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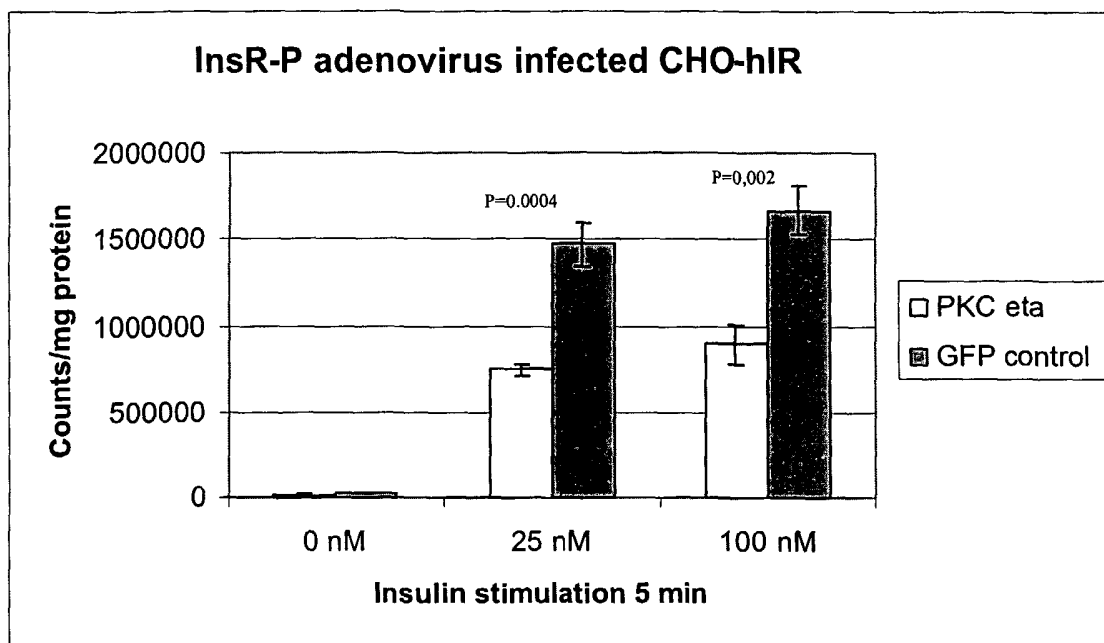
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(54) Title: USE OF HUMAN PROTEIN KINASE C-ETA IN METHODS FOR IDENTIFICATION OF PHARMACEUTICALLY USEFUL AGENTS



(57) Abstract: The invention relates to the use of the human Protein Kinase C η (PKC-eta) isoform, in methods for identification of pharmaceutically useful agents, in particular agents useful for the treatment of type 2 diabetes.

PHARMACEUTICALLY USEFUL AGENTS

TECHNICAL FIELD

The invention relates to the use of the human Protein Kinase C η (PKC- η) isoform, in methods for identification of pharmaceutically useful agents, in particular
5 agents useful for the treatment of type 2 diabetes.

BACKGROUND ART

One of the major hormones that influence metabolism is insulin, which is synthesized in the beta cells of the islets of Langerhans of the pancreas. Insulin
10 primarily regulates the direction of metabolism, shifting many processes toward the storage of substrates and away from their degradation [1,2]. Insulin acts to increase the transport of glucose and amino acids as well as key minerals such as potassium, magnesium, and phosphate from the blood into cells. It also regulates a variety of enzymatic reactions within the cells, all of which have a common overall direction,
15 namely the synthesis of large molecules from small units. A deficiency in the action of insulin (diabetes mellitus) causes severe impairment in (i) the storage of glucose in the form of glycogen and the oxidation of glucose for energy; (ii) the synthesis and storage of fat from fatty acids and their precursors and the completion of fatty-acid oxidation; and (iii) the synthesis of proteins from amino acids.

20 There are two varieties of diabetes. Type 1 is insulin-dependent diabetes mellitus (IDDM), for which insulin injection is required; it was formerly referred to as juvenile onset diabetes. In this type, insulin is not secreted by the pancreas and hence must be taken by injection. Type 2 diabetes, non-insulin-dependent diabetes mellitus (NIDDM), is characterized clinically by hyperglycemia and insulin resistance and is
25 commonly associated with obesity. Type 2 diabetes is a heterogeneous group of disorders in which hyperglycemia results from both an impaired insulin secretory response to glucose and decreased insulin effectiveness in stimulating glucose uptake by skeletal muscle and in restraining hepatic glucose production (insulin resistance). Before diabetes develops, patients generally lose the early insulin secretory response to
30 glucose and may secrete relatively large amounts of pro-insulin. In established diabetes, although fasting plasma insulin levels may be normal or even increased in type 2 diabetes patients, glucose-stimulated insulin secretion is clearly decreased. The

decreased insulin levels reduce insulin-mediated glucose uptake and fail to restrain hepatic glucose production.

Glucose homeostasis depends upon a balance between glucose production by the liver and glucose utilization by insulin-dependent tissues, such as fat and muscle, and
5 insulin-independent tissues, such as brain and kidney. In type 2 diabetes, the entry of glucose into fat and muscle is reduced and glucose production in the liver is increased, due to insulin resistance in the tissues.

The receptor tyrosine kinases (RTKs) are a major type of cell-surface receptors. The ligands for RTKs are peptide/protein hormones including nerve growth factor
10 (NGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin. Binding of a ligand to an RTK stimulates the receptor's intrinsic protein-tyrosine kinase activity, which subsequently stimulates a signal-transduction cascade leading to changes in cellular physiology and patterns of gene expression. RTK signaling pathways have a wide spectrum of functions including regulation of cell
15 proliferation and differentiation, promotion of cell survival, and modulation of cellular metabolism.

Protein phosphorylation is one of the most versatile posttranslational modifications used in eukaryotic cells and plays a crucial role in the continuous remodeling of different transcriptional regulators. The protein kinase C (PKC) family of
20 serine-threonine kinases encompasses nine different genes encoding isozymes that have been shown to transduce a myriad of signals mediated by phospholipid hydrolysis as a consequence of the activation of G protein-coupled receptors, tyrosine kinase receptors, and non-receptor tyrosine kinases [6]. Three categories of PKC have been described depending on their mechanisms of activation: conventional PKC (α , β and γ) novel PKC
25 (δ , ϵ , η and θ) and atypical PKC (ι , λ , and ζ). Although the analysis of PKC activity in many systems has provided crucial insights to its biological function, unraveling the molecular mechanisms that underlie isozyme-specific modulation of gene expression within the complexity of genome structure and function remains a challenging issue.

A reduced capacity for insulin to elicit increases in glucose uptake and
30 metabolism in target tissues such as skeletal muscle is a common feature of obesity and diabetes. The association between lipid oversupply and such insulin resistance is well established, and evidence for mechanisms through which lipids could play a causative role in the generation of muscle insulin resistance is increasing. While the effects of

lipids may in part be mediated by substrate competition through the glucose-fatty acid cycle, interference with insulin signal transduction by lipid-activated signaling pathways is also likely to play an important role. Thus, studies of insulin resistance in Type 2 diabetes, obesity, fat-fed animals and lipid-treated cells have identified defects both at the level of insulin receptor-mediated tyrosine phosphorylation and at downstream sites such as protein kinase B (PKB) activation. Lipid signaling molecules can be derived from free fatty acids, and include diacylglycerol, which activates isozymes of the protein kinase C (PKC) family, and ceramide, which has several effectors including PKCs and a protein phosphatase. In addition, elevated lipid availability can increase flux through the hexosamine biosynthesis pathway which can also lead to activation of PKC as well as protein glycosylation and modulation of gene expression. The mechanisms giving rise to decreased insulin signaling include serine/threonine phosphorylation of insulin receptor substrate-1, but also direct inhibition of components such as PKB. Thus lipids can inhibit glucose disposal by causing interference with insulin signal transduction, and most likely by more than one pathway depending on the prevalent species of fatty acids.

Various results [3-7, 10, 13] suggest that isoform-selective activation of PKC involves phosphorylation and down-regulation of one or more substrates involved in glucose transport and metabolism (e.g. glycogen synthase and the insulin receptor) and studies [4] have shown increased expression of calcium-independent isozymes (PKC-epsilon and PKC-theta) in the membrane fraction of skeletal muscle in fructose- and fat-fed rat models of insulin resistance. PKC-alpha knockouts show enhanced insulin signaling [14], and it was recently described that PKC could attenuate insulin secretion [15].

However, it has not previously been disclosed that PKC-eta is involved in the maintenance/development of insulin resistance. It has been believed [16] that PKC-eta is expressed mainly in epithelial cells, which would speak against such a function.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph depicting the effect of PKC-eta over-expression in adipocytes 3T3-L1 transfected with GLU-REx3, CRE, and GRE respectively. Control cells were transfected with an empty plasmid vector and the control expression level was set to 1.

Fig. 2 is a graph depicting the effect of PKC-eta on glucose uptake, when over-expressed in (A) non-differentiated L6 muscle cells; and (B) differentiated adipocytes

3T3-L1. Control cells (ctrl) were transfected with an empty plasmid vector. Grey staples indicate non-stimulated cells and white staples indicate insulin-stimulated cells.

Figure 3 is a graph depicting the effect of PKC-eta over-expression on insulin receptor tyrosine-phosphorylation in CHO-IR cells.

5

DISCLOSURE OF THE INVENTION

It has surprisingly been found that the mammalian PKC-eta protein is involved in the insulin-signaling pathway.

Consequently, in a first aspect this invention provides a method for identifying
10 an agent useful for the treatment of a medical condition relating to insulin resistance, said method comprising the steps: (i) contacting a candidate agent with a mammalian PKC-eta polypeptide; and (ii) determining whether said candidate agent decreases or inhibits the biological activities of the polypeptide, such decrease or inhibition being indicative for an agent useful for the treatment of a medical condition relating to insulin
15 resistance.

In another aspect, the method for identifying an agent useful for the treatment of a medical condition relating to insulin resistance, comprises the steps: (i) contacting a candidate agent with a nucleic acid molecule encoding a mammalian PKC-eta polypeptide; and (ii) determining whether said candidate agent decreases or inhibits the
20 expression of the said nucleic acid molecule, such decrease or inhibition being indicative for an agent useful for the treatment of a medical condition relating to insulin resistance.

In one embodiment, the invention features a method for identifying an agent that increases glucose uptake by a cell, the method comprising: (i) contacting a cell with a
25 candidate agent that inhibits an activity of a mammalian (e.g., human) PKC-eta polypeptide; (ii) measuring glucose uptake by the cell in the presence of the candidate agent; and (iii) determining whether the candidate agent increases glucose uptake by the cell. The candidate agent can optionally bind to the mammalian PKC-eta polypeptide.

In another embodiment, the invention features a method for identifying an agent
30 that increases glucose uptake by a cell, the method comprising: (i) contacting a cell with a candidate agent that inhibits expression of a nucleic acid encoding a mammalian (e.g., human) PKC-eta polypeptide; (ii) measuring glucose uptake by the cell in the presence of the candidate agent; and (iii) determining whether the candidate agent

increases glucose uptake by the cell. The candidate agent can optionally bind to the mammalian PKC- η nucleic acid.

The medical condition relating to insulin resistance could in particular be associated with reduced glucose uptake and could more specifically be type 2 diabetes.

- 5 The mammalian PKC- η polypeptide is optionally a human PKC- η polypeptide. Preferably, a human PKC- η polypeptide comprises, consists essentially of, or consists of, an amino acid sequence of SEQ ID NO:3; SEQ ID NO:12; or SEQ ID NO:13.

- 10 Candidate agents that can be used in the methods described herein include, for example, polypeptides, peptides, antibodies or antibody fragments, non-peptide compounds, carbohydrates, small molecules, lipids, single or double stranded DNA, single or double stranded RNA, antisense nucleic acid molecules, and ribozymes.

An identification method can additionally include a step of comparing glucose uptake by a cell in the presence of the candidate agent with glucose uptake by a cell in the absence of the candidate agent.

- 15 For screening purposes, appropriate host cells can be transformed with a vector having a reporter gene under the control of the PKC- η polypeptide. The expression of the reporter gene can be measured in the presence or absence of an agent with known activity (i.e. a standard agent) or putative activity (i.e. a "test agent" or "candidate agent"). A change in the level of expression of the reporter gene in the presence of the
20 test agent is compared with that effected by the standard agent. In this way, active agents are identified and their relative potency in this assay determined.

- A transfection assay can be a particularly useful screening assay for identifying an effective agent. In a transfection assay, a nucleic acid containing a gene such as a reporter gene that is operably linked to a PKC- η promoter, or an active fragment
25 thereof, is transfected into the desired cell type. A test level of reporter gene expression is assayed in the presence of a candidate agent and compared to a control level of expression. An effective agent is identified as an agent that results in a test level of expression that is different than a control level of reporter gene expression, which is the level of expression determined in the absence of the agent.

- 30 As used herein, the term "reporter gene" means a gene encoding a gene product that can be identified using simple, inexpensive methods or reagents and that can be operably linked to PKC- η or an active fragment thereof. Reporter genes such as, for example, a luciferase, β -galactosidase, alkaline phosphatase, or green fluorescent

protein reporter gene, can be used to determine transcriptional activity in screening assays according to the invention (see, for example, Goeddel (ed.), *Methods Enzymol.*, Vol. 185, San Diego: Academic Press, Inc. (1990); see also Sambrook, *supra*).

In another aspect, the invention provides a method for stimulating glucose uptake in a subject (e.g., a human host), comprising administering to a subject in need of such treatment an amount of an inhibitor (e.g., a selective inhibitor) of PKC-eta effective to increase glucose uptake in the subject. The subject may have a condition relating to insulin resistance and/or a condition relating to reduced glucose uptake, such as type 2 diabetes. In some embodiments, the subject has been diagnosed as having such a particular condition. The method can include an additional step of detecting an increase in glucose uptake in the subject after administering the inhibitor to the subject.

The invention further includes a method, which can be carried out *in vivo*, *ex vivo*, or *in vitro* (i.e., outside the body of the host) for increasing glucose uptake in a mammalian cell (e.g., a muscle cell or an adipocyte), the method comprising contacting a mammalian cell with an amount of an inhibitor (e.g., a selective inhibitor) of PKC-eta effective to increase glucose uptake by the cell. The method can include an additional step of detecting an increase in glucose uptake by the cell after the contacting of the cell with the inhibitor.

In yet another aspect, this invention provides a method for the treatment of a medical condition relating to reduced glucose uptake, in particular type 2 diabetes, comprising administering to a subject an effective amount of an agent identified by the method according to the invention for identification of agents useful for such treatment.

In one embodiment, a method of treatment includes: (i) selecting an individual diagnosed as having a medical condition characterized by insulin resistance; and (ii) administering to the individual an amount of an inhibitor of PKC-eta effective to reduce insulin resistance in the individual. The method can include an additional step of detecting a reduction in insulin resistance in the individual after the administration of the inhibitor.

The medical condition can be characterized by reduced glucose uptake and the method can include detecting a reduction in blood glucose levels in the individual after the administration of the inhibitor. An exemplary condition that can be treated by such as method is diabetes, e.g., type II diabetes.

In one aspect, the invention features an isolated nucleic acid molecule containing a nucleotide sequence that is at least 60% identical to the nucleotide

sequence shown in SEQ ID NO:6. More preferably, the nucleotide sequence is at least 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more, identical to the nucleotide sequence shown in SEQ ID NO:6. In the case of a nucleotide sequence that is longer than or equivalent in length to the reference
5 sequence, SEQ ID NO:6, the comparison is made with the full length of the reference sequence. Where the nucleotide sequence is shorter than the reference sequence, SEQ ID NO:6, the comparison is made to a segment of the reference sequence of the same length (excluding any loop required by the homology calculation). Preferably, the nucleotide sequence encodes a polypeptide having PKC-eta activity (e.g., serine-
10 threonine kinase activity). In one example, the nucleotide sequence is identical to SEQ ID NO:6.

In one embodiment, the invention features an isolated nucleic acid comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence that is at least about 60% identical to a sequence shown as SEQ ID NO:13 or a fragment
15 thereof. Preferably, the amino acid sequence is at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% or more identical to SEQ ID NO:13 and has a PKC-eta activity (e.g., serine-threonine kinase activity). For example, the amino acid sequence can be identical to the sequence of SEQ ID NO:13.

Also included in the invention is an isolated nucleic acid molecule comprising a
20 nucleotide sequence that hybridizes under high stringency conditions to the nucleotide sequence of SEQ ID NO:6, the complete complement of SEQ ID NO:6, or a segment thereof as described herein. "High stringency conditions" refers to hybridization in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C. Preferably, the nucleotide sequence encodes a polypeptide having PKC-eta activity
25 (e.g., serine-threonine kinase activity).

Also included in the invention is an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising at least 20, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, or more contiguous amino acid residues of SEQ ID NO:13. In some embodiments, the polypeptide comprises an
30 immunogenic fragment of at least 20 amino acids of SEQ ID NO:13. Preferably, the nucleotide sequence encodes a polypeptide having PKC-eta activity (e.g., serine-threonine kinase activity).

As used herein, an "isolated nucleic acid" is a nucleic acid, the structure of which is not identical to that of any naturally occurring nucleic acid or to that of any fragment of a naturally occurring genomic nucleic acid spanning more than three genes. The term therefore covers, for example, (a) a DNA which has the sequence of part of a naturally occurring genomic DNA molecule but is not flanked by both of the coding sequences that flank that part of the molecule in the genome of the organism in which it naturally occurs; (b) a nucleic acid incorporated into a vector or into the genomic DNA of a prokaryote or eukaryote in a manner such that the resulting molecule is not identical to any naturally occurring vector or genomic DNA; (c) a separate molecule such as a cDNA, a genomic fragment, a fragment produced by polymerase chain reaction (PCR), or a restriction fragment; and (d) a recombinant nucleotide sequence that is part of a hybrid gene, i.e., a gene encoding a fusion protein. Specifically excluded from this definition are nucleic acids present in random, uncharacterized mixtures of different DNA molecules, transfected cells, or cell clones, e.g., as these occur in a DNA library such as a cDNA or genomic DNA library.

As used herein, "% identity" of two amino acid sequences or of two nucleic acid sequences is determined using the algorithm of Karlin and Altschul (PNAS USA 87:2264-2268, 1990), modified as in Karlin and Altschul, PNAS USA 90:5873-5877, 1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al. (J. Mol. Biol. 215:403-410, 1990). BLAST nucleotide searches are performed with the NBLAST program, score = 100, wordlength = 12. BLAST protein searches are performed with the XBLAST program, score = 50, wordlength = 3. To obtain gapped alignment for comparison purposes GappedBLAST is utilized as described in Altschul et al (Nucleic Acids Res. 25:3389-3402, 1997). When utilizing BLAST and GappedBLAST programs the default parameters of the respective programs (e.g., XBLAST and NBLAST) are used to obtain nucleotide sequences homologous to a nucleic acid molecule of the invention.

In another aspect, the invention features a substantially pure polypeptide containing an amino acid sequence shown as SEQ ID NO:13. The invention also includes a polypeptide, or fragment thereof, that differs from the corresponding sequence shown as SEQ ID NO:13. The differences are, preferably, differences or changes at a non-essential residue or a conservative substitution. In one embodiment, the polypeptide includes an amino acid sequence at least about 60% identical to a sequence shown as SEQ ID NO:13, or a fragment thereof. Preferably, the amino acid

sequence is at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% or more identical to SEQ ID NO:13 and has a PKC-eta activity (e.g., serine-threonine kinase activity). For example, the amino acid sequence can be identical to SEQ ID NO:13.

Preferred polypeptide fragments of the invention are at least 10%, preferably at least 20%, 30%, 40%, 50%, 60%, 70%, or more, of the length of the sequence shown as SEQ ID NO:13 and have a PKC-eta activity (e.g., serine-threonine kinase activity). Alternatively, the fragment can be merely an immunogenic fragment, e.g., a fragment that can be used to raise monoclonal and/or polyclonal antibodies that specifically bind to a polypeptide of the sequence of SEQ ID NO:13.

10 The invention encompasses polypeptides carrying modifications such as substitutions, small deletions, insertions or inversions, which polypeptides nevertheless have substantially the biological activities of a PKC-eta. Also included in the invention is a polypeptide encoded by a nucleic acid molecule described herein.

Also included in the invention is a substantially pure polypeptide comprising at least 20, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, or more contiguous amino acid residues of SEQ ID NO:13. In some embodiments, the polypeptide comprises an immunogenic fragment of at least 20 amino acids of SEQ ID NO:13. Preferably, the polypeptide has PKC-eta activity (e.g., serine-threonine kinase activity).

20 The term "substantially pure" as used herein in reference to a given polypeptide means that the polypeptide is substantially free from other biological macromolecules. For example, the substantially pure polypeptide is at least 75%, 80, 85, 95, or 99% pure by dry weight. Purity can be measured by any appropriate standard method known in the art, for example, by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

The present invention also relates to vectors comprising the nucleic acid molecules of the invention, as well as host cells transformed with such vectors. Any of the nucleic acid molecules of the invention may be joined to a vector, which generally includes a selectable marker and an origin of replication for propagation in a host cell. 30 Because the invention also provides polypeptides expressed from the nucleic acid molecules described above, vectors for the expression of a polypeptide are preferred. Such expression vectors include DNA encoding a polypeptide described herein, operably linked to suitable transcriptional or translational regulatory sequences, such as those derived from a mammalian, microbial, viral, or insect gene. Examples of regulatory

sequences include transcriptional promoters, operators, or enhancers, mRNA ribosomal binding sites, and appropriate sequences, which control transcription and translation. Nucleotide sequences are operably linked when the regulatory sequence functionally relates to the DNA encoding a polypeptide. Thus, for example, a promoter nucleotide sequence is operably linked to a PKC-eta DNA sequence if the promoter nucleotide sequence directs the transcription of the PKC-eta sequence.

The vector may be any vector, which conveniently may be subjected to recombinant DNA procedures, and the choice of vector will often depend on the host cell into which it is to be introduced. Thus, the vector may be an autonomously replicating vector, e.g., a vector that exists as an extrachromosomal entity, the replication of which is independent of chromosomal replication (examples of such a vector are a plasmid, phage, cosmid, mini-chromosome or virus). Alternatively, the vector may be one which, when introduced in a host cell, is integrated in the host cell genome and replicated together with the chromosome(s) into which it has been integrated. Examples of suitable vectors are a bacterial expression vector and a yeast expression vector. The vector of the invention may carry any of the DNA molecules of the invention as defined above.

A suitable host cell can be a prokaryotic cell, a unicellular eukaryotic cell, or a cell derived from a multicellular organism. The host cell can thus, e.g., be a bacterial cell such as an *E. coli* cell, a cell from a yeast such as *Saccharomyces cerevisiae* or *Pichia pastoris*, an insect cell, or a mammalian cell, such as HEK293, CHO or an equivalent. The methods employed to effect introduction of the vector into the host cell are standard methods well known to a person familiar with recombinant DNA methods.

Included in the invention is a process for production of a polypeptide described herein, which comprises culturing a host cell as described above under conditions whereby said polypeptide is produced, and optionally recovering said polypeptide, using standard biochemical procedures.

A further aspect of the invention is a nucleic acid probe comprising at least 15 nucleotides, which probe specifically hybridizes with at least a part of the nucleic acid molecule according to the invention, said part having a sequence shown in SEQ ID NO:6. The invention also provides an antisense oligonucleotide having a sequence capable of specifically hybridizing to at least a part of the nucleic acid molecule according to the invention, said part having a sequence shown in SEQ ID NO:6.

Fragments of the nucleic acid molecules described herein, as well as polynucleotides capable of hybridizing to such nucleic acid molecules may be used as a probe or as primers in a polymerase chain reaction (PCR). Such probes may be used, *e.g.*, to detect the presence of nucleic acids coding for PKC-eta in *in vitro* assays, as well as in Southern and Northern blots. Cell types expressing PKC-eta may also be identified by the use of such probes. Such procedures are well known, and the skilled artisan will be able to choose a probe of a length suitable to the particular application. For PCR, 5' and 3' primers corresponding to the termini of a desired PKC-eta nucleic acid molecule are employed to isolate and amplify that sequence using conventional techniques.

The polypeptides of the present invention may also be used to raise polyclonal and monoclonal antibodies, which are useful in diagnostic assays for detecting PKC-eta polypeptide expression. Such antibodies may be prepared by conventional techniques. See, for example, *Antibodies: A Laboratory Manual*, Harlow and Land (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1988); *Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses*, Kennet *et al.* (eds.), Plenum Press, New York (1980).

Throughout this description the terms "standard protocols" and "standard procedures", when used in the context of molecular biology techniques, are to be understood as protocols and procedures found in an ordinary laboratory manual such as: Current Protocols in Molecular Biology, editors F. Ausubel *et al.*, John Wiley and Sons, Inc. 1994, or Sambrook, J., Fritsch, E.F. and Maniatis, T., *Molecular Cloning: A laboratory manual*, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY 1989.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Suitable methods and materials are described below, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Below, the invention is described in the appended examples, which are intended to illustrate the invention, without limiting the scope of protection.

EXAMPLES

5 EXAMPLE 1: Identification of kin-13 and PKC-eta.

In *Caenorhabditis elegans*, injection of double-stranded RNA (dsRNA) results in the specific inactivation of genes containing homologous sequences, a technique termed RNA-mediated interference (RNAi; see Carthew, R.W. (2001) Gene silencing by double-stranded RNA. Curr. Opin. Cell. Biol. 13: 244-248). It has previously been
10 shown that RNAi can also be achieved by feeding worms *E. coli* expressing dsRNA corresponding to a specific gene; this mode of dsRNA introduction is conventionally considered to be less efficient than direct injection, however, and has therefore seen limited use, even though it is considerably less labor-intensive.

The *Caenorhabditis elegans* PKC gene kin-13 was identified by RNAi to
15 suppress the insulin receptor loss of function phenotype *daf-2*, which is the dauer state, a sort of hibernation in the worm. The kin-13 protein (GenBank accession No. P34885; SEQ ID NO: 1) was used in a TBLASTN search (<http://www.ncbi.nlm.nih.gov/Education/blasttutorial.html>) in the public nucleotide databases (<http://www.ncbi.nlm.nih.gov/blast/>). Two human homologues to the *C.*
20 *elegans* kin-13 protein were identified: PKC-eta (PKC η ; GenBank accession No. M55284; SEQ ID NOS: 2 and 3) and PKCepsilon (PKC ϵ ; GenBank accession No. X65293). The kin-13 protein was determined to be ~58% identical with the human PKCepsilon isoform, and 55% identical with the eta isoform.

25 EXAMPLE 2: Cloning of PKC-eta

The PKC-eta gene was cloned using sequence information from the public databases. As template for cloning, cDNA from human lung was used (Invitrogen; Cat. # D8090-1) with the primers BEKA234 (SEQ ID NO: 4) and BEKA235 (SEQ ID NO: 5).

30 PCR was performed using the Advantage 2 PCR Enzyme System (Clontech; Cat. # PT3281-1) with the following parameters: 94°C 30 s and 40 cycles of 94°C 5 s, 72°C 4 min, and finally 72°C 7 min. An aliquot of the PCR reaction was loaded on a 1.2 % E-Gel (Invitrogen; Cat. # 45-0111). A band of approximately 2 kb was cut out and

purified using QIAquick Gel Extraction Kit (Qiagen, Cat; # 28704) and subsequent elution in 50 µl H₂O. The PCR fragment was cloned into pCR2.1-TOPO using the TOPO TA Cloning Kit (Invitrogen; Cat. # K4500-01).

Plasmid DNA from 5 clones was obtained by using the QIAprep Spin Miniprep Kit (QIAGEN; Cat. # 27104). Sequencing was performed using the ABI PrismBigDye Terminator Cycle Sequencing Ready Reaction Kit, on Applied Biosystems Model ABI 377 XL/96 DNA sequencing system.

Sequencing revealed that all clones contained common differences compared to the public sequence, and also some PCR errors. A correct clone was constructed by a three-fragment ligation where the 3'-end from clone #3 was joined to the 5'-end from clone #10, by the use of an internal *Bgl*III site. 1 µg of clone #3 was digested with *Not*I and *Hind*III, 1.3 µg of clone #3 was digested with *Not*I and *Bgl*III, and 1.2 µg of clone #10 was digested with *Bgl*III and *Hind*III. Half of the digestions were loaded on a 1.2% E-Gel. A band of approximately 3800 bp (fragment A) was cut out from the *Not*I-*Hind*III digestion, and a band of approximately 650 bp (fragment B) was cut out from the *Not*I-*Bgl*III digestion, and a band of approximately 1500 bp (fragment C) was cut out from the *Hind*III-*Bgl*III digestion. The fragments were purified using QIAquick Gel Extraction Kit, (Qiagen; Cat # 28704) and subsequent elution in 50 µl H₂O.

Ligation was performed using Ready-To-Go T4 DNA ligase (Amersham Pharmacia Biotech; Cat # 27-0361-01). 2 µl of fragment A was mixed with 6 µl of fragment B and 6 µl of fragment C. The ligation mix was transformed into One Shot chemically competent Top10 *E. coli* cells (Invitrogen), and plasmid DNA was obtained as above.

The resulting plasmid was designated pMB1549, and the insert (SEQ ID NOS: 6 and 7) was verified by control digestions using the restriction enzymes *Bam*HI and *Hin*FI, which give unique patterns for clone #3, clone #10 and pMB1549.

PKC-eta for mammalian expression was made by using Gateway™ Cloning Technology (Life Technologies). Gateway compatible primers were designed and PCR was performed using pMB1549 as a template. The PCR was performed in 50 µl using Taq DNA Polymerase, Roche (Cat. # 1 435 094) and 1 µl each of the primers BEKA243 (SEQ ID NO: 8) and BEKA244 (SEQ ID NO: 9). The Perkin Elmer Gene Amp PCR system 9700 was used with the following program: 95°C, 5 min; (95°C 30 s, 55°C 30 s, 72°C 2 min) x 20; and 72°C, 7 min; followed by cooling to 4°C. 10 µl of the

reaction was loaded on a 1.2% E-Gel, and a fragment of approximately 2000bp was cut out from the gel, and purified using QIAquick Gel Extraction Kit (Qiagen; Cat # 28704).

The PCR fragment was cloned into pDONR201 (Life Technologies; Cat. # 11798-014), according to the manufacturer's instructions. The resulting entry clone was designated pBV39, and the insert was confirmed by sequencing. A mammalian expression clone, designated pBV66, comprising PKC-eta as a 5'-GST fusion protein (SEQ ID NO: 10 and 11), was constructed according to the manufacturer's instructions using the destination vector pDEST27 (Life Technologies; Cat. # 11812-013). In SEQ ID NO: 11, amino acids 1 to 226 represents the GST domain, while amino acids 237 to 918 represent human PKC-eta.

Another clone comprising PKC-eta fused to a histidine tag (SEQ ID NO: 12) was prepared according to known methods.

SEQ ID NO:13 represents the native PKC-eta polypeptide encoded by the gene cloned according to the above Example.

EXAMPLE 3: Expression profiling

To determine the relative expression levels of PKC-eta in different tissues, a Multiple Tissue Expression Array (CLONTECH; Cat. #775) was used in a hybridization experiment with a 269 bp gene specific probe. The PKC-eta cDNA clone, pBV39, was digested with the restriction enzymes *Xmn*I and *Bam*HI. The fragments were separated on a 1.2% agarose gel (Invitrogen; Cat. #G5018-01). The 269 bp fragment was excised from the gel and purified using QIA quick Gel Extraction Kit (QIAGEN; Cat. #28704). 25 ng of the purified fragment was used in a ³²P labeling reaction, performed with reagents as recommended in the Strip-EZ DNA probe synthesis instruction manual (Ambion; Cat. #1470). [α -³²P]dATP used in the reaction was purchased from Amersham Pharmacia Biotech (Cat. #AA0004). Hybridization and washing conditions were performed as recommended by CLONTECH manual PT3307-1. The MTE Array was exposed in a STORM860 Phosphor Screen for 70 h. ImageQuant was used to analyze the hybridization signal.

The results indicated the highest expression levels for PKC-eta in placenta, cardiovascular system, skeletal muscle, lung, liver, pancreas, and adipose tissue. This

was unexpected, since previous results [16] indicated that PKC-eta was expressed mainly in epithelial cells.

EXAMPLE 4: Reporter assay

5 Inducible reporter vectors that contain the *Photinus pyralis* (firefly) luciferase reporter gene, driven by a basic promoter element (TATA box), as well as inducible *cis*-enhancer elements (direct repeats from the promoter regions of various genes), were prepared or purchased. The reporter vectors are designed for the *in vivo* readouts of signal transduction pathways, since the enhancers are convergent points of many signal
10 transduction pathways. When a plasmid expressing the gene of interest is cotransfected into mammalian cells with a *cis*-reporter plasmid, increased luciferase expression indicates either direct or indirect transcriptional activation.

A vector designated pGluREx3-Luciferase ((gtgCACGTGtgaCAGCTGcaa)x3) was prepared using the pTAL promoter vector (Clontech; cat. #6252). The pGluREx3
15 vector is designed to monitor effects on glucose response (Portois L., et al. (1999) J. Biol. Chem. 274: 8181-8190). The vector pCRE-Luciferase, designed to monitor the activation of cAMP binding protein (CREB) and cAMP-mediated signal transduction pathways, was purchased from Stratagene (cat. #219075). A vector designated pGRE-Luciferase, designed to monitor the activation of Glucocorticoid response elements
20 (GRE) mediated signal transduction pathways, was purchased from Clontech (Cat. No. K2049-1).

Mouse adipocytes (differentiated 3T3-L1 cells) were transiently transfected with the response element construct of interest, in combination with PKC-eta or a backbone (control) plasmid construct, using LipofectAmine™2000 (Life Technologies). After 48
25 hrs, the cells were lysed using a lysis buffer (Tris-EDTA + 0.25% Triton-X100) for 10 min at room temperature, and the luciferase activity was measured using a luciferase activity assay (BioThema).

The results (Fig. 1) indicate that overexpression of PKC-eta in mouse adipocytes resulted in a 70% decrease of the activity of the GLUx3-Luciferase reporter, indicating
30 a decrease in glucose responsiveness in the cells. Overexpression of PKC-eta in mouse adipocytes also leads to decreased activity of the reporters pCRE and pGRE.

EXAMPLE 5: Glucose uptake assay

Glucose uptake was measured as described by Hundal et al. (1994) *Biochem. J.* 297: 289-295. Briefly, after incubation with hormones for 45 minutes, if not otherwise stated, cell monolayers were rinsed with glucose free PBS. Glucose uptake was

5 quantified by incubating the cells in the presence of 1 $\mu\text{Ci/ml}$ ^3H -2-deoxy-glucose in PBS for 8 min. Non-specific uptake was determined by quantifying cell-associated radioactivity in the presence of 10 μM cytochalasin B. Uptake of 2-deoxy-glucose was terminated by rapidly aspirating the medium, followed by three successive washes of

10 cell monolayers with ice cold PBS. The cells were lysed in 0.5 M NaOH, followed by liquid scintillation counting. Rates of transport were normalized for protein content in each well.

The results (Figs. 2A and 2B) indicate that over-expression of PKC- η in muscle cells (non-differentiated L6) and adipocytes (differentiated 3T3-L1 cells) decreased the rate of glucose-uptake in an insulin-dependent manner. The results

15 confirm the results from the reporter assay (Example 4) and further indicate that one effect of PKC- η over-expression is reduction of glucose uptake.

EXAMPLE 6: Down-regulation of insulin receptor tyrosine phosphorylation in CHO-hIR cells overexpressing PKC- η .

20 Tyrosine phosphorylation of the insulin receptor (IR) and insulin receptor substrates (IRS) are essential early steps in insulin signaling. The effect of PKC- η over-expression on insulin receptor phosphorylation was studied. A DELFIA assay (Dissociation Enhanced Lanthanide Fluoro-Immuno Assay; PerkinElmer Life Sciences) was used to measure phosphorylated tyrosines on the IR in lysates from cells infected

25 with an adenovirus containing the PKC- η gene (Fig.3).

CHO-hIR (Chinese hamster ovary cells over expressing the human IR) were grown in Alpha MEM supplemented with 10% fetal bovine serum (FBS) in T75 flasks (costar). The cells were infected with adenovirus at a MOI 7 giving approximately 95% of the cell population overexpressing the PKC- η gene. As a control of the infection,

30 adenovirus containing GFP was used. After infection the cells were incubated for 72 hours prior to determination of insulin receptor phosphorylation.

Confluent CHO-hIR cells, plated in T75 flasks (Costar), were infected with adenovirus. The virus stock was diluted in cell medium and incubated with the cells for

6 hours. The medium was subsequently replaced with fresh medium. 48 hours after infection the cells were plated in 12-well cell culture plates. Prior to insulin stimulation the cells were starved for at least 6 hours and then stimulated with 0, 25, or 100 nM insulin for 5 minutes at 37°C. Insulin stimulation was terminated by washing the cells
5 with cold PBS followed by shock freezing with liquid nitrogen (LN₂). The cells were thawed, lysed and scraped with cold lysis buffer and transferred to Eppendorf tubes. The lysates were frozen in LN₂ and moved to -70°C.

DELFA: A Clear FluroNunc 96-well plate (Nunc) was coated overnight at room temperature with goat anti-rabbit IgG 10µg/ml in PBS/MgCl₂ (Dia-Service
10 #55641). All other incubations were performed 1-2 hours (except enhancement) under agitation (Delfia Shaker) at room temperature. The coated wells were washed 2 times with 300 µl Delfia Wash Buffer (WB) followed by blocking with Superblock (Ready to use, Pierce). All washing steps were performed with a Delfia Platewasher from Wallac with at least 300 µl/well. The wells coated with anti-rabbit IgG antibodies were
15 incubated with a capturing anti-IR-β-chain antibody diluted in Delfia Assay Buffer to 1µg/ml (Santa Cruz #sc-711) followed by four washes. Insulin stimulated and untreated control cell lysates were thawed and centrifuged at 14,000 rpm, 4°C, for 10 minutes. After centrifugation, 100 µl of the supernatants were added to the wells and lysis buffer was used as blank. In the remaining cell lysates protein concentration were measured
20 with a kit from Pierce (Protein assay Reagent Kit, # 23227). After incubation and 4 washes the detecting antibody, biotin-labeled antibodies to phosphorylated tyrosine diluted to 0.2 ng/ml in assay buffer (Santa Cruz #sc-7020B), was added. The wells were washed 3-4 times before incubation with eu-labeled streptavidin diluted 1/1000 in assay buffer (PerkinElmer Instruments #1244-360). Finally, after incubation with eu-labeled
25 streptavidin, the wells were washed six times and the fluorescence was developed by 5-10 minutes incubation with acidic enhancement solution 100µl/well. The europium was released from its polycarboxylate-based chelate and immediately a new highly fluorescent hydrophobic chelate was formed that was measured with a time-resolved fluorometer (Wallac VICTOR). The europium-chelates were excited at 340 nm and the
30 emission was measured at 615 nm after a delay of 400 µs.

The fluorescence of each sample is proportional to tyrosine phosphorylation. The counts from each well were normalized to protein concentration, and the average counts from wells treated the same was calculated. The significance of the effect was

evaluated with a student T-test. P-values less than 0.05 or preferably 0.005 were considered significant.

Increased activity of PKC enzymes have previously been shown to cause insulin resistance by increasing phosphorylation on insulin receptor Ser/Thr residues [4, 10, 14]. The results shown in Fig. 3 indicate that PKC-eta is responsible for up-regulation of Ser/Thr phosphorylation at the expense of tyrosine phosphorylation.

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OTHER EMBODIMENTS

It is to be understood that, while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. Other aspects, advantages, and modifications of the invention are within the scope of the claims set forth below.

CLAIMS

1. A method for identifying an agent useful for the treatment of a medical condition relating to insulin resistance, said method comprising the steps
 - (i) contacting a candidate agent with a mammalian PKC-eta polypeptide; and
 - (ii) determining whether said candidate agent decreases or inhibits the biological activities of the said polypeptide, such decrease or inhibition being indicative for an agent useful for the treatment of a medical condition relating to insulin resistance.
2. A method for identifying an agent useful for the treatment of a medical condition relating to insulin resistance, said method comprising the steps
 - (i) contacting a candidate agent with a nucleic acid molecule encoding a mammalian PKC-eta polypeptide; and
 - (ii) determining whether said candidate agent decreases or inhibits the expression of the said nucleic acid molecule, such decrease or inhibition being indicative for an agent useful for the treatment of a medical condition relating to insulin resistance.
3. The method according to claim 1 or 2, wherein the medical condition relating to insulin resistance is associated with reduced glucose uptake.
4. The method according to any one of claims 1 to 3, wherein the medical condition relating to insulin resistance is type 2 diabetes.
5. The method according to any one of claims 1 to 4, wherein the mammalian PKC-eta polypeptide is a human PKC-eta polypeptide.
6. The method according to claim 5, wherein the human PKC-eta polypeptide comprises the amino acid sequence of SEQ ID NO:3, SEQ ID NO: 12 or SEQ ID NO:13.
7. A substantially pure polypeptide comprising the amino acid sequence of SEQ ID NO:13.

8. A substantially pure polypeptide consisting of the amino acid sequence of SEQ ID NO:13.

5 9. An isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:13.

10. A vector comprising the polynucleotide of claim 9.

10 11. A host cell comprising the vector of claim 10.

12. A method for producing a polypeptide, the method comprising culturing the cell of claim 11 under conditions whereby the polypeptide is produced.

15 13. A method for stimulating glucose uptake in a subject, the method comprising administering to a subject in need of such treatment an amount of an inhibitor of PKC-eta effective to increase glucose uptake in the subject.

14. The method of claim 13, wherein the subject is a human.

20 15. The method of claim 13 or 14, wherein the subject has type 2 diabetes.

16. The method of any of claims 13-15, further comprising detecting an increase in glucose uptake in the subject after administering the inhibitor to the subject.

25 17. A method for increasing glucose uptake in a mammalian cell, the method comprising contacting a mammalian cell with an amount of an inhibitor of PKC-eta effective to increase glucose uptake by the cell.

30 18. The method of claim 17, wherein the method is carried out *in vitro*.

19. The method of claim 17, wherein the method is carried out *in vivo*.

20. The method of any of claims 17-19, further comprising detecting an increase in glucose uptake by the cell after the contacting of the cell with the inhibitor.

21. The method of any of claims 17-20, wherein the cell is a muscle cell.

22. The method of any of claims 17-20, wherein the cell is an adipocyte.

5

23. A method for the treatment of a medical condition, the method comprising:
selecting an individual diagnosed as having a medical condition characterized by
insulin resistance; and

administering to the individual an amount of an inhibitor of PKC-eta effective to
10 reduce insulin resistance in the individual.

24. The method of claim 23, further comprising detecting a reduction in insulin
resistance in the individual after the administration of the inhibitor.

15 25. The method of claim 23, wherein the medical condition is characterized by
reduced glucose uptake.

26. The method of claim 25, further comprising detecting a reduction in blood
glucose levels in the individual after the administration of the inhibitor.

20

27. The method of any of claims 23-26, wherein the medical condition is
diabetes.

28. The method of any of claims 23-27, wherein the medical condition is type II
25 diabetes.

29. A method for identifying an agent that increases glucose uptake by a cell,
the method comprising:

contacting a cell with a candidate agent that inhibits an activity of a mammalian
30 PKC-eta polypeptide;
measuring glucose uptake by the cell in the presence of the candidate agent; and
determining whether the candidate agent increases glucose uptake by the cell.

30. The method of claim 29, wherein the candidate agent binds to the mammalian PKC-eta polypeptide.

31. The method of claim 29 or 30, wherein the mammalian PKC-eta polypeptide is a human PKC-eta polypeptide.

32. The method of claim 31, wherein the human PKC-eta polypeptide comprises the amino acid sequence of SEQ ID NO:3, SEQ ID NO: 12 or SEQ ID NO:13.

33. The method of any of claims 29-32, further comprising comparing glucose uptake by the cell in the presence of the candidate agent with glucose uptake by a cell in the absence of the candidate agent.

34. A method for identifying an agent that increases glucose uptake by a cell, the method comprising:
contacting a cell with a candidate agent that inhibits expression of a nucleic acid encoding a mammalian PKC-eta polypeptide;
measuring glucose uptake by the cell in the presence of the candidate agent; and
determining whether the candidate agent increases glucose uptake by the cell.

35. The method of claim 34, wherein the candidate agent binds to the nucleic acid.

36. The method of claim 34 or 35, wherein the mammalian PKC-eta polypeptide is a human PKC-eta polypeptide.

37. The method of claim 36, wherein the human PKC-eta polypeptide comprises the amino acid sequence of SEQ ID NO:3, SEQ ID NO: 12 or SEQ ID NO:13.

38. The method of any of claims 34-37, further comprising comparing glucose uptake by the cell in the presence of the candidate agent with glucose uptake by a cell in the absence of the candidate agent.

Fig. 1

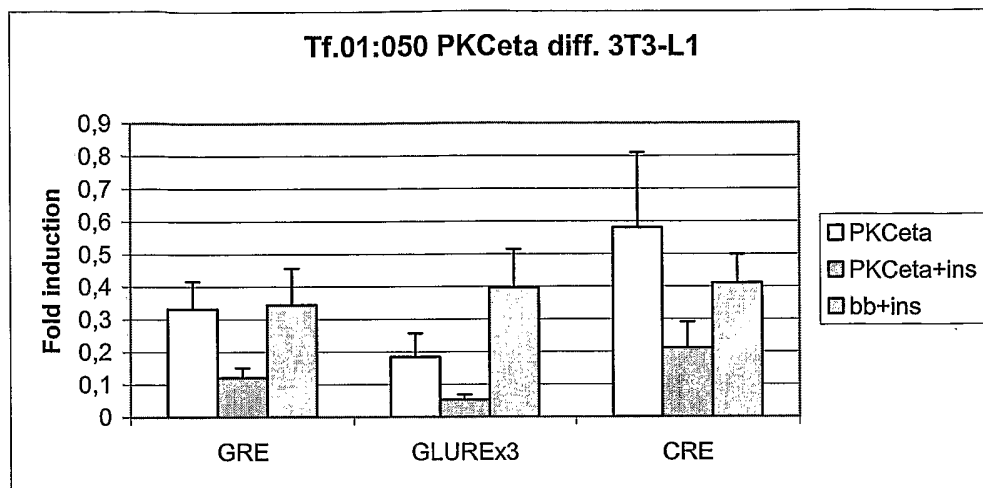


Fig. 2A

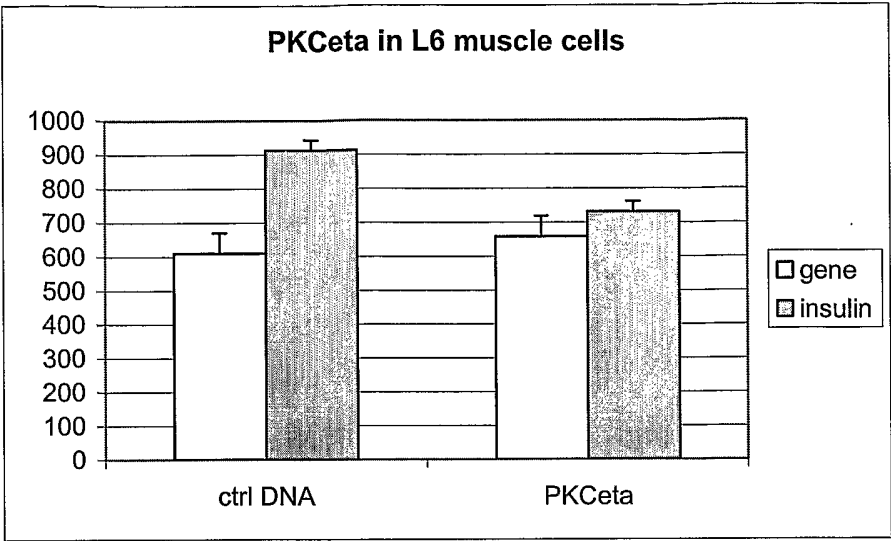


Fig. 2B

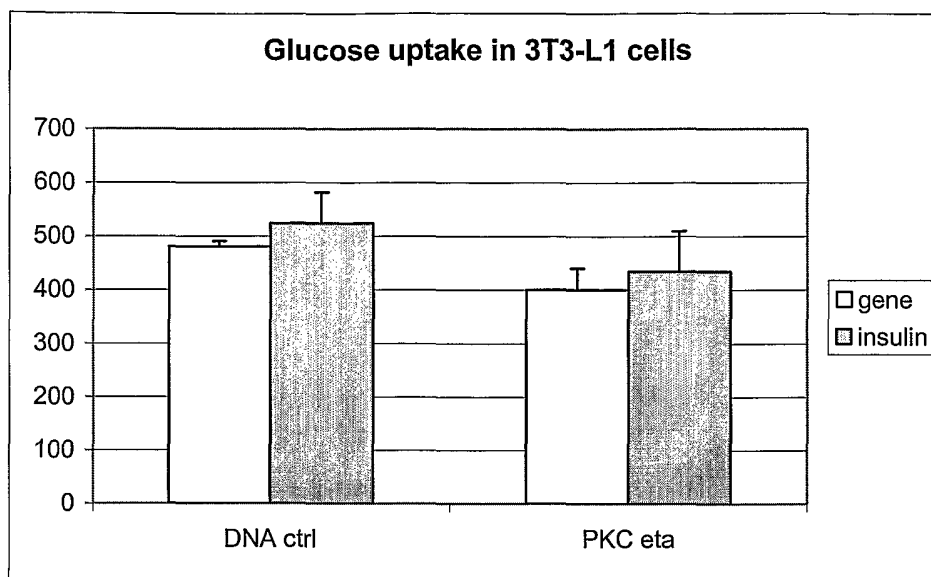
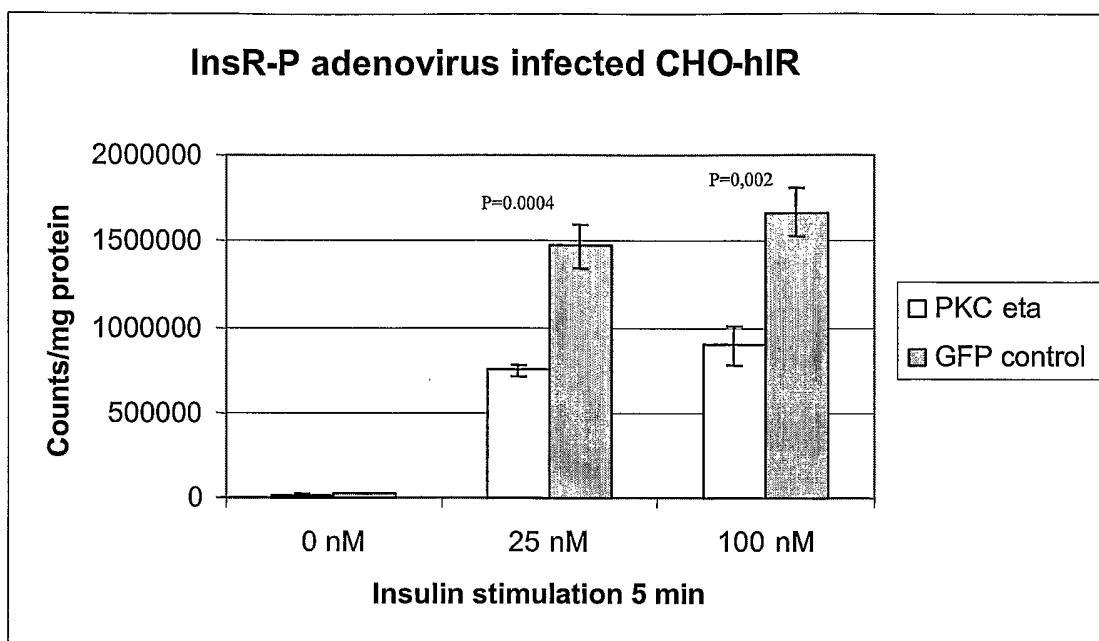


Fig. 3



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ttc atc cga gtg ttg ggg aag ggg agt ttt ggg aag gtg atg ctt gca	1279
Phe Ile Arg Val Leu Gly Lys Gly Ser Phe Gly Lys Val Met Leu Ala	
360 365 370	
aga gta aaa gaa aca gga gac ctc tat gct gtg aag gtg ctg aag aag	1327
Arg Val Lys Glu Thr Gly Asp Leu Tyr Ala Val Lys Val Leu Lys Lys	
375 380 385	
gac gtg att ctg ctg gat gat gat gtg gaa tgc acc atg acc gag aaa	1375
Asp Val Ile Leu Leu Asp Asp Asp Val Glu Cys Thr Met Thr Glu Lys	
390 395 400	
agg atc ctg tct ctg gcc cgc aat cac ccc ttc ctc act cag ttg ttc	1423
Arg Ile Leu Ser Leu Ala Arg Asn His Pro Phe Leu Thr Gln Leu Phe	
405 410 415	
tgc tgc ttt cag acc ccc gat cgt ctg ttt ttt gtg atg gag ttt gtg	1471
Cys Cys Phe Gln Thr Pro Asp Arg Leu Phe Phe Val Met Glu Phe Val	
420 425 430 435	
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Asn Gly Gly Asp Leu Met Phe His Ile Gln Lys Ser Arg Arg Phe Asp	
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gaa gca cga gct cgc ttc tat gct gca gaa atc att tcg gct ctc atg	1567
Glu Ala Arg Ala Arg Phe Tyr Ala Ala Glu Ile Ile Ser Ala Leu Met	
455 460 465	
ttc ctc cat gat aaa gga atc atc tat aga gat ctg aaa ctg gac aat	1615
Phe Leu His Asp Lys Gly Ile Ile Tyr Arg Asp Leu Lys Leu Asp Asn	
470 475 480	

gtc ctg ttg gac cac gag ggt cac tgt aaa ctg gca gac ttc gga atg Val Leu Leu Asp His Glu Gly His Cys Lys Leu Ala Asp Phe Gly Met 485 490 495	1663
tgc aag gag ggg att tgc aat ggt gtc acc acg gcc aca ttc tgt ggc Cys Lys Glu Gly Ile Cys Asn Gly Val Thr Thr Ala Thr Phe Cys Gly 500 505 510 515	1711
acg cca gac tat atc gct cca gag atc ctc cag gaa atg ctg tac ggg Thr Pro Asp Tyr Ile Ala Pro Glu Ile Leu Gln Glu Met Leu Tyr Gly 520 525 530	1759
cct gca gta gac tgg tgg gca atg ggc gtg ttg ctc tat gag atg ctc Pro Ala Val Asp Trp Trp Ala Met Gly Val Leu Leu Tyr Glu Met Leu 535 540 545	1807
tgt ggt cac gcg cct ttt gag gca gag aat gaa gat gac ctc ttt gag Cys Gly His Ala Pro Phe Glu Ala Glu Asn Glu Asp Asp Leu Phe Glu 550 555 560	1855
gcc ata ctg aat gat gag gtg gtc tac cct acc tgg ctc cat gaa gat Ala Ile Leu Asn Asp Glu Val Val Tyr Pro Thr Trp Leu His Glu Asp 565 570 575	1903
gcc aca ggg atc cta aaa tct ttc atg acc aag aac ccc acc atg cgc Ala Thr Gly Ile Leu Lys Ser Phe Met Thr Lys Asn Pro Thr Met Arg 580 585 590 595	1951
ttg ggc agc ctg act cag gga ggc gag cac gcc atc ttg aga cat cct Leu Gly Ser Leu Thr Gln Gly Gly Glu His Ala Ile Leu Arg His Pro 600 605 610	1999
ttt ttt aag gaa atc gac tgg gcc cag ctg aac cat cgc caa ata gaa Phe Phe Lys Glu Ile Asp Trp Ala Gln Leu Asn His Arg Gln Ile Glu 615 620 625	2047
ccg cct ttc aga ccc aga atc aaa tcc cga gaa gat gtc agt aat ttt Pro Pro Phe Arg Pro Arg Ile Lys Ser Arg Glu Asp Val Ser Asn Phe 630 635 640	2095
gac cct gac ttc ata aag gaa gag cca gtt tta act cca att gat gag Asp Pro Asp Phe Ile Lys Glu Glu Pro Val Leu Thr Pro Ile Asp Glu 645 650 655	2143
gga cat ctt cca atg att aac cag gat gag ttt aga aac ttt tcc tat Gly His Leu Pro Met Ile Asn Gln Asp Glu Phe Arg Asn Phe Ser Tyr 660 665 670 675	2191
gtg tct cca gaa ttg caa cca tag ccttatgggg agtgagagag agggcacgag Val Ser Pro Glu Leu Gln Pro 680	2245
aacccaaagg aatagagatt ctccaggaat ttcctctatc ggaccttccc agcatcagcc	2305
ttagaacaag aaccttacct tcaaggagca agtgaagaac tctgtcgaag gatggaactt	2365
tcagatatca actatattaga gtcc	2389

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 <212> PRT
 <213> human

<400> 3

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

Val Asp Gln Val Arg Val Gly Gln Thr Ser Thr Lys Gln Lys Thr Asn
          50          55          60

Lys Pro Thr Tyr Asn Glu Glu Phe Cys Ala Asn Val Thr Asp Gly Gly
65          70          75          80

His Leu Glu Leu Ala Val Phe His Glu Thr Pro Leu Gly Tyr Asp Phe
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Val Ala Asn Cys Thr Leu Gln Phe Gln Glu Leu Val Gly Thr Thr Gly
          100          105          110

Ala Ser Asp Thr Phe Glu Gly Trp Val Asp Leu Glu Pro Glu Gly Lys
          115          120          125

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

Gln Arg Asp Arg Ile Phe Lys His Phe Thr Arg Lys Arg Gln Arg Ala
145          150          155          160

Met Arg Arg Arg Val His Gln Ile Asn Gly His Lys Phe Met Ala Thr
          165          170          175

Tyr Leu Arg Gln Pro Thr Tyr Cys Ser His Cys Arg Glu Phe Ile Trp
          180          185          190

Gly Val Phe Gly Lys Gln Gly Tyr Gln Cys Gln Val Cys Thr Cys Val
          195          200          205

Val His Lys Arg Cys His His Leu Ile Val Thr Ala Cys Thr Cys Gln
          210          215          220

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

Ile Asn Ile Pro His Lys Phe Ser Ile His Asn Tyr Lys Val Pro Thr
          245          250          255

Phe Cys Asp His Cys Gly Ser Leu Leu Trp Gly Ile Met Arg Gln Gly
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Leu Gln Cys Lys Ile Cys Lys Met Asn Val His Ile Arg Cys Gln Ala
          275          280          285

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

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Arg His Pro Phe Phe Lys Glu Ile Asp Trp Ala Gln Leu Asn His Arg
 610 615 620

Gln Ile Glu Pro Pro Phe Arg Pro Arg Ile Lys Ser Arg Glu Asp Val
 625 630 635 640

Ser Asn Phe Asp Pro Asp Phe Ile Lys Glu Glu Pro Val Leu Thr Pro
 645 650 655

Ile Asp Glu Gly His Leu Pro Met Ile Asn Gln Asp Glu Phe Arg Asn
 660 665 670

Phe Ser Tyr Val Ser Pro Glu Leu Gln Pro
 675 680

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<220>
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 <212> DNA
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<220>
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<400> 5
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<210> 6
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 <213> human

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 Arg Val Arg Ile Gly Glu Ala Val Gly Leu Gln Pro Thr Arg Trp Ser
 15 20 25

ctg cgc cac tcg ctc ttc aag aag ggc cac cag ctg ctg gac ccc tat 146
 Leu Arg His Ser Leu Phe Lys Lys Gly His Gln Leu Leu Asp Pro Tyr
 30 35 40

ctg acg gtg agc gtg gac cag gtg cgc gtg ggc cag acc agc acc aag	194
Leu Thr Val Ser Val Asp Gln Val Arg Val Gly Gln Thr Ser Thr Lys	
45 50 55 60	
cag aag acc aac aaa ccc acg tac aac gag gag ttt tgc gct aac gtc	242
Gln Lys Thr Asn Lys Pro Thr Tyr Asn Glu Glu Phe Cys Ala Asn Val	
65 70 75	
acc gac ggc ggc cac ctc gag ttg gcc gtc ttc cac gag acg ccc ctg	290
Thr Asp Gly Gly His Leu Glu Leu Ala Val Phe His Glu Thr Pro Leu	
80 85 90	
ggc tac gac cac ttc gtg gcc aac tgc acc ctg cag ttc cag gag ctg	338
Gly Tyr Asp His Phe Val Ala Asn Cys Thr Leu Gln Phe Gln Glu Leu	
95 100 105	
ctg cgc acg acc ggc gcc tcg gac acc ttc gag ggt tgg gtg gat ctc	386
Leu Arg Thr Thr Gly Ala Ser Asp Thr Phe Glu Gly Trp Val Asp Leu	
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gag cca gag ggg aaa gta ttt gtg gta ata acc ctt acc ggg agt ttc	434
Glu Pro Glu Gly Lys Val Phe Val Val Ile Thr Leu Thr Gly Ser Phe	
125 130 135 140	
act gaa gct act ctc cag aga gac cgg atc ttc aaa cat ttt acc agg	482
Thr Glu Ala Thr Leu Gln Arg Asp Arg Ile Phe Lys His Phe Thr Arg	
145 150 155	
aag cgc caa agg gct atg cga agg cga gtc cac cag atc aat gga cac	530
Lys Arg Gln Arg Ala Met Arg Arg Arg Val His Gln Ile Asn Gly His	
160 165 170	
aag ttc atg gcc acg tat ctg agg cag ccc acc tac tgc tct cac tgc	578
Lys Phe Met Ala Thr Tyr Leu Arg Gln Pro Thr Tyr Cys Ser His Cys	
175 180 185	
agg gag ttt atc tgg gga gtg ttt ggg aaa cag ggt tat cag tgc caa	626
Arg Glu Phe Ile Trp Gly Phe Gly Lys Gln Tyr Gln Cys Gln	
190 195 200	
gtg tgc acc tgt gtc gtc cat aaa cgc tgc cat cat cta att gtt aca	674
Val Cys Thr Cys Val Val His Lys Arg Cys His His Leu Ile Val Thr	
205 210 215 220	
gcc tgt act tgc caa aac aat att aac aaa gtg gat tca aag att gca	722
Ala Cys Thr Cys Gln Asn Asn Ile Asn Lys Val Asp Ser Lys Ile Ala	
225 230 235	
gaa cag agg ttc ggg atc aac atc cca cac aag ttc agc atc cac aac	770
Glu Gln Arg Phe Gly Ile Asn Ile Pro His Lys Phe Ser Ile His Asn	
240 245 250	
tac aaa gtg cca aca ttc tgc gat cac tgt ggc tca ctg ctc tgg gga	818
Tyr Lys Val Pro Thr Phe Cys Asp His Cys Gly Ser Leu Leu Trp Gly	
255 260 265	
ata atg cga caa gga ctt cag tgt aaa ata tgt aaa atg aat gtg cat	866
Ile Met Arg Gln Gly Leu Gln Cys Lys Ile Cys Lys Met Asn Val His	
270 275 280	

att cga tgt caa gcg aac gtg gcc cct aac tgt ggg gta aat gcg gtg Ile Arg Cys Gln Ala Asn Val Ala Pro Asn Cys Gly Val Asn Ala Val 285 290 295 300	914
gaa ctt gcc aag acc ctg gca ggg atg ggt ctc caa ccc gga aat att Glu Leu Ala Lys Thr Leu Ala Gly Met Gly Leu Gln Pro Gly Asn Ile 305 310 315	962
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 Ile Leu Gln Glu Met Leu Tyr Gly Pro Ala Val Asp Trp Trp Ala Met
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ggc gtg ttg ctc tat gag atg ctc tgt ggt cac gcg cct ttt gag gca 1682
 Gly Val Leu Leu Tyr Glu Met Leu Cys Gly His Ala Pro Phe Glu Ala
 545 550 555

gag aat gaa gat gac ctc ttt gag gcc ata ctg aat gat gag gtg gtc 1730
 Glu Asn Glu Asp Asp Leu Phe Glu Ala Ile Leu Asn Asp Glu Val Val
 560 565 570

tac cct acc tgg ctc cat gaa gat gcc aca ggg atc cta aaa tct ttc 1778
 Tyr Pro Thr Trp Leu His Glu Asp Ala Thr Gly Ile Leu Lys Ser Phe
 575 580 585

atg acc aag aac ccc acc atg cgc ttg ggc agc ctg act cag gga ggc 1826
 Met Thr Lys Asn Pro Thr Met Arg Leu Gly Ser Leu Thr Gln Gly Gly
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gag cac gcc atc ttg aga cat cct ttt ttt aag gaa atc gac tgg gcc 1874
 Glu His Ala Ile Leu Arg His Pro Phe Phe Lys Glu Ile Asp Trp Ala
 605 610 615 620

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 Gln Leu Asn His Arg Gln Ile Glu Pro Pro Phe Arg Pro Arg Ile Lys
 625 630 635

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 Ser Arg Glu Asp Val Ser Asn Phe Asp Pro Asp Phe Ile Lys Glu Glu
 640 645 650

cca gtt tta act cca att gat gag gga cat ctt cca atg att aac cag 2018
 Pro Val Leu Thr Pro Ile Asp Glu Gly His Leu Pro Met Ile Asn Gln
 655 660 665

gat gag ttt aga aac ttt tcc tat gtg tct cca gaa ttg caa cca tag 2066
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Leu Phe Lys Lys Gly His Gln Leu Leu Asp Pro Tyr Leu Thr Val Ser
 35 40 45

Val Asp Gln Val Arg Val Gly Gln Thr Ser Thr Lys Gln Lys Thr Asn
 50 55 60

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

Val Leu Lys Lys Asp Val Ile Leu Gln Asp Asp Asp Val Glu Cys Thr
 385 390 395 400
 Met Thr Glu Lys Arg Ile Leu Ser Leu Ala Arg Asn His Pro Phe Leu
 405 410 415
 Thr Gln Leu Phe Cys Cys Phe Gln Thr Pro Asp Arg Leu Phe Phe Val
 420 425 430
 Met Glu Phe Val Asn Gly Gly Asp Leu Met Phe His Ile Gln Lys Ser
 435 440 445
 Arg Arg Phe Asp Glu Ala Arg Ala Arg Phe Tyr Ala Ala Glu Ile Ile
 450 455 460
 Ser Ala Leu Met Phe Leu His Asp Lys Gly Ile Ile Tyr Arg Asp Leu
 465 470 475 480
 Lys Leu Asp Asn Val Leu Leu Asp His Glu Gly His Cys Lys Leu Ala
 485 490 495
 Asp Phe Gly Met Cys Lys Glu Gly Ile Cys Asn Gly Val Thr Thr Ala
 500 505 510
 Thr Phe Cys Gly Thr Pro Asp Tyr Ile Ala Pro Glu Ile Leu Gln Glu
 515 520 525
 Met Leu Tyr Gly Pro Ala Val Asp Trp Trp Ala Met Gly Val Leu Leu
 530 535 540
 Tyr Glu Met Leu Cys Gly His Ala Pro Phe Glu Ala Glu Asn Glu Asp
 545 550 555 560
 Asp Leu Phe Glu Ala Ile Leu Asn Asp Glu Val Val Tyr Pro Thr Trp
 565 570 575
 Leu His Glu Asp Ala Thr Gly Ile Leu Lys Ser Phe Met Thr Lys Asn
 580 585 590
 Pro Thr Met Arg Leu Gly Ser Leu Thr Gln Gly Gly Glu His Ala Ile
 595 600 605
 Leu Arg His Pro Phe Phe Lys Glu Ile Asp Trp Ala Gln Leu Asn His
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 Arg Gln Ile Glu Pro Pro Phe Arg Pro Arg Ile Lys Ser Arg Glu Asp
 625 630 635 640
 Val Ser Asn Phe Asp Pro Asp Phe Ile Lys Glu Glu Pro Val Leu Thr
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 Pro Ile Asp Glu Gly His Leu Pro Met Ile Asn Gln Asp Glu Phe Arg
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<210> 9

<211> 52

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<213> unknown

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<211> 2784

<212> DNA

<213> human

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<222> (1)..(2757)

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act cga ctt ctt ttg gaa tat ctt gaa gaa aaa tat gaa gag cat ttg 96
 Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
 20 25 30

tat gag cgc gat gaa ggt gat aaa tgg cga aac aaa aag ttt gaa ttg 144
 Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 35 40 45

ggg ttg gag ttt ccc aat ctt cct tat tat att gat ggt gat gtt aaa 192
 Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
 50 55 60

tta aca cag tct atg gcc atc ata cgt tat ata gct gac aag cac aac 240
 Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
 65 70 75 80

atg ttg ggt ggt tgt cca aaa gag cgt gca gag att tca atg ctt gaa 288
 Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
 85 90 95

gga gcg gtt ttg gat att aga tac ggt gtt tcg aga att gca tat agt 336
 Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
 100 105 110

aaa gac ttt gaa act ctc aaa gtt gat ttt ctt agc aag cta cct gaa 384
 Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120 125

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Met	Leu	Lys	Met	Phe	Glu	Asp	Arg	Leu	Cys	His	Lys	Thr	Tyr	Leu	Asn	
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Gly	Asp	His	Val	Thr	His	Pro	Asp	Phe	Met	Leu	Tyr	Asp	Ala	Leu	Asp	
145					150					155					160	
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Val	Val	Leu	Tyr	Met	Asp	Pro	Met	Cys	Leu	Asp	Ala	Phe	Pro	Lys	Leu	
				165					170					175		
gtt	tgt	ttt	aaa	aaa	cgt	att	gaa	gct	atc	cca	caa	att	gat	aag	tac	576
Val	Cys	Phe	Lys	Lys	Arg	Ile	Glu	Ala	Ile	Pro	Gln	Ile	Asp	Lys	Tyr	
			180					185					190			
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Leu	Lys	Ser	Ser	Lys	Tyr	Ile	Ala	Trp	Pro	Leu	Gln	Gly	Trp	Gln	Ala	
		195					200					205				
acg	ttt	ggc	ggc	ggc	gac	cat	cct	cca	aaa	tcg	gat	ctg	ggt	ccg	cgt	672
Thr	Phe	Gly	Gly	Gly	Asp	His	Pro	Pro	Lys	Ser	Asp	Leu	Val	Pro	Arg	
	210					215					220					
tct	aga	tca	aca	agt	ttg	tac	aaa	aaa	gca	ggc	ttc	tcg	tct	ggc	acc	720
Ser	Arg	Ser	Thr	Ser	Leu	Tyr	Lys	Lys	Ala	Gly	Phe	Ser	Ser	Gly	Thr	
225					230					235					240	
atg	aag	ttc	aat	ggc	tat	ttg	agg	gtc	cgc	atc	ggc	gag	gca	gtg	ggg	768
Met	Lys	Phe	Asn	Gly	Tyr	Leu	Arg	Val	Arg	Ile	Gly	Glu	Ala	Val	Gly	
				245					250					255		
ctg	cag	ccc	acc	cgc	tgg	tcc	ctg	cgc	cac	tcg	ctc	ttc	aag	aag	ggc	816
Leu	Gln	Pro	Thr	Arg	Trp	Ser	Leu	Arg	His	Ser	Leu	Phe	Lys	Lys	Gly	
			260					265					270			
cac	cag	ctg	ctg	gac	ccc	tat	ctg	acg	gtg	agc	gtg	gac	cag	gtg	cgc	864
His	Gln	Leu	Leu	Asp	Pro	Tyr	Leu	Thr	Val	Ser	Val	Asp	Gln	Val	Arg	
		275					280					285				
gtg	ggc	cag	acc	agc	acc	aag	cag	aag	acc	aac	aaa	ccc	acg	tac	aac	912
Val	Gly	Gln	Thr	Ser	Thr	Lys	Gln	Lys	Thr	Asn	Lys	Pro	Thr	Tyr	Asn	
	290					295					300					
gag	gag	ttt	tgc	gct	aac	gtc	acc	gac	ggc	ggc	cac	ctc	gag	ttg	gcc	960
Glu	Glu	Phe	Cys	Ala	Asn	Val	Thr	Asp	Gly	Gly	His	Leu	Glu	Leu	Ala	
305					310					315					320	
gtc	ttc	cac	gag	acg	ccc	ctg	ggc	tac	gac	cac	ttc	gtg	gcc	aac	tgc	1008
Val	Phe	His	Glu	Thr	Pro	Leu	Gly	Tyr	Asp	His	Phe	Val	Ala	Asn	Cys	
				325					330					335		
acc	ctg	cag	ttc	cag	gag	ctg	ctg	cgc	acg	acc	ggc	gcc	tcg	gac	acc	1056
Thr	Leu	Gln	Phe	Gln	Glu	Leu	Leu	Arg	Thr	Thr	Gly	Ala	Ser	Asp	Thr	
			340					345					350			
ttc	gag	ggc	tgg	gtg	gat	ctc	gag	cca	gag	ggg	aaa	gta	ttt	gtg	gta	1104
Phe	Glu	Gly	Trp	Val	Asp	Leu	Glu	Pro	Glu	Gly	Lys	Val	Phe	Val	Val	
		355					360					365				

ata acc ctt acc ggg agt ttc act gaa gct act ctc cag aga gac cgg	1152
Ile Thr Leu Thr Gly Ser Phe Thr Glu Ala Thr Leu Gln Arg Asp Arg	
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Ile Phe Lys His Phe Thr Arg Lys Arg Gln Arg Ala Met Arg Arg Arg	
385 390 395 400	
gtc cac cag atc aat gga cac aag ttc atg gcc acg tat ctg agg cag	1248
Val His Gln Ile Asn Gly His Lys Phe Met Ala Thr Tyr Leu Arg Gln	
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ccc acc tac tgc tct cac tgc agg gag ttt atc tgg gga gtg ttt ggg	1296
Pro Thr Tyr Cys Ser His Cys Arg Glu Phe Ile Trp Gly Val Phe Gly	
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aaa cag ggt tat cag tgc caa gtg tgc acc tgt gtc gtc cat aaa cgc	1344
Lys Gln Gly Tyr Gln Cys Gln Val Cys Thr Cys Val Val His Lys Arg	
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tgc cat cat cta att gtt aca gcc tgt act tgc caa aac aat att aac	1392
Cys His His Leu Ile Val Thr Ala Cys Thr Cys Gln Asn Asn Ile Asn	
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aaa gtg gat tca aag att gca gaa cag agg ttc ggg atc aac atc cca	1440
Lys Val Asp Ser Lys Ile Ala Glu Gln Arg Phe Gly Ile Asn Ile Pro	
465 470 475 480	
cac aag ttc agc atc cac aac tac aaa gtg cca aca ttc tgc gat cac	1488
His Lys Phe Ser Ile His Asn Tyr Lys Val Pro Thr Phe Cys Asp His	
485 490 495	
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Cys Gly Ser Leu Leu Trp Gly Ile Met Arg Gln Gly Leu Gln Cys Lys	
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ata tgt aaa atg aat gtg cat att cga tgt caa gcg aac gtg gcc cct	1584
Ile Cys Lys Met Asn Val His Ile Arg Cys Gln Ala Asn Val Ala Pro	
515 520 525	
aac tgt ggg gta aat gcg gtg gaa ctt gcc aag acc ctg gca ggg atg	1632
Asn Cys Gly Val Asn Ala Val Glu Leu Ala Lys Thr Leu Ala Gly Met	
530 535 540	
ggg ctc caa ccc gga aat att tct cca acc tcg aaa ctc gtt tcc aga	1680
Gly Leu Gln Pro Gly Asn Ile Ser Pro Thr Ser Lys Leu Val Ser Arg	
545 550 555 560	
tcg acc cta aga cga cag gga aag gag agc agc aaa gaa gga aat ggg	1728
Ser Thr Leu Arg Arg Gln Gly Lys Glu Ser Ser Lys Glu Gly Asn Gly	
565 570 575	
att ggg gtt aat tct tcc aac cga ctt ggt atc gac aac ttt gag ttc	1776
Ile Gly Val Asn Ser Ser Asn Arg Leu Gly Ile Asp Asn Phe Glu Phe	
580 585 590	
atc cga gtg ttg ggg aag ggg agt ttt ggg aag gtg atg ctt gca aga	1824
Ile Arg Val Leu Gly Lys Gly Ser Phe Gly Lys Val Met Leu Ala Arg	
595 600 605	

gta aaa gaa aca gga gac ctc tat gct gtg aag gtg ctg aag aag gac Val Lys Glu Thr Gly Asp Leu Tyr Ala Val Lys Val Leu Lys Lys Asp 610 615 620	1872
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tgc ttt cag acc ccc gat cgt ctg ttt ttt gtg atg gag ttt gtg aat Cys Phe Gln Thr Pro Asp Arg Leu Phe Phe Val Met Glu Phe Val Asn 660 665 670	2016
ggg ggt gac ttg atg ttc cac att cag aag tct cgt cgt ttt gat gaa Gly Gly Asp Leu Met Phe His Ile Gln Lys Ser Arg Arg Phe Asp Glu 675 680 685	2064
gca cga gct cgc ttc tat gct gca gaa atc att tgc gct ctc atg ttc Ala Arg Ala Arg Phe Tyr Ala Ala Glu Ile Ile Ser Ala Leu Met Phe 690 695 700	2112
ctc cat gat aaa gga atc atc tat aga gat ctg aaa ctg gac aat gtc Leu His Asp Lys Gly Ile Ile Tyr Arg Asp Leu Lys Leu Asp Asn Val 705 710 715 720	2160
ctg ttg gac cac gag ggt cac tgt aaa ctg gca gac ttc gga atg tgc Leu Leu Asp His Glu Gly His Cys Lys Leu Ala Asp Phe Gly Met Cys 725 730 735	2208
aag gag ggg att tgc aat ggt gtc acc acg gcc aca ttc tgt ggc acg Lys Glu Gly Ile Cys Asn Gly Val Thr Thr Ala Thr Phe Cys Gly Thr 740 745 750	2256
cca gac tat atc gct cca gag atc ctc cag gaa atg ctg tac ggg cct Pro Asp Tyr Ile Ala Pro Glu Ile Leu Gln Glu Met Leu Tyr Gly Pro 755 760 765	2304
gca gta gac tgg tgg gca atg ggc gtg ttg ctc tat gag atg ctc tgt Ala Val Asp Trp Trp Ala Met Gly Val Leu Leu Tyr Glu Met Leu Cys 770 775 780	2352
ggt cac gcg cct ttt gag gca gag aat gaa gat gac ctc ttt gag gcc Gly His Ala Pro Phe Glu Ala Glu Asn Glu Asp Asp Leu Phe Glu Ala 785 790 795 800	2400
ata ctg aat gat gag gtg gtc tac cct acc tgg ctc cat gaa gat gcc Ile Leu Asn Asp Glu Val Val Tyr Pro Thr Trp Leu His Glu Asp Ala 805 810 815	2448
aca ggg atc cta aaa tct ttc atg acc aag aac ccc acc atg cgc ttg Thr Gly Ile Leu Lys Ser Phe Met Thr Lys Asn Pro Thr Met Arg Leu 820 825 830	2496
ggc agc ctg act cag gga ggc gag cac gcc atc ttg aga cat cct ttt Gly Ser Leu Thr Gln Gly Gly Glu His Ala Ile Leu Arg His Pro Phe 835 840 845	2544

ttt aag gaa atc gac tgg gcc cag ctg aac cat cgc caa ata gaa ccg 2592
 Phe Lys Glu Ile Asp Trp Ala Gln Leu Asn His Arg Gln Ile Glu Pro
 850 855 860

cct ttc aga ccc aga atc aaa tcc cga gaa gat gtc agt aat ttt gac 2640
 Pro Phe Arg Pro Arg Ile Lys Ser Arg Glu Asp Val Ser Asn Phe Asp
 865 870 875 880

cct gac ttc ata aag gaa gag cca gtt tta act cca att gat gag gga 2688
 Pro Asp Phe Ile Lys Glu Glu Pro Val Leu Thr Pro Ile Asp Glu Gly
 885 890 895

cat ctt cca atg att aac cag gat gag ttt aga aac ttt tcc tat gtg 2736
 His Leu Pro Met Ile Asn Gln Asp Glu Phe Arg Asn Phe Ser Tyr Val
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tct cca gaa ttg caa cca tag gacccagctt tcttgtacaa agtgggtt 2784
 Ser Pro Glu Leu Gln Pro
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<400> 11

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Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
 35 40 45

Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
 50 55 60

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

Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
 85 90 95

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

Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
 115 120 125

Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
 130 135 140

Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
 145 150 155 160

Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
 165 170 175

Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
 180 185 190
 Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
 195 200 205
 Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
 210 215 220
 Ser Arg Ser Thr Ser Leu Tyr Lys Lys Ala Gly Phe Ser Ser Gly Thr
 225 230 235 240
 Met Lys Phe Asn Gly Tyr Leu Arg Val Arg Ile Gly Glu Ala Val Gly
 245 250 255
 Leu Gln Pro Thr Arg Trp Ser Leu Arg His Ser Leu Phe Lys Lys Gly
 260 265 270
 His Gln Leu Leu Asp Pro Tyr Leu Thr Val Ser Val Asp Gln Val Arg
 275 280 285
 Val Gly Gln Thr Ser Thr Lys Gln Lys Thr Asn Lys Pro Thr Tyr Asn
 290 295 300
 Glu Glu Phe Cys Ala Asn Val Thr Asp Gly Gly His Leu Glu Leu Ala
 305 310 315 320
 Val Phe His Glu Thr Pro Leu Gly Tyr Asp His Phe Val Ala Asn Cys
 325 330 335
 Thr Leu Gln Phe Gln Glu Leu Leu Arg Thr Thr Gly Ala Ser Asp Thr
 340 345 350
 Phe Glu Gly Trp Val Asp Leu Glu Pro Glu Gly Lys Val Phe Val Val
 355 360 365
 Ile Thr Leu Thr Gly Ser Phe Thr Glu Ala Thr Leu Gln Arg Asp Arg
 370 375 380
 Ile Phe Lys His Phe Thr Arg Lys Arg Gln Arg Ala Met Arg Arg Arg
 385 390 395 400
 Val His Gln Ile Asn Gly His Lys Phe Met Ala Thr Tyr Leu Arg Gln
 405 410 415
 Pro Thr Tyr Cys Ser His Cys Arg Glu Phe Ile Trp Gly Val Phe Gly
 420 425 430
 Lys Gln Gly Tyr Gln Cys Gln Val Cys Thr Cys Val Val His Lys Arg
 435 440 445
 Cys His His Leu Ile Val Thr Ala Cys Thr Cys Gln Asn Asn Ile Asn
 450 455 460
 Lys Val Asp Ser Lys Ile Ala Glu Gln Arg Phe Gly Ile Asn Ile Pro
 465 470 475 480
 His Lys Phe Ser Ile His Asn Tyr Lys Val Pro Thr Phe Cys Asp His
 485 490 495

Cys	Gly	Ser	Leu	Leu	Trp	Gly	Ile	Met	Arg	Gln	Gly	Leu	Gln	Cys	Lys	500	505	510	
Ile	Cys	Lys	Met	Asn	Val	His	Ile	Arg	Cys	Gln	Ala	Asn	Val	Ala	Pro	515	520	525	
Asn	Cys	Gly	Val	Asn	Ala	Val	Glu	Leu	Ala	Lys	Thr	Leu	Ala	Gly	Met	530	535	540	
Gly	Leu	Gln	Pro	Gly	Asn	Ile	Ser	Pro	Thr	Ser	Lys	Leu	Val	Ser	Arg	545	550	555	560
Ser	Thr	Leu	Arg	Arg	Gln	Gly	Lys	Glu	Ser	Ser	Lys	Glu	Gly	Asn	Gly	565	570	575	
Ile	Gly	Val	Asn	Ser	Ser	Asn	Arg	Leu	Gly	Ile	Asp	Asn	Phe	Glu	Phe	580	585	590	
Ile	Arg	Val	Leu	Gly	Lys	Gly	Ser	Phe	Gly	Lys	Val	Met	Leu	Ala	Arg	595	600	605	
Val	Lys	Glu	Thr	Gly	Asp	Leu	Tyr	Ala	Val	Lys	Val	Leu	Lys	Lys	Asp	610	615	620	
Val	Ile	Leu	Gln	Asp	Asp	Asp	Val	Glu	Cys	Thr	Met	Thr	Glu	Lys	Arg	625	630	635	640
Ile	Leu	Ser	Leu	Ala	Arg	Asn	His	Pro	Phe	Leu	Thr	Gln	Leu	Phe	Cys	645	650	655	
Cys	Phe	Gln	Thr	Pro	Asp	Arg	Leu	Phe	Phe	Val	Met	Glu	Phe	Val	Asn	660	665	670	
Gly	Gly	Asp	Leu	Met	Phe	His	Ile	Gln	Lys	Ser	Arg	Arg	Phe	Asp	Glu	675	680	685	
Ala	Arg	Ala	Arg	Phe	Tyr	Ala	Ala	Glu	Ile	Ile	Ser	Ala	Leu	Met	Phe	690	695	700	
Leu	His	Asp	Lys	Gly	Ile	Ile	Tyr	Arg	Asp	Leu	Lys	Leu	Asp	Asn	Val	705	710	715	720
Leu	Leu	Asp	His	Glu	Gly	His	Cys	Lys	Leu	Ala	Asp	Phe	Gly	Met	Cys	725	730	735	
Lys	Glu	Gly	Ile	Cys	Asn	Gly	Val	Thr	Thr	Ala	Thr	Phe	Cys	Gly	Thr	740	745	750	
Pro	Asp	Tyr	Ile	Ala	Pro	Glu	Ile	Leu	Gln	Glu	Met	Leu	Tyr	Gly	Pro	755	760	765	
Ala	Val	Asp	Trp	Trp	Ala	Met	Gly	Val	Leu	Leu	Tyr	Glu	Met	Leu	Cys	770	775	780	
Gly	His	Ala	Pro	Phe	Glu	Ala	Glu	Asn	Glu	Asp	Asp	Leu	Phe	Glu	Ala	785	790	795	800
Ile	Leu	Asn	Asp	Glu	Val	Val	Tyr	Pro	Thr	Trp	Leu	His	Glu	Asp	Ala	805	810	815	

Thr Gly Ile Leu Lys Ser Phe Met Thr Lys Asn Pro Thr Met Arg Leu
820 825 830

Gly Ser Leu Thr Gln Gly Gly Glu His Ala Ile Leu Arg His Pro Phe
835 840 845

Phe Lys Glu Ile Asp Trp Ala Gln Leu Asn His Arg Gln Ile Glu Pro
850 855 860

Pro Phe Arg Pro Arg Ile Lys Ser Arg Glu Asp Val Ser Asn Phe Asp
865 870 875 880

Pro Asp Phe Ile Lys Glu Glu Pro Val Leu Thr Pro Ile Asp Glu Gly
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His Leu Pro Met Ile Asn Gln Asp Glu Phe Arg Asn Phe Ser Tyr Val
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Ser Pro Glu Leu Gln Pro
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Gly Ser Ser Gly Thr Met Lys Phe Asn Gly Tyr Leu Arg Val Arg Ile
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Gly Glu Ala Val Gly Leu Gln Pro Thr Arg Trp Ser Leu Arg His Ser
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Leu Phe Lys Lys Gly His Gln Leu Leu Asp Pro Tyr Leu Thr Val Ser
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Val Asp Gln Val Arg Val Gly Gln Thr Ser Thr Lys Gln Lys Thr Asn
85 90 95

Lys Pro Thr Tyr Asn Glu Glu Phe Cys Ala Asn Val Thr Asp Gly Gly
100 105 110

His Leu Glu Leu Ala Val Phe His Glu Thr Pro Leu Gly Tyr Asp His
115 120 125

Phe Val Ala Asn Cys Thr Leu Gln Phe Gln Glu Leu Leu Arg Thr Thr
130 135 140

Gly Ala Ser Asp Thr Phe Glu Gly Trp Val Asp Leu Glu Pro Glu Gly
145 150 155 160

Lys Val Phe Val Val Ile Thr Leu Thr Gly Ser Phe Thr Glu Ala Thr
165 170 175

Leu Gln Arg Asp Arg Ile Phe Lys His Phe Thr Arg Lys Arg Gln Arg
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 Ala Met Arg Arg Arg Val His Gln Ile Asn Gly His Lys Phe Met Ala
 195 200 205
 Thr Tyr Leu Arg Gln Pro Thr Tyr Cys Ser His Cys Arg Glu Phe Ile
 210 215 220
 Trp Gly Val Phe Gly Lys Gln Gly Tyr Gln Cys Gln Val Cys Thr Cys
 225 230 235 240
 Val Val His Lys Arg Cys His His Leu Ile Val Thr Ala Cys Thr Cys
 245 250 255
 Gln Asn Asn Ile Asn Lys Val Asp Ser Lys Ile Ala Glu Gln Arg Phe
 260 265 270
 Gly Ile Asn Ile Pro His Lys Phe Ser Ile His Asn Tyr Lys Val Pro
 275 280 285
 Thr Phe Cys Asp His Cys Gly Ser Leu Leu Trp Gly Ile Met Arg Gln
 290 295 300
 Gly Leu Gln Cys Lys Ile Cys Lys Met Asn Val His Ile Arg Cys Gln
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 Ala Asn Val Ala Pro Asn Cys Gly Val Asn Ala Val Glu Leu Ala Lys
 325 330 335
 Thr Leu Ala Gly Met Gly Leu Gln Pro Gly Asn Ile Ser Pro Thr Ser
 340 345 350
 Lys Leu Val Ser Arg Ser Thr Leu Arg Arg Gln Gly Lys Glu Ser Ser
 355 360 365
 Lys Glu Gly Asn Gly Ile Gly Val Asn Ser Ser Asn Arg Leu Gly Ile
 370 375 380
 Asp Asn Phe Glu Phe Ile Arg Val Leu Gly Lys Gly Ser Phe Gly Lys
 385 390 395 400
 Val Met Leu Ala Arg Ile Lys Glu Thr Gly Asp Leu Tyr Ala Val Lys
 405 410 415
 Val Leu Lys Lys Asp Val Ile Leu Gln Asp Asp Asp Val Glu Cys Thr
 420 425 430
 Met Thr Glu Lys Arg Ile Leu Ser Leu Ala Arg Asn His Pro Phe Leu
 435 440 445
 Thr Gln Leu Phe Cys Cys Phe Gln Thr Pro Asp Arg Leu Phe Phe Val
 450 455 460
 Met Glu Phe Val Asn Gly Gly Asp Leu Met Phe His Ile Gln Lys Ser
 465 470 475 480
 Arg Arg Phe Asp Glu Ala Arg Ala Arg Phe Tyr Ala Ala Glu Ile Ile
 485 490 495

Ser Ala Leu Met Phe Leu His Asp Lys Gly Ile Ile Tyr Arg Asp Leu
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 Lys Leu Asp Asn Val Leu Leu Asp His Glu Gly His Cys Lys Leu Ala
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 Asp Phe Gly Met Cys Lys Glu Gly Ile Cys Asn Gly Val Thr Thr Ala
 530 535 540
 Thr Phe Cys Gly Thr Pro Asp Tyr Ile Ala Pro Glu Ile Leu Gln Glu
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 Met Leu Tyr Gly Pro Ala Val Asp Trp Trp Ala Met Gly Val Leu Leu
 565 570 575
 Tyr Glu Met Leu Cys Gly His Ala Pro Phe Glu Ala Glu Asn Glu Asp
 580 585 590
 Asp Leu Phe Glu Ala Ile Leu Asn Asp Glu Val Val Tyr Pro Thr Trp
 595 600 605
 Leu His Glu Asp Ala Thr Gly Ile Leu Lys Ser Phe Met Thr Lys Asn
 610 615 620
 Pro Thr Met Arg Leu Gly Ser Leu Thr Gln Gly Gly Glu His Ala Ile
 625 630 635 640
 Leu Arg His Pro Phe Phe Lys Glu Ile Asp Trp Ala Gln Leu Asn His
 645 650 655
 Arg Gln Ile Glu Pro Pro Phe Arg Pro Arg Ile Lys Ser Arg Glu Asp
 660 665 670
 Val Ser Asn Phe Asp Pro Asp Phe Ile Lys Glu Glu Pro Val Leu Thr
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 35 40 45
 Val Asp Gln Val Arg Val Gly Gln Thr Ser Thr Lys Gln Lys Thr Asn
 50 55 60

Lys Pro Thr Tyr Asn Glu Glu Phe Cys Ala Asn Val Thr Asp Gly Gly
 65 70 75 80
 His Leu Glu Leu Ala Val Phe His Glu Thr Pro Leu Gly Tyr Asp His
 85 90 95
 Phe Val Ala Asn Cys Thr Leu Gln Phe Gln Glu Leu Leu Arg Thr Thr
 100 105 110
 Gly Ala Ser Asp Thr Phe Glu Gly Trp Val Asp Leu Glu Pro Glu Gly
 115 120 125
 Lys Val Phe Val Val Ile Thr Leu Thr Gly Ser Phe Thr Glu Ala Thr
 130 135 140
 Leu Gln Arg Asp Arg Ile Phe Lys His Phe Thr Arg Lys Arg Gln Arg
 145 150 155 160
 Ala Met Arg Arg Arg Val His Gln Ile Asn Gly His Lys Phe Met Ala
 165 170 175
 Thr Tyr Leu Arg Gln Pro Thr Tyr Cys Ser His Cys Arg Glu Phe Ile
 180 185 190
 Trp Gly Val Phe Gly Lys Gln Gly Tyr Gln Cys Gln Val Cys Thr Cys
 195 200 205
 Val Val His Lys Arg Cys His His Leu Ile Val Thr Ala Cys Thr Cys
 210 215 220
 Gln Asn Asn Ile Asn Lys Val Asp Ser Lys Ile Ala Glu Gln Arg Phe
 225 230 235 240
 Gly Ile Asn Ile Pro His Lys Phe Ser Ile His Asn Tyr Lys Val Pro
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 Thr Phe Cys Asp His Cys Gly Ser Leu Leu Trp Gly Ile Met Arg Gln
 260 265 270
 Gly Leu Gln Cys Lys Ile Cys Lys Met Asn Val His Ile Arg Cys Gln
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 Ala Asn Val Ala Pro Asn Cys Gly Val Asn Ala Val Glu Leu Ala Lys
 290 295 300
 Thr Leu Ala Gly Met Gly Leu Gln Pro Gly Asn Ile Ser Pro Thr Ser
 305 310 315 320
 Lys Leu Val Ser Arg Ser Thr Leu Arg Arg Gln Gly Lys Glu Ser Ser
 325 330 335
 Lys Glu Gly Asn Gly Ile Gly Val Asn Ser Ser Asn Arg Leu Gly Ile
 340 345 350
 Asp Asn Phe Glu Phe Ile Arg Val Leu Gly Lys Gly Ser Phe Gly Lys
 355 360 365
 Val Met Leu Ala Arg Ile Lys Glu Thr Gly Asp Leu Tyr Ala Val Lys
 370 375 380

Val	Leu	Lys	Lys	Asp	Val	Ile	Leu	Gln	Asp	Asp	Asp	Val	Glu	Cys	Thr	385	390	395	400
Met	Thr	Glu	Lys	Arg	Ile	Leu	Ser	Leu	Ala	Arg	Asn	His	Pro	Phe	Leu	405	410	415	
Thr	Gln	Leu	Phe	Cys	Cys	Phe	Gln	Thr	Pro	Asp	Arg	Leu	Phe	Phe	Val	420	425	430	
Met	Glu	Phe	Val	Asn	Gly	Gly	Asp	Leu	Met	Phe	His	Ile	Gln	Lys	Ser	435	440	445	
Arg	Arg	Phe	Asp	Glu	Ala	Arg	Ala	Arg	Phe	Tyr	Ala	Ala	Glu	Ile	Ile	450	455	460	
Ser	Ala	Leu	Met	Phe	Leu	His	Asp	Lys	Gly	Ile	Ile	Tyr	Arg	Asp	Leu	465	470	475	480
Lys	Leu	Asp	Asn	Val	Leu	Leu	Asp	His	Glu	Gly	His	Cys	Lys	Leu	Ala	485	490	495	
Asp	Phe	Gly	Met	Cys	Lys	Glu	Gly	Ile	Cys	Asn	Gly	Val	Thr	Thr	Ala	500	505	510	
Thr	Phe	Cys	Gly	Thr	Pro	Asp	Tyr	Ile	Ala	Pro	Glu	Ile	Leu	Gln	Glu	515	520	525	
Met	Leu	Tyr	Gly	Pro	Ala	Val	Asp	Trp	Trp	Ala	Met	Gly	Val	Leu	Leu	530	535	540	
Tyr	Glu	Met	Leu	Cys	Gly	His	Ala	Pro	Phe	Glu	Ala	Glu	Asn	Glu	Asp	545	550	555	560
Asp	Leu	Phe	Glu	Ala	Ile	Leu	Asn	Asp	Glu	Val	Val	Tyr	Pro	Thr	Trp	565	570	575	
Leu	His	Glu	Asp	Ala	Thr	Gly	Ile	Leu	Lys	Ser	Phe	Met	Thr	Lys	Asn	580	585	590	
Pro	Thr	Met	Arg	Leu	Gly	Ser	Leu	Thr	Gln	Gly	Gly	Glu	His	Ala	Ile	595	600	605	
Leu	Arg	His	Pro	Phe	Phe	Lys	Glu	Ile	Asp	Trp	Ala	Gln	Leu	Asn	His	610	615	620	
Arg	Gln	Ile	Glu	Pro	Pro	Phe	Arg	Pro	Arg	Ile	Lys	Ser	Arg	Glu	Asp	625	630	635	640
Val	Ser	Asn	Phe	Asp	Pro	Asp	Phe	Ile	Lys	Glu	Glu	Pro	Val	Leu	Thr	645	650	655	
Pro	Ile	Asp	Glu	Gly	His	Leu	Pro	Met	Ile	Asn	Gln	Asp	Glu	Phe	Arg	660	665	670	
Asn	Phe	Ser	Tyr	Val	Ser	Pro	Glu	Leu	Gln	Pro						675	680		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01361

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **13-17, 19-38**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01361

Claims 13-17, 19-38 relates to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01361

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07K 14/47, C12Q 1/68, C12N 9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07K, C12Q, C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, BIOSIS, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0205566 A2,(EXELIXIS, INC.), 18 July 2002, (18.07.2002), & DATABASE GeneSeq [Online], Accession No. AA018491 11 Oct 2002, retrieved from EBI, 99,268 % identity in a 683 aa overlap with SEQ ID NO:13. 100,000 % identity in a 682 aa overlap with SEQ ID NO:3. page 3, lines 27-29; page 11, lines 17-38; SEQ ID NO 4; page 22, lines 6-12 --	1-38

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

2 December 2003

Date of mailing of the international search report

03-12-2003

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01361

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE SwissProt [Online], Accession No. P24723, 1 Mar 1992, retrieved from EBI, 99,268 % identity in a 683 aa overlap with SEQ ID NO:13. & National Library of Medicine (NLM), file Medline, Accession No. NLM1986216, Bacher N et al., Isolation and characterization of PKC-L, a new member of the protein kinase C-related gene family specifically expressed in lung, skin and heart.,Molecular and cellular biology, 1991, vol. 11, nr. 1,pg. 126-133, abstract	7-12
A	--	1-6,13-38
P,X	DATABASE SwissProt [Online] Accession No. Q8NE03 1 Oct 2002, retrieved from EBI 99,854 % identity in a 683 aa overlap with SEQ ID NO:13.	7-12
P,A	-----	1-6,13-38