119 wherein the amino acid residue corresponding to amino acid residue 499 of SEQ ID NO:119 is an amino acid residue other than serine or threonine.

8. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 189-198 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 194 of SEQ ID NO:120 is an amino acid residue other than serine or threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 185-202 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 194 of SEQ ID NO:120 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 182-206 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 194 of SEQ ID NO:120 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 179-209 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 194 of SEQ ID NO:120 is an amino acid residue other than serine or threonine.

9. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino

acid residues 216-225 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 220 of SEQ ID NO:120 is an amino acid residue other than serine or threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 212-230 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 220 of SEQ ID NO:120 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 209-234 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 220 of SEQ ID NO:120 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 204-238 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 220 of SEQ ID NO:120 is an amino acid residue other than serine or threonine.

10. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 483-492 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 488 of SEQ ID NO:120 is an amino acid residue other than serine or threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 479-496 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 488 of SEQ ID NO:120 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 476-502 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 488 of SEQ ID NO:120 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 472-508 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 488 of SEQ ID NO:120 is an amino acid residue other than serine or threonine.

11. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

- a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 355-364 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 360 of SEQ ID NO:120 is an amino acid residue other than serine or threonine;
- b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 351-367 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 360 of SEQ ID NO:120 is an amino acid residue other than serine or threonine;
- c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 348-376 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 360 of SEQ ID NO:120 is an amino acid residue other than serine or threonine; and
- d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 344-380 of the amino acid sequence of SEQ ID NO:120, wherein the amino acid residue corresponding to amino acid residue 360 of SEQ ID NO:120 is an amino acid residue other than serine or threonine.

12. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

- a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 166-175 of the amino acid sequence of SEQ ID NO:121, wherein the amino acid residue corresponding to amino acid residue 171 of SEQ ID NO:121 is an amino acid residue other than serine or threonine;
- b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 164-180 of the amino acid sequence of SEQ ID NO:121, wherein the amino acid residue corresponding to amino acid residue 171 of SEQ ID NO:121 is an amino acid residue other than serine or threonine;
- c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 160-184 of the amino acid sequence of SEQ ID NO:121, wherein the amino acid residue corresponding to amino acid residue 171 of SEQ ID NO:121 is an amino acid residue other than serine or threonine; and
- d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 157-188 of the amino acid sequence of SEQ ID NO:121, wherein the amino acid residue corresponding to amino acid residue 171 of SEQ ID NO:121 is an amino acid residue other than serine or

threonine.

13. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

- a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 77-85 of the amino acid sequence of SEQ ID NO:122, wherein the amino acid residue corresponding to amino acid residue 82 of SEQ ID NO:122 is an amino acid residue other than serine or threonine;
- b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 73-88 of the amino acid sequence of SEQ ID NO:122, wherein the amino acid residue corresponding to amino acid residue 82 of SEQ ID NO:122 is an amino acid residue other than serine or threonine;
- c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 70-92 of the amino acid sequence of SEQ ID NO:122, wherein the amino acid residue corresponding to amino acid residue 82 of SEQ ID NO:122 is an amino acid residue other than serine or threonine; and
- d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 66-97 of the amino acid sequence of SEQ ID NO:122, wherein the amino acid residue corresponding to amino acid residue 82 of SEQ ID NO:122 is an amino acid residue other than serine or threonine.

14. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

- a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 913-922 of the amino acid sequence of SEQ ID NO:123, wherein the amino acid residue corresponding to amino acid residue 918 of SEQ ID NO:123 is an amino acid residue other than serine or threonine;
- b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 909-926 of the amino acid sequence of SEQ ID NO:123, wherein the amino acid residue corresponding to amino acid residue 918 of SEQ ID NO:123 is an amino acid residue other than serine or threonine;
- c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 904-931 of the amino acid sequence of SEQ ID NO:123, wherein the amino acid residue corresponding to amino acid residue 918 of SEQ ID NO:123 is an amino acid residue other than serine or threonine; and
- d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino

acid residues 902-936 of the amino acid sequence of SEQ ID NO:123, wherein the amino acid residue corresponding to amino acid residue 918 of SEQ ID NO:123 is an amino acid residue other than serine or threonine.

15. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

- a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 289-298 of the amino acid sequence of SEQ ID NO:124, wherein the amino acid residue corresponding to amino acid residue 294 of SEQ ID NO:124 is an amino acid residue other than serine or threonine;
- b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 287-302 of the amino acid sequence of SEQ ID NO:124, wherein the amino acid residue corresponding to amino acid residue 294 of SEQ ID NO:124 is an amino acid residue other than serine or threonine;
- c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 283-308 of the amino acid sequence of SEQ ID NO:124, wherein the amino acid residue corresponding to amino acid residue 294 of SEQ ID NO:124 is an amino acid residue other than serine or threonine; and
- d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 279-313 of the amino acid sequence of SEQ ID NO:124, wherein the amino acid residue corresponding to amino acid residue 294 of SEQ ID NO:124 is an amino acid residue other than serine or threonine.

16. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

- a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 381-390 of the amino acid sequence of SEQ ID NO:125, wherein the amino acid residue corresponding to amino acid residue 386 of SEQ ID NO:125 is an amino acid residue other than serine or threonine;
- b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 379-393 of the amino acid sequence of SEQ ID NO:125, wherein the amino acid residue corresponding to amino acid residue 386 of SEQ ID NO:125 is an amino acid residue other than serine or threonine;
- c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 374-398 of the amino acid sequence of SEQ ID NO:125, wherein the amino acid residue corresponding to amino acid residue 386 of SEQ ID NO:125 is an amino acid residue other than serine or

threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 371-402 of the amino acid sequence of SEQ ID NO:125, wherein the amino acid residue corresponding to amino acid residue 386 of SEQ ID NO:125 is an amino acid residue other than serine or threonine.

17. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 381-390 of the amino acid sequence of SEQ ID NO:126, wherein the amino acid residue corresponding to amino acid residue 386 of SEQ ID NO:126 is an amino acid residue other than serine or threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 376-391 of the amino acid sequence of SEQ ID NO:126, wherein the amino acid residue corresponding to amino acid residue 386 of SEQ ID NO:126 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 365-395 of the amino acid sequence of SEQ ID NO:126, wherein the amino acid residue corresponding to amino acid residue 386 of SEQ ID NO:126 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 362-398 of the amino acid sequence of SEQ ID NO:126, wherein the amino acid residue corresponding to amino acid residue 386 of SEQ ID NO:126 is an amino acid residue other than serine or threonine.

18. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 386-394 of the amino acid sequence of SEQ ID NO:127, wherein the amino acid residue corresponding to amino acid residue 390 of SEQ ID NO:127 is an amino acid residue other than serine or threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 384-397 of the amino acid sequence of SEQ ID NO:127, wherein the amino acid residue corresponding to amino acid residue 390 of SEQ ID NO:127 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino

acid residues 381-399 of the amino acid sequence of SEQ ID NO:127, wherein the amino acid residue corresponding to amino acid residue 390 of SEQ ID NO:127 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 374-395 of the amino acid sequence of SEQ ID NO:127, wherein the amino acid residue corresponding to amino acid residue 390 of SEQ ID NO:127 is an amino acid residue other than serine or threonine.

19. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 346-355 of the amino acid sequence of SEQ ID NO:128, wherein the amino acid residue corresponding to amino acid residue 351 of SEQ ID NO:128 is an amino acid residue other than serine or threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 344-359 of the amino acid sequence of SEQ ID NO:128, wherein the amino acid residue corresponding to amino acid residue 351 of SEQ ID NO:128 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 341-364 of the amino acid sequence of SEQ ID NO:128, wherein the amino acid residue corresponding to amino acid residue 351 of SEQ ID NO:128 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 337-367 of the amino acid sequence of SEQ ID NO:128, wherein the amino acid residue corresponding to amino acid residue 351 of SEQ ID NO:128 is an amino acid residue other than serine or threonine.

20. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 674-682 of the amino acid sequence of SEQ ID NO:129, wherein the amino acid residue corresponding to amino acid residue 678 of SEQ ID NO:129 is an amino acid residue other than serine or threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 670-687 of the amino acid sequence of SEQ ID NO:129, wherein the amino acid residue corresponding to amino acid residue 678 of SEQ ID NO:129 is an amino acid residue other than serine or

threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 668-690 of the amino acid sequence of SEQ ID NO:129, wherein the amino acid residue corresponding to amino acid residue 678 of SEQ ID NO:129 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 665-692 of the amino acid sequence of SEQ ID NO:129, wherein the amino acid residue corresponding to amino acid residue 678 of SEQ ID NO:129 is an amino acid residue other than serine or threonine.

21. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 689-696 of the amino acid sequence of SEQ ID NO:129, wherein the amino acid residue corresponding to amino acid residue 693 of SEQ ID NO:129 is an amino acid residue other than serine or threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 687-698 of the amino acid sequence of SEQ ID NO:129, wherein the amino acid residue corresponding to amino acid residue 693 of SEQ ID NO:129 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 683-702 of the amino acid sequence of SEQ ID NO:129, wherein the amino acid residue corresponding to amino acid residue 693 of SEQ ID NO:129 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 679-706 of the amino acid sequence of SEQ ID NO:129, wherein the amino acid residue corresponding to amino acid residue 693 of SEQ ID NO:129 is an amino acid residue other than serine or threonine.

22. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 111-121 of the amino acid sequence of SEQ ID NO:130, wherein the amino acid residue corresponding to amino acid residue 117 of SEQ ID NO:130 is an amino acid residue other than serine or threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino

acid residues 107-125 of the amino acid sequence of SEQ ID NO:130, wherein the amino acid residue corresponding to amino acid residue 117 of SEQ ID NO:130 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 104-130 of the amino acid sequence of SEQ ID NO:130, wherein the amino acid residue corresponding to amino acid residue 117 of SEQ ID NO:130 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 100-133 of the amino acid sequence of SEQ ID NO:130, wherein the amino acid residue corresponding to amino acid residue 117 of SEQ ID NO:130 is an amino acid residue other than serine or threonine.

23. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 870-877 of the amino acid sequence of SEQ ID NO:131, wherein the amino acid residue corresponding to amino acid residue 876 of SEQ ID NO:131 is an amino acid residue other than serine or threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 868-878 of the amino acid sequence of SEQ ID NO:131, wherein the amino acid residue corresponding to amino acid residue 876 of SEQ ID NO:131 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 865-878 of the amino acid sequence of SEQ ID NO:131, wherein the amino acid residue corresponding to amino acid residue 876 of SEQ ID NO:131 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 860-878 of the amino acid sequence of SEQ ID NO:131, wherein the amino acid residue corresponding to amino acid residue 876 of SEQ ID NO:131 is an amino acid residue other than serine or threonine.

24. An inhibitor of PKD comprising at least one copy of a peptide selected from the group consisting of:

a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 867-874 of the amino acid sequence of SEQ ID NO:132, wherein the amino acid residue corresponding to amino acid residue 873 of SEQ ID NO:132 is an amino acid residue other than serine or

threonine;

b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 865-875 of the amino acid sequence of SEQ ID NO:132, wherein the amino acid residue corresponding to amino acid residue 873 of SEQ ID NO:132 is an amino acid residue other than serine or threonine;

c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 861-875 of the amino acid sequence of SEQ ID NO:132, wherein the amino acid residue corresponding to amino acid residue 873 of SEQ ID NO:132 is an amino acid residue other than serine or threonine; and

d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 857-875 of the amino acid sequence of SEQ ID NO:132, wherein the amino acid residue corresponding to amino acid residue 873 of SEQ ID NO:132 is an amino acid residue other than serine or threonine.

25. A nucleic acid molecule comprising a polynucleotide sequence encoding at least one copy of the polypeptide of any one of claims 1-24

26. The nucleic acid molecule of claim 25 wherein the polynucleotide sequence encodes at least a number of copies of the peptide selected from the group consisting of 2, 3, 4, 5, 6, 7, 8, 9 or 10.

27. A vector comprising the nucleic acid molecule of claim 25.

28. A recombinant host cell comprising the vector of claim 27.

29. A method of inhibiting PKD in a cell comprising transfecting the vector of claim 27 into a host cell and culturing the transfected host cell under conditions suitable to produce at least one copy of the polypeptide.

30. A composition comprising at least two monomeric ligands, wherein at least a portion of each of said ligands is capable of being recognized by PKD and wherein at least one of said ligands does not contain a phosphorylatable amino acid residue.

31. The composition of claim 30, wherein said composition is a homopolymeric ligand.

32. The composition of claim 31, further comprising spacer amino acids between at least two of said monomeric ligands.
33. The composition of claim 31, further comprising a localization signal.
34. The composition of claim 31, further comprising an epitopic peptide.
35. The composition of claim 30, wherein said composition is a heteropolymeric ligand.
36. The composition of claim 35, further comprising spacer amino acids between at least two of said monomeric ligands.
37. The composition of claim 35, further comprising a localization signal.
38. The composition of claim 35, further comprising an epitopic peptide.
39. An isolated polypeptide comprising an amino acid sequence at least about 80% identical to SEQ ID NO:105.
40. An isolated polypeptide comprising an amino acid sequence at least about 80% identical to SEQ ID NO:109.
41. An isolated polypeptide comprising an amino acid sequence at least about 80% identical to SEQ ID NO:113.
42. An isolated polynucleotide encoding a polypeptide of claims 39, 40, or 41.
43. An isolated polynucleotide comprising SEQ ID NO:106 or SEQ ID NO:107 or SEQ ID NO:108 or SEQ ID NO:110 or SEQ ID NO:111 or SEQ ID NO:112 or SEQ ID NO:114 or SEQ ID NO:115 or SEQ ID NO:116.
44. An isolated fusion polypeptide comprising two or more polypeptides selected from SEQ ID NOS:1-104, wherein at least one amino acid designated as Xaa is an amino acid other than serine or threonine.

45. An isolated fusion polypeptide comprising two or more polypeptides selected from SEQ ID NOS:53-104, wherein at least one amino acid designated as Xaa is an amino acid other than serine or threonine.
46. An isolated polypeptide homopolyligand whose monomers are selected from the group consisting of SEQ ID NOS:1-104, wherein Xaa is any amino acid.
47. An isolated polypeptide heteropolyligand whose monomers are selected from the group consisting of SEQ ID NOS:1-104, wherein at least one amino acid designated as Xaa is an amino acid other than serine or threonine.
48. An isolated polypeptide homopolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 80% identical to any one of SEQ ID NOS:1-104.
49. An isolated polypeptide heteropolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 80% identical to any one of SEQ ID NOS:1-104.
50. An isolated polypeptide homopolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 85% identical to any one of SEQ ID NOS:1-104.
51. An isolated polypeptide heteropolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 85% identical to any one of SEQ ID NOS:1-104.
52. An isolated polypeptide homopolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 90% identical to any one of SEQ ID NOS:1-104.
53. An isolated polypeptide heteropolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 90% identical to any one of SEQ ID NOS:1-104.
54. An isolated polypeptide homopolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 95% identical to any one of SEQ ID NOS:1-104.
55. An isolated polypeptide heteropolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 95% identical to any one of SEQ ID NOS:1-104.

56. An isolated polypeptide homopolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 96% identical to any one of SEQ ID NOS:1-104.
57. An isolated polypeptide heteropolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 96% identical to any one of SEQ ID NOS:1-104.
58. An isolated polypeptide homopolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 97% identical to any one of SEQ ID NOS:1-104.
59. An isolated polypeptide heteropolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 97% identical to any one of SEQ ID NOS:1-104.
60. An isolated polypeptide homopolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 98% identical to any one of SEQ ID NOS:1-104.
61. An isolated polypeptide heteropolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 98% identical to any one of SEQ ID NOS:1-104.
62. An isolated polypeptide homopolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 99% identical to any one of SEQ ID NOS:1-104.
63. An isolated polypeptide heteropolyligand whose monomers are selected from the group consisting of peptides comprising an amino acid sequence at least 99% identical to any one of SEQ ID NOS:1-104.
64. The polyligand of each of claims 44-63 linked to a subcellular localization signal.
65. The polyligand of each of claims 44-63 linked to an epitope.
66. The polyligand of each of claims 44-63 linked to a reporter.
67. An isolated polynucleotide comprising a nucleotide sequence encoding the polypeptide of each of claims 44-66.
68. A vector comprising a polynucleotide of claim 67.

69. A host cell comprising a vector of claim 68.

70. A method of inhibiting PKD in a cell comprising transfecting a vector of claim 68 into a host cell and culturing the transfected host cell under conditions suitable to produce at least one copy of the polypeptide.

71. An isolated polypeptide homopolyligand, wherein the homopolyligand modulates PKD activity.

72. An isolated polypeptide heteropolyligand, wherein the heteropolyligand modulates PKD activity.

73. An isolated polynucleotide encoding each of the polypeptides of claims 44-63, wherein the polynucleotide is flanked on one end by a sequence cleavable by a first restriction endonuclease, and wherein the polynucleotide is flanked on the other end by a sequence cleavable by a second restriction endonuclease, and wherein the first and second restriction endonucleases generate noncompatible cohesive ends.

74. An isolated polynucleotide encoding each of the polypeptides of claims 44-63, wherein the polynucleotide is flanked on one end by a sequence cleavable by NgoM IV, and wherein the polynucleotide is flanked on the other end by sequences cleavable by Xma I and Cla I.

LIGAND X	LIGAND X
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FIGURE 1A

LIGAND X	LIGAND X	LIGAND X
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FIGURE 1B

LIGAND X	LIGAND X	LIGAND X	LIGAND X	LIGAND X
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FIGURE 1C

LIGAND X	SPACER	LIGAND X
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FIGURE 2A

LIGAND X	SPACER	LIGAND X	SPACER	LIGAND X
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FIGURE 2B

LIGAND X	LIGAND X	SPACER	LIGAND X	SPACER	LIGAND X
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FIGURE 2C

LIGAND X	LIGAND Y
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FIGURE 3A

LIGAND X	LIGAND Y	LIGAND Z
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FIGURE 3B

LIGAND X	LIGAND Y	LIGAND X	LIGAND Z	LIGAND Z
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FIGURE 3C

LIGAND B	SPACER	LIGAND A
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FIGURE 4A

LIGAND X	SPACER	LIGAND Y	SPACER	LIGAND Z
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FIGURE 4B

LIGAND X	LIGAND Y	SPACER	LIGAND Y	LIGAND X
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FIGURE 4C

LIGAND X	LIGAND X	EPITOPE
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FIGURE 5A

EPITOPE	LIGAND X	LIGAND Y
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FIGURE 5B

LIGAND X	SPACER	LIGAND X	EPITOPE
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FIGURE 5C

EPITOPE	LIGAND X	SPACER	LIGAND Y
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FIGURE 5D

LIGAND X	SPACER	LIGAND Y	SPACER	LIGAND B	EPITOPE
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FIGURE 5E

EPITOPE	LIGAND X	SPACER	LIGAND Y	LIGAND B
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FIGURE 5F

LIGAND X	EPITOPE
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FIGURE 5G

LIGAND X	LIGAND X	REPORTER
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FIGURE 6A

REPORTER	LIGAND X	LIGAND Y
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FIGURE 6B

LIGAND X	SPACER	LIGAND X	REPORTER
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FIGURE 6C

REPORTER	LIGAND X	SPACER	LIGAND Y
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FIGURE 6D

LIGAND X	SPACER	LIGAND Y	SPACER	LIGAND B	REPORTER
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FIGURE 6E

REPORTER	LIGAND X	SPACER	LIGAND Y	LIGAND B
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FIGURE 6F

LIGAND X	REPORTER
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FIGURE 6G

LIGAND X	LIGAND X	LOCALIZATION SIGNAL
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FIGURE 7A

LOCALIZATION SIGNAL	LIGAND X	LIGAND Y
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FIGURE 7B

LIGAND X	SPACER	LIGAND X	LOCALIZATION SIGNAL
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FIGURE 7C

LOCALIZATION SIGNAL	LIGAND X	SPACER	LIGAND Y
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FIGURE 7D

LIGAND X	SPACER	LIGAND Y	LIGAND B	LOCALIZATION SIGNAL
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FIGURE 7E

LOCALIZATION SIGNAL	LIGAND X	SPACER	LIGAND Y	SPACER	LIGAND B
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FIGURE 7F

LOCALIZATION SIGNAL	LIGAND Y
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FIGURE 7G

EPITOPE	LIGAND X	LIGAND X	LOCALIZATION SIGNAL
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FIGURE 8A

LOCALIZATION SIGNAL	LIGAND X	LIGAND Y	EPITOPE
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FIGURE 8B

EPITOPE	LIGAND X	SPACER	LIGAND X	LOCALIZATION SIGNAL
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FIGURE 8C

LOCALIZATION SIGNAL	LIGAND X	SPACER	LIGAND Y	EPITOPE
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FIGURE 8D

EPITOPE	LIGAND X	LIGAND Y	LIGAND B	LOCALIZATION SIGNAL
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FIGURE 8E

LOCALIZATION SIGNAL	LIGAND Z	SPACER	LIGAND Y	LIGAND B	EPITOPE
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FIGURE 8F

EPITOPE	LIGAND B	LOCALIZATION SIGNAL
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FIGURE 8G

PROMOTER	OPTIONAL EPI TOPE	OPTIONAL REPORTER	LIGAND, HOMOPOLY LIGAND, or HETEROPOLY LIGAND	OPTIONAL LOCALIZATION SIGNAL	STOP	POLY-A
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FIGURE 9A

PROMOTER	OPTIONAL REPORTER	OPTIONAL EPI TOPE	LIGAND, HOMOPOLY LIGAND, or HETEROPOLY LIGAND	OPTIONAL LOCALIZATION SIGNAL	STOP	POLY-A
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FIGURE 9B

PROMOTER	LIGAND, HOMOPOLY LIGAND, or HETEROPOLY LIGAND	OPTIONAL REPORTER	OPTIONAL EPI TOPE	OPTIONAL LOCALIZATION SIGNAL	STOP	POLY-A
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FIGURE 9C

PROMOTER	LIGAND, HOMOPOLY LIGAND, or HETEROPOLY LIGAND	OPTIONAL EPI TOPE	OPTIONAL REPORTER	OPTIONAL LOCALIZATION SIGNAL	STOP	POLY-A
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FIGURE 9D

PROMOTER	LIGAND, HOMOPOLY LIGAND, or HETEROPOLY LIGAND	LOCALIZATION SIGNAL	STOP	POLY-A
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FIGURE 9E

PROMOTER	LOCALIZATION SIGNAL	LIGAND, HOMOPOLY LIGAND, or HETEROPOLY LIGAND	STOP	POLY-A
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FIGURE 9F

PROMOTER	LIGAND, HOMOPOLY LIGAND, or HETEROPOLY LIGAND	STOP	POLY-A
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FIGURE 9G

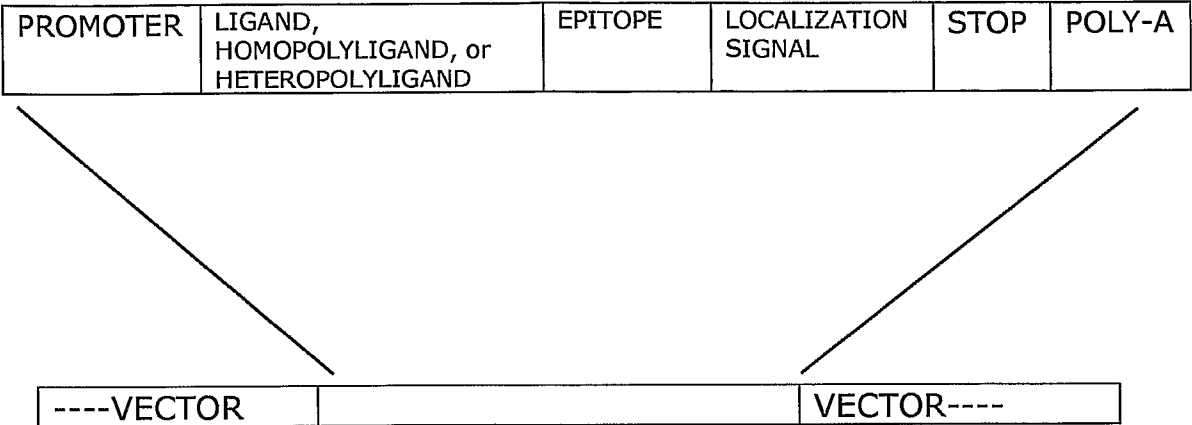


FIGURE 10A

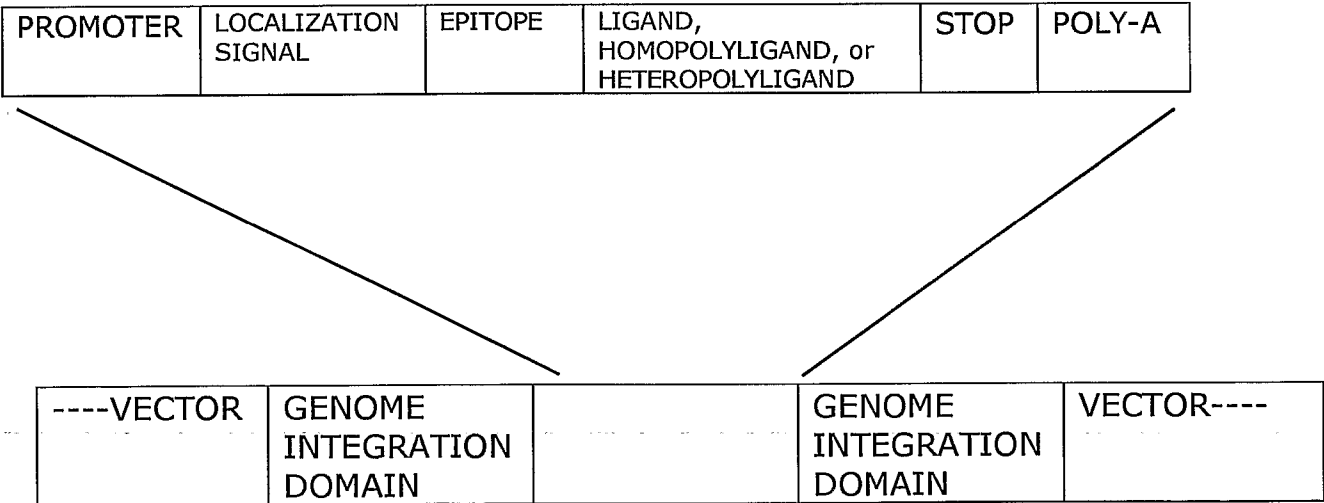


FIGURE 10B

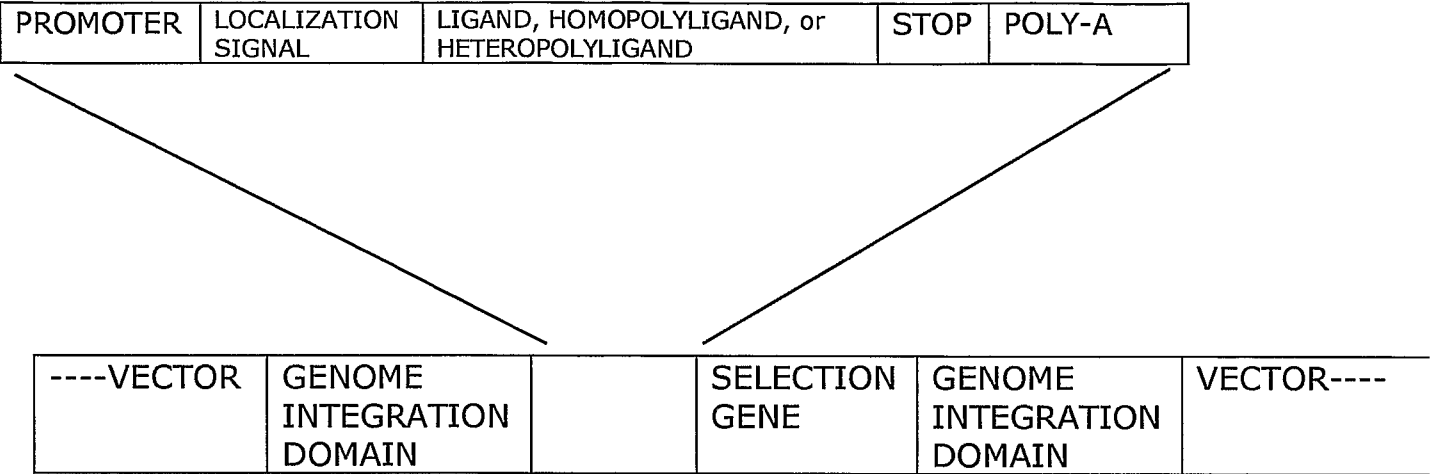


FIGURE 10C

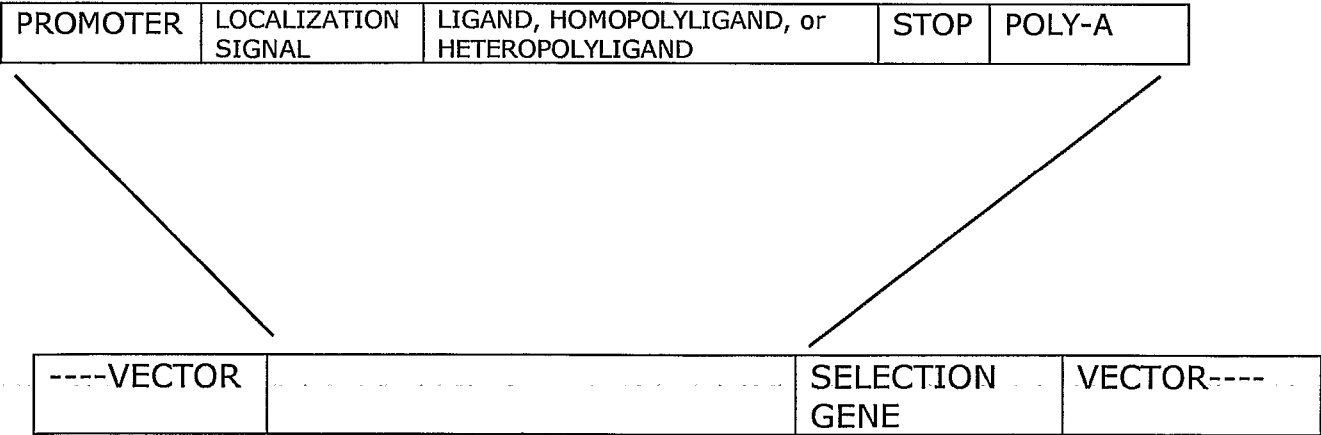
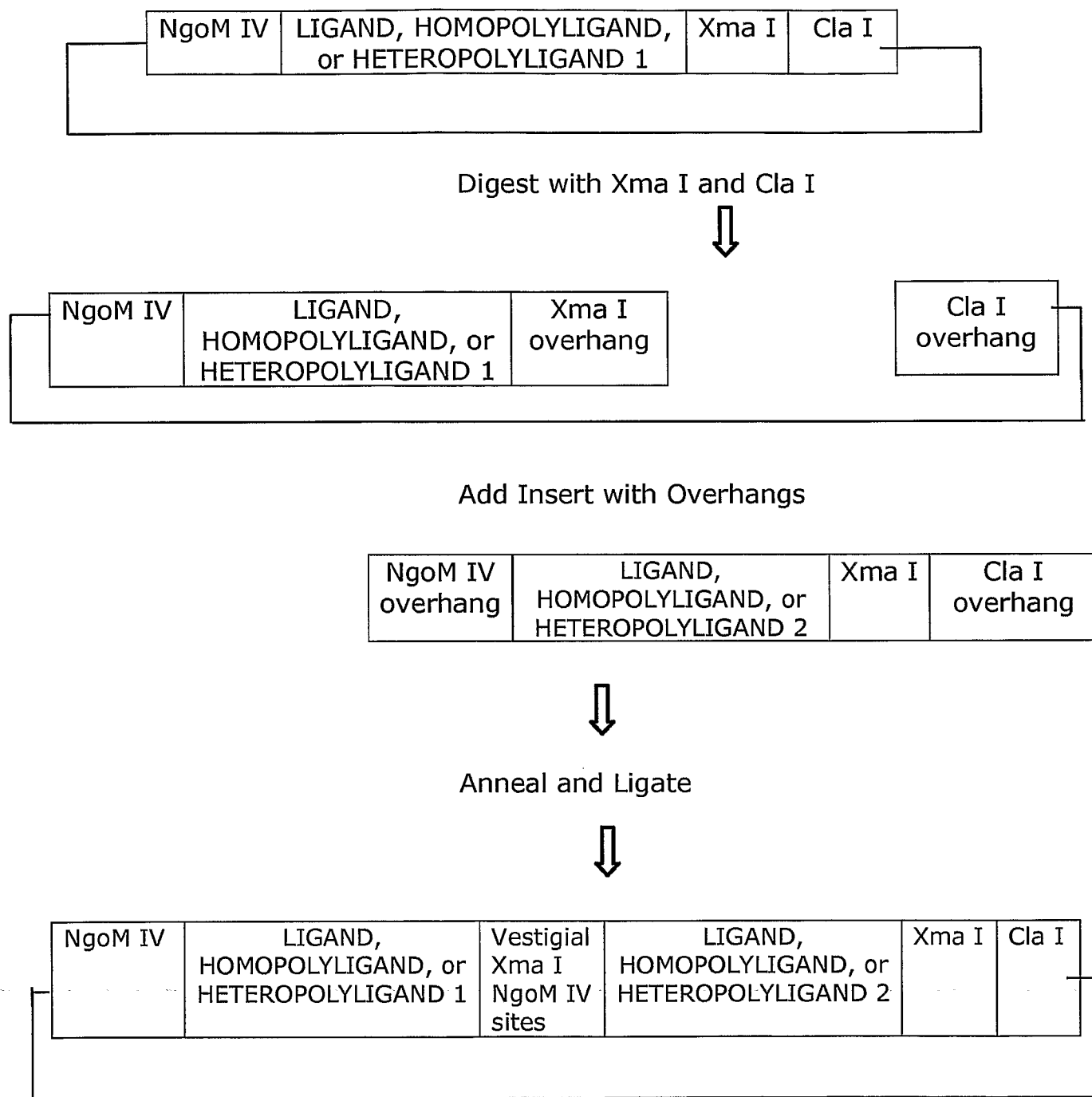


FIGURE 10D

**FIGURE 11**