



(86) Date de dépôt PCT/PCT Filing Date: 1995/10/10
(87) Date publication PCT/PCT Publication Date: 1996/04/25
(45) Date de délivrance/Issue Date: 2012/12/11
(85) Entrée phase nationale/National Entry: 1997/04/11
(86) N° demande PCT/PCT Application No.: EP 1995/003990
(87) N° publication PCT/PCT Publication No.: 1996/012024
(30) Priorités/Priorities: 1994/10/13 (DEP 44 36 696.5);
1994/12/20 (DEP 44 45 562.3)

(51) Cl.Int./Int.Cl. *C12N 15/54* (2006.01),
A61K 31/70 (2006.01), *A61K 38/45* (2006.01),
A61K 39/395 (2006.01), *A61K 48/00* (2006.01),
C07H 21/04 (2006.01), *C07K 16/40* (2006.01),
C12N 9/12 (2006.01), *C12Q 1/48* (2006.01),
C12Q 1/68 (2006.01), *G01N 33/53* (2006.01),
A61K 38/00 (2006.01)

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(54) Titre : CLONAGE, EXPRESSION ET CARACTERISATION D'UNE NOUVELLE FORME DE
PHOSPHATIDYLINOSITOL-3-KINASE

(54) Title: CLONING, EXPRESSION AND CHARACTERISATION OF A NEW FORM OF PHOSPHATIDYLINOSITOL-3-
KINASE

(57) **Abrégé/Abstract:**

The present invention relates to a novel phosphatidylinositol-3-kinase (PI3K γ), a nucleic acid coding it, an antibody directed against the protein and the diagnostic and therapeutic use of the protein, the nucleic acid and the antibody.

Abstract

The present invention concerns a new phosphatidyl-inositol-3-kinase (PI3K γ), a nucleic acid coding for it, an antibody directed against the protein as well as the diagnostic and therapeutic use of the protein, the nucleic acid and the antibody.

- 1 -

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Cloning, expression and characterization of a new form
of phosphatidylinositol-3-kinase

Description

The present invention concerns a new phosphatidyl-
inositol-3-kinase (PI3K γ), a nucleic acid which codes
for it, an antibody directed against the protein as well
as the diagnostic and therapeutic use of the protein, of
the nucleic acid and of the antibody.

Phosphatidylinositol-kinases belong, together with
specific phospholipases, to an enzyme group which
catalyses the formation of intracellular messenger
substances from the membrane lipid phosphatidyl inositol
(PI). The activity of these enzymes is regulated by
extracellular effectors such as hormones, growth factors
and neurotransmitters. It is assumed that the PI
dependent messenger substances are involved among other
processes in the regulation of important cells functions
such as cell proliferation, secretion of cellular
constituents, endocytotic processes, the targetted
movement of certain cells, controlled changes of the
cytoskeleton. Correspondingly the physiological
importance of the PI kinases and phospholipases
correlates with a series of disease states involving
changes of the functions of these enzymes.

From various experimental results it is possible to
conclude that the product of the reaction catalysed by

- 2 -

PI3 kinase, PI-3,4,5 triphosphate plays an important role in the regulation of the following physiological cell functions:

- Regulation of cell proliferation and cell differentiation by PI 3 kinase

Mitogens such as growth factors and cytokines generally lead to a stimulation of the PI 3 kinase activity in cells capable of division. The oncogenic transformation of cells is also often accompanied by an increase in the measurable PI 3 kinase activity (Varticovski et al., Biochim. Biophys. Acta 1226, 1-11 (1994), Berggren et al., Cancer Research 53, 4297-4302 (1993), Soldi et al., Oncogene 9, 2253-2260 (1994)). Inhibitors of PI 3 kinase are able to inhibit the PDGF-stimulated growth of normal connective tissue cells or smooth muscle cells and the proliferation of src-supratransformed fibroblasts (cancer cells) (Berggren et al., Cancer Research 53, 4297-4302 (1993), Vlahos et al., J.Biol.Chem. 269, 5241-5248 (1994)). Berggren et al., have speculated that the tumorstatic effect of ether lipid analogues is mainly based on their inhibitory action on PI 3 kinase.

The differentiation of the nerve cell line PC12 is suppressed by wortmannin an inhibitor of PI 3 kinase (Kimurea et al., J.Biol.Chem. 269, 18961-18967 (1994)). These findings as well as a clinical study in which there was shown to be a selective loss of PI 3 kinase activity in the brain of Alzheimer patients (Bothmer et al., Dementia 5, 6-11 (1994)) indicate that the enzyme has an important function in the formation and maintenance of nerve tissue.

- 3 -

- Regulation of cytoskeletal-dependent processes by PI 3 kinase

Microscopically visible changes of cells often progress with the involvement of the cytoskeleton. A series of results shows that at least some of these processes are regulated by PI 3 kinase and its enzymatic products (PI3,4,5,P₃, PI3,4P₂ and PI3P). Thus the membrane ruffling of epidermal cells induced by insulin or PDGF can be suppressed by the PI 3 kinase inhibitor wortmannin (Kotani et al., EMBO J. 13, 2313-2321 (1994), Wennström et al., Curr. Biol. 4, 385-393 (1994)).

Basophilic leucocytes are able to secrete histamine - a mediator of inflammations and allergic symptoms. The cytoskeleton of the cells is involved in this secretion process. Yano et al., J. Biol.Chem. 268, 25846-25856 (1993) were able to show that the antibody-induced histamine secretion can in turn be inhibited by the PI 3 kinase inhibitor wortmannin i.e. it is apparently controlled by 3-phosphorylated phosphoinositides.

- Involvement of PI 3 kinase in intracellular transport processes

Investigations on yeast mutants show that one form of PI 3 kinase (Vps 34) is involved in these organisms in the selective distribution of proteins towards the yeast vacuoles (Schu et al., Science 260, 88-91 (1993)). Similar mechanisms may be the basis of the insulin-stimulated translocation of glucose transport protein (GLUT 4) from the interior of the cell to the plasma membrane (Kanai et al., Biochem.Biophys.Res.Comm. 195, 762-768 (1993)). This important process in various

- 4 -

organs is also inhibited by wortmannin and apparently involves PI 3 kinase.

- Inhibition of the O_2^- production in neutrophilic granulocytes

Granulocytes produce superoxide anions (O_2^-) with the aim of destroying phagocytised foreign cells. This process is stimulated by the chemoattractant fMLP. The blocking of the fMLP-induced O_2^- formation by wortmannin indicates a regulatory function of a PI 3 kinase species in this important process for the immune response of the body.

The above-mentioned results underline the central importance of PI 3 kinase and 3-phosphorylated inositol lipids in the regulation of important cell functions. Acquired or inherited defects of the said cell functions are undoubtedly the underlying cause of important clinical syndromes. Examples are: cancer, arteriosclerosis, immunopathies, skin diseases (such as psoriasis), degenerative diseases of the nervous system.

Since PI 3 kinase is an essential element in the regulation of the said cell functions it is very probable that some of the clinical syndromes are due to malfunctions of PI 3 kinase species. The clinical study on PI 3 kinase in the brain of Alzheimer patients, the findings on the role of PI 3 kinase in the formation of the allergy inducer histamine and also the cancerostatic effect of PI 3 kinase-inhibiting ether lipids point in this direction.

A central concern of cell biology is to discover the

- 5 -

mechanisms of intracellular signal transmission and the messenger substances that are involved. The final goal of these investigations is to selectively influence cell functions in a medical sense.

The present application describes the identification, cloning, expression and characterization of a new species of PI 3 kinase. This new species is activated by G protein subunits and hence differs from the previous species PI3K α (Hiles et al., Cell 70 (1992) 419-429) and PI3K β (Hu et al., J.Mol.Cell. Biol. 13, (1993), 7677-7688) cloned from mammalian cells and from the PI3K-Vps34 from yeast (Schu et al., supra and Herman et al., Cell 64 (1991), 425-438) with regard to the regulation mechanism. The functional differences between the known enzymes PI3K α and PI3K β on the one hand as well as the enzyme PI3K γ according to the invention on the other hand are reflected in differences in the sequences of the important regulatory domains of the enzyme.

Hence a subject matter of the invention is a protein with phosphatidylinositol-3-kinase activity which is characterized in that it comprises

- a) the amino acid sequence shown in SEQ ID NO. 2
- b) the amino acid sequence shown in SEQ ID NO. 4 or
- c) variants of the sequence from (a).

The PI3K γ according to the invention is preferably a protein obtainable from humans i.e. it is the protein shown in SEQ ID NO. 1 and NO. 2, the protein shown in SEQ ID NO. 3 and NO. 4 or a naturally occurring human variant thereof.

The invention also concerns a new protein which

- 6 -

comprises parts of the amino acid sequence shown in SEQ ID NO. 1 and 2 or SEQ ID NO. 3 and 4. The invention preferably concerns a PI3K which comprises the amino acid sequence shown in SEQ ID NO. 1 and 2 or the amino acid sequence shown in SEQ ID NO. 3 and 4; it can, however, also contain variants of this sequence. The term "variant" within the sense of the present invention is understood as sequences which differ from the amino acid sequence shown in SEQ ID NO. 1 and 2 or in SEQ ID NO. 3 and 4 by substitution, deletion or/and insertion of individual amino acids or short sections of amino acids.

The term "variant" includes naturally occurring allelic variations of PI3Ky as well as proteins produced by recombinant DNA technology (in particular by in vitro mutagenesis with the aid of chemically synthesized oligonucleotides) which, with regard to their biological or/and immunological activity, essentially correspond to the protein shown in SEQ ID NO. 1 and 2 or to the protein shown in SEQ ID NO. 3 and 4.

A preferred characteristic of proteins according to the invention is that at the amino acid level they have a homology of at least 80 % particularly preferably of 90 % and most preferably of 95 % to the amino acid sequence shown in SEQ ID NO. 1 and 2 or to the amino acid sequences shown in SEQ ID NO. 3 and 4.

The amino acid sequence shown in SEQ ID NO. 1 and 2 represents a whole PI3Ky. This protein has 1049 amino acids and has a molecular mass of ca. 120 kDa. The amino acid sequence shown in SEQ ID NO. 3 and 4 represents a PI3Ky with 1050 amino acids.

- 7 -

The amino acid sequence of PI3Ky has a homology of 19 to 39 % to the sequences of other known PI3K such as human PI3K α (36 % homology), human PI3K β (33.5 % homology) and PI3KVps34 from yeast (27.7 %). The most highly conserved region in this group of enzymes are the 400 C-terminal amino acid residues which presumably contain the kinase domain. There is no significant homology between PI3Ky and the other enzymes in the amino-terminal region which is known to be responsible for the binding of PI3K α and β -enzyme subunits to the regulatory and adaptory subunits p85 α and p85 β (Dhand et al., EMBO J. 13 (1994), 511-521).

PI3Ky can be detected in the cell as a 110 kDa protein by immunoprecipitation and Western blot analysis of U937 and K562 cells using antipeptide antisera. A Northern blot analysis showed a 5.3 kb long mRNA in several different tissue types.

A further subject matter of the present invention is a nucleic acid which codes for a phosphatidylinositol-3-kinase or parts thereof according to the invention. This nucleic acid can for example be genomic DNA, cDNA or RNA. It is preferably a recombinant DNA molecule.

Another subject matter of the invention is a nucleic acid which contains

- a) the coding sequence shown in SEQ ID NO. 1
- b) the protein-coding sequence shown in SEQ ID NO. 3
- c) a nucleic acid sequence corresponding to the sequence from (a) or (b) within the scope of the degeneracy of the genetic code or
- d) a sequence hybridizing with the sequences from (a), (b) and/or (c) under stringent hybridization

conditions.

Stringent hybridization conditions within the sense of the present invention are understood as a hybridization which also still occurs after washing at 55°C, preferably at 62°C, particularly preferably at 68°C in an aqueous low salt buffer (e.g. 0.2 x SSC, 0.1 % SDS) (see also Sambrook et al. (1989) Molecular Cloning, A Laboratory Manual).

The invention also concerns nucleic acids which contain at least a 20 nucleotide long section of the sequence shown in SEQ ID NO. 1 or SEQ ID NO. 3. This section preferably has a specific nucleotide sequence for the PI3Ky. These nucleic acids are especially suitable for the production of therapeutically applicable antisense nucleic acids which are preferably up to 50 nucleotides long.

Yet a further subject matter of the invention is a vector which contains at least one copy of a nucleic acid or a part thereof according to the invention. The vector can be capable of replication in eukaryotes or prokaryotes. It can be a vector which can be integrated into the genome of the host cell e.g. bacteriophage lambda, or a vector which is present extrachromosomally (e.g. a plasmid). The vector according to the invention can be obtained by subcloning the PI3Ky DNA into a basic vector. Such basic vectors in particular vectors containing the necessary elements for protein expression are familiar to a person skilled in the art.

When a nucleic acid coding for PI3Ky is cloned it is possible to construct an expression vector which can be

made to express in a suitable host cell to form the protein according to the invention. Preferred host cells are microorganisms such as *E. coli* or yeast and also higher cells (e.g. mammalian or insect cells). Preferred expression vectors are e.g. plasmids, bacteriophage lambda for prokaryotes, yeast vectors or viral vectors for higher cells (e.g. SV40, vaccinia, baculoviruses). With regard to the expression of a nucleic acid coding for PI3Ky particular reference is made to the methods mentioned in Sambrook et al. (1989) *supra*.

A specific example of a system suitable for the expression of PI3Ky is the expression as a GST fusion protein in Sf9-insect cells using baculovectors according to the method described by Davis et al. (Biotechnology 11 (1993), 933-936).

A further subject matter of the present invention is a cell which is transformed with a nucleic acid according to the invention or a vector according to the invention. The cell can be a eukaryotic as well as a prokaryotic cell. Methods for the transformation of cells with nucleic acids are general state of the art and do not therefore need to be elucidated in more detail.

The use of the PI3Ky protein or fragments of this protein as an immunogen for the production of antibodies is also a subject matter of the present invention. In this case the antibodies can be produced in the usual manner by immunizing experimental animals with the complete PI3Ky protein or fragments thereof and subsequently isolating the resulting polyclonal antisera. The method of Köhler and Milstein or further developments thereof can be used to obtain monoclonal

antibodies in a known manner from the antibody-producing cells of the experimental animals by cell fusion. It is also possible to produce human monoclonal antibodies.

Hence a further subject matter of the present invention is an antibody against a protein with phosphatidylinositol-3-kinase activity which is specific for phosphatidylinositol-3-kinase γ and does not exhibit any cross-reaction with other phosphatidylinositol-3-kinases. Such an antibody can for example be obtained by using a PI3K γ -specific peptide sequence as the immunogen e.g. a peptide sequence which corresponds to the amino acids 741 to 755 of the amino acid sequence shown in SEQ ID NO. 1 and 2 or to the amino acids 742 to 756 of the amino acid sequence shown in SEQ ID NO. 3 and 4.

The provision of PI3 kinase γ , a nucleic acid which codes for it and an antibody which is directed towards it creates the basis for a specific search for effectors of this protein. The target for these substances should be the regulatory domains of the enzyme which are located in the region of the amino acid residues 1 to 700 of the amino acid sequences shown in SEQ ID NO. 1 and 2 or SEQ ID NO. 3 and 4. Substances which, via this region of the protein, have an inhibitory or activating effect on the activity are able to selectively influence the cell functions regulated by PI3K γ . Consequently they can be used for the treatment of corresponding clinical pictures. In the case of clinical pictures which are due to a loss of PI3K γ it may be possible to carry out a gene therapy treatment in which a nucleic acid coding for PI3K γ optionally together with a nucleic acid which codes for the activating G proteins is transferred by means of vectors e.g. viral vectors into the appropriate target tissue.

- 11 -

Moreover the results that have been presented form the basis for a specific diagnosis of diseases which are causally linked to changes in PI3Ky activity. These investigations can be carried out with the aid of specific nucleic acid probes for tests at the DNA level i.e. at the gene or transcription level or with the aid of antibodies against PI3Ky for tests at the protein level.

Hence the present invention also concerns a pharmaceutical composition which comprises a PI3Ky protein, an antibody directed towards it or a nucleic acid which codes for it as the active component optionally together with standard pharmaceutical auxiliary substances, carrier substances, fillers and diluents.

The pharmaceutical composition according to the invention can be used in particular to influence cell proliferation, receptor-mediated signal transmission, the structure of the cell membrane, the secretion of histamines, the differentiation of nerve cells, glucose transport and anti-lipolysis. Furthermore it can also be used in connection with the therapy of Alzheimer's disease.

The invention is elucidated in more detail by the following examples, figures and sequence protocols.

Fig. 1 shows the detection of PI3Ky in human blood cells by specific antibodies,

Fig. 2a shows the recombinant expression of PI3Ky in insect cells,

Fig. 2b shows the detection of the enzymatic activity of purified recombinant PI3K γ ,

Fig. 3 shows the absence of interaction between PI3K γ and the proteins p85 α and p85 β ,

SEQ ID NO. 1 shows a nucleic acid sequence which contains genetic information coding for PI3K γ and

SEQ ID NO. 2 shows the amino acid sequence of a PI3K γ .

SEQ ID NO: 3 shows a nucleic acid sequence which contains genetic information coding for a further PI3K γ and

SEQ ID NO. 4 shows the amino acid sequence of a further PI3K γ .

Example 1

Isolation of PI3K γ cDNA

In order to isolate cDNA sequences which code for new PI3K a human bone marrow cDNA library was screened using the polymerase chain reaction (PCR). For this degenerate oligonucleotide primers were used corresponding to the amino acid sequences KNGDDL R and HIDFG. A 402 bp long fragment was obtained. This fragment was subcloned and sequenced.

Several overlapping clones from a human U937 cDNA library were isolated using this PCR fragment as a probe. The largest clone contained the nucleic acid

- 13 -

sequence shown in SEQ ID NO. 1 with an open reading frame which codes for a protein with 1049 amino acids (SEQ ID NO. 2). This protein named PI3Ky has a molecular mass of approximately 120 kDa.

A further PI3Ky sequence which was obtained from a cDNA library is shown in SEQ ID NO. 3 and codes for a protein with 1050 amino acids (SEQ ID NO. 4).

Example 2

Detection of PI3Ky at a protein and transcript level

A polyclonal rabbit antiserum against PI3Ky was produced by immunization with a 15 amino acid long peptide of the sequence NSQLPESFRVPYDPG (corresponding to amino acids 741 to 755 in SEQ ID NO. 2 or amino acids 742 to 756 in SEQ ID NO. 4). The serum was purified by protein A chromatography and affinity chromatography using the peptide antigen coupled to Actigel* (Sterogene).

PI3Ky can be detected as a 110 kDa protein using this antiserum by immunoprecipitation and Western blot analysis of U937 and K562 cells (Fig. 1). The immunoprecipitation and Western blot were carried out according to the method of Hiles et al. (Cell 70 (1992) 419-429). A conjugate of horseradish peroxidase and anti-rabbit antiserum (Sigma, 1:2000 dilution) was used as the secondary antibody. The bound peroxidase was visualized by chemiluminescence.

A Northern blot analysis of human tissue from the pancreas, kidney, skeletal muscle, liver, lung, placenta, brain and heart each showed different concentrations of a 5.3 kb long mRNA.

*Trade-mark

- 14 -

Example 3Recombinant expression of PI3K γ

The DNA coding for PI3K γ was cloned into the vector pAcG2T (Davis et al., *Biotechnology* 11 (1993), 933-936). The resulting recombinant vector pAcG2T-PI3K γ contained the PI3K γ cDNA from codon 4 onwards in a fusion with the glutathione S transferase (GST) gene. Sf9 cells were cotransfected with pAcG2T-PI3K γ and linearized baculovirus DNA (BaculoGold*, Pharmingen). Individual recombinant baculovirus GST-PI3K γ plaques were purified and amplified. The expression and purification of recombinant protein were carried out using standard protocols (Dhand et al., *EMBO J.* 13 (1994), 511-521). Figure 2a shows the expression of recombinant PI3K γ GST fusion protein or GST alone after fractionation on a SDS polyacrylamide gel. The detection was carried out by staining with coomassie blue.

Figure 2b shows a detection of the enzymatic activity of purified recombinant PI3K γ . Phosphatidylinositol (PI, lane 1), phosphatidylinositol-4-phosphate (PI4-P, lane 2) and phosphatidylinositol-4,5-diphosphate (PI 4,5-P₂, lane 3) were used as substrates. The test was carried out essentially according to the method of Stephens et al. (*Cell* 77 (1994), 83-93) but without cholate. 30 μ l sonicated lipid vesicles containing 320 μ M phosphatidyl ethanolamine, 140 μ M phosphatidyl choline, 300 μ M phosphatidyl serine, 30 μ M sphingomyelin and 320 μ M substrate were added to 10 μ l enzyme (0.1 ng) and incubated for 8 minutes on ice. The test was started by addition of 10 μ l 20 μ M ATP containing 10 μ Ci γ (³²P)ATP and incubated for 15 minutes at room temperature. The extracted lipids were separated and visualized. The identity of the 3-phosphorylated phosphoinositides was

*Trade-mark

- 15 -

confirmed by anion exchange HPLC after deacylation of the lipids (Auger et al., Cell 57 (1989), 167-175).

Figure 2b shows that the substrates were phosphorylated in the D-3 position of the inositol ring. In addition it was found that PI3Ky was inhibited by wortmannin at nanomolar concentrations.

Example 4

Regulation of PI3Ky

In order to detect an interaction between the regulatory and adaptory subunits of p85 (p85 α and p85 β) and PI3Ky, human PI3Ky and bovine PI3K α (Hiles et al., supra) were expressed in Sf9 insect cells according to the process described in example 3 as GST fusion proteins either alone or together with p85 α and p85 β . After lysis and centrifugation of the cells, glutathione-Sepharose was added to the supernatant in order to bind the GST fusion proteins. The particles were washed and analysed by SDS-PAGE and Western-blot. PI3Ky was detected using the polyclonal antipeptide antibody described in example 2. Appropriate mixtures of specific monoclonal antibodies (Dhand et al., supra) as a primary antibody and conjugates of horseradish peroxidase and anti-mouse antibodies (Dianova, 1:4000 dilution) as the secondary antibody were used to detect p85 α , p85 β and bovine PI3K α .

Figure 3 shows that PI3Ky in contrast to PI3K α does not bind to p85 α and p85 β subunits. The regulation mechanism of PI3Ky is therefore different from PI3K α .

In order to detect an interaction between PI3Ky and G

- 16 -

proteins, purified recombinant human PI3K γ and bovine PI3K α was incubated with the transducin species G $_t$ $\beta\gamma$. A substantial amplification of the kinase activity of PI3K γ was found. This stimulation was suppressed by adding GTP-loaded G $_t\alpha$ which confirms the specificity of the interaction.

In contrast the enzymatic activity of PI3K α could not be stimulated by addition of G $_t\beta\gamma$. A similar activation of the enzyme was found after addition of G α in the presence of 20 μ M AlCl $_3$ and 10 mM NaF. The complex G α -GDP-AlF $_4^-$ acts as an activating species.

The determination of activity was carried out as described in example 3. The G $_t$ proteins purified from bovine retina according to the method of Camps et al. (Nature 360 (1992) 684-686) were incubated on ice with the lipid vesicles for 5 min (G $_t\beta\gamma$) or for 20 min (G $_t\beta\gamma$ plus G $_t\alpha$ -GTP) before adding the enzyme.

Binding studies with recombinant PI3K γ showed that the regulator protein Ras in its active GTP-loaded form associates with the enzyme. Ras in its constitutively active version is able to oncogenically transform cells. Hence this is a further indication for the potential importance of PI3K γ in the regulation of cellular proliferation.

- 17 -

SEQUENCE PROTOCOLS

(1) GENERAL INFORMATION

(i) APPLICANT:

(A) NAME: Max-Planck-Gesellschaft zur Foerderung der
Wissenschaften
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(C) CITY: Muenchen
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(F) POSTAL CODE: 80539

(ii) TITLE OF APPLICATION: Cloning, expression and
characterization of a new form of phosphatidylinositol-3-
kinase

(iii) NUMBER OF SEQUENCES: 4

(iv) COMPUTER-READABLE FORM:

(A) DATA CARRIER: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, version 1.25 (EPA)

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 4134 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) TYPE OF MOLECULE: cDNA

(vi) INITIAL ORIGIN:

(A) ORGANISM: Homo sapiens

(ix) CHARACTERISTICS:

(A) NAME/KEY: CDS
(B) LOCATION: 423..3569

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GAATTCGGCA CGAGCACTTC CTTCTCGGCT AGATTATCTG AAACGTGTTGT CGGTTCTTGA	60
GATGATACTA CCACCGAATG TCTGTGTTTC ATTGTCTAGT CCAACCTGTA TTGTGGATAT	120
CTACAACGTT CCGGCAATAG TTTTGCAGGT GCATCACATT TTTGTTTTTG TTTTGGGAGG	180
AAAAGGGAGG GCACGGCAGC CAGGCTTCAT ATTCCTACAA GTGCATGCTT CAAGATTACT	240
GTACTTACAG TGTTTCCAAC ATCTTCTCAT AAAAGGGGAA AGCTTCATAG CCTCAACCAT	300
GAAGGAAACC AGTCGCATAG GGCATGGAGC TGGAGAACTA TAAACAGCCC GTGGTGCTGA	360
GAGAGGACAA CTGCCGAAGG CGCCGGAGGA TGAAGCCGCG CAGTGCTGCC AGCCTGTCCT	420
CC ATG GAG CTC ATC CCC ATC GAG TTC GTG CTG CCC ACC AGC CAG CGC	467
Met Glu Leu Ile Pro Ile Glu Phe Val Leu Pro Thr Ser Gln Arg	
1 5 10 15	
AAA TGC AAG AGC CCC GAA ACG GCG CTG CTG CAC GTG GCC GGC CAC GGC	515
Lys Cys Lys Ser Pro Glu Thr Ala Leu Leu His Val Ala Gly His Gly	
20 25 30	
AAC GTG GAG CAG ATG AAG GCC CAG GTG TGG CTG CGA GCG CTG GAG ACC	563
Asn Val Glu Gln Met Lys Ala Gln Val Trp Leu Arg Ala Leu Glu Thr	
35 40 45	

- 18 -

AGC	TGG	CGC	GGA	CTT	CTA	CCA	CCG	GCT	GGG	ACC	GCA	TCA	CTT	CCT	CCT	611
Ser	Trp	Arg	Gly	Leu	Leu	Pro	Pro	Ala	Gly	Thr	Ala	Ser	Leu	Pro	Pro	
	50						55					60				
GCT	CTA	TCA	GAA	GAA	GGG	CAG	TGG	TAC	GAG	ATC	TAC	GAC	AAG	TAC	CAG	659
Ala	Leu	Ser	Glu	Glu	Gly	Gln	Trp	Tyr	Glu	Ile	Tyr	Asp	Lys	Tyr	Gln	
	65					70				75						
GTG	GTG	CAG	ACT	CTG	GAC	TGC	CTG	CGC	TAC	TGG	AAG	GCC	ACG	CAC	CGG	707
Val	Val	Gln	Thr	Leu	Asp	Cys	Leu	Arg	Tyr	Trp	Lys	Ala	Thr	His	Arg	
	80				85					90					95	
AGC	CCG	GGC	CAG	ATC	CAC	CTG	GTG	CAG	CGG	CAC	CCG	CCC	TCC	GAG	GAG	755
Ser	Pro	Gly	Gln	Ile	His	Leu	Val	Gln	Arg	His	Pro	Pro	Ser	Glu	Glu	
				100					105					110		
TCC	CAA	GCC	TTC	CAG	CGG	CAG	CTC	ACG	GCG	CTG	ATT	GGC	TAT	GAC	GTC	803
Ser	Gln	Ala	Phe	Gln	Arg	Gln	Leu	Thr	Ala	Leu	Ile	Gly	Tyr	Asp	Val	
			115					120					125			
ACT	GAC	GTC	AGC	AAC	GTG	CAC	GAC	GAT	GAG	CTG	GAG	TTC	ACG	CGC	CGT	851
Thr	Asp	Val	Ser	Asn	Val	His	Asp	Asp	Glu	Leu	Glu	Phe	Thr	Arg	Arg	
		130					135					140				
GGC	TTG	GTG	ACC	CCG	CGC	ATG	GCG	GAG	GTG	GCC	AGC	CGC	GAC	CCC	AAG	899
Gly	Leu	Val	Thr	Pro	Arg	Met	Ala	Glu	Val	Ala	Ser	Arg	Asp	Pro	Lys	
	145					150					155					
CTC	TAC	GCC	ATG	CAC	CCG	TGG	GTG	ACG	TCC	AAG	CCC	CTC	CCG	GAG	TAC	947
Leu	Tyr	Ala	Met	His	Pro	Trp	Val	Thr	Ser	Lys	Pro	Leu	Pro	Glu	Tyr	
	160				165				170					175		
CTG	TGG	AAG	AAG	ATT	GCC	AAC	AAC	TGC	ATC	TTC	ATC	GTC	ATT	CAC	CGC	995
Leu	Trp	Lys	Lys	Ile	Ala	Asn	Asn	Cys	Ile	Phe	Ile	Val	Ile	His	Arg	
				180				185						190		
AGC	ACC	ACC	AGC	CAG	ACC	ATT	AAG	GTC	TCA	CCC	GAC	GAC	ACC	CCC	GGC	1043
Ser	Thr	Thr	Ser	Gln	Thr	Ile	Lys	Val	Ser	Pro	Asp	Asp	Thr	Pro	Gly	
			195					200					205			
GCC	ATC	CTG	CAG	AGC	TTC	TTC	ACC	AAG	ATG	GCC	AAG	AAG	AAA	TCT	CTG	1091
Ala	Ile	Leu	Gln	Ser	Phe	Phe	Thr	Lys	Met	Ala	Lys	Lys	Lys	Ser	Leu	
		210					215					220				
ATG	GAT	ATT	CCC	GAA	AGC	CAA	AGC	GAA	CAG	GAT	TTT	GTG	CTG	CGC	GTC	1139
Met	Asp	Ile	Pro	Glu	Ser	Gln	Ser	Glu	Gln	Asp	Phe	Val	Leu	Arg	Val	
	225					230					235					
TGT	GGC	CGG	GAT	GAG	TAC	CTG	GTG	GGC	GAA	ACG	CCC	ATC	AAA	AAC	TTC	1187
Cys	Gly	Arg	Asp	Glu	Tyr	Leu	Val	Gly	Glu	Thr	Pro	Ile	Lys	Asn	Phe	
	240				245					250				255		
CAG	TGG	GTG	AGG	CAC	TGC	CTC	AAG	AAC	GGA	GAA	GAG	ATT	CAC	GTG	GTA	1235
Gln	Trp	Val	Arg	His	Cys	Leu	Lys	Asn	Gly	Glu	Glu	Ile	His	Val	Val	
				260				265						270		
CTG	GAC	ACG	CCT	CCA	GAC	CCG	GCC	CTA	GAC	GAG	GTG	AGG	AAG	GAA	GAG	1283
Leu	Asp	Thr	Pro	Pro	Asp	Pro	Ala	Leu	Asp	Glu	Val	Arg	Lys	Glu	Glu	
			275					280					285			
TGG	CCG	CTG	GTG	GAC	GAC	TGC	ACG	GGA	GTC	ACC	GGC	TAC	CAT	GAG	CAG	1331
Trp	Pro	Leu	Val	Asp	Asp	Cys	Thr	Gly	Val	Thr	Gly	Tyr	His	Glu	Gln	
		290					295					300				
CTT	ACC	ATC	CAC	GGC	AAG	GAC	CAC	GAG	AGT	GTG	TTC	ACC	GTG	TCC	CTG	1379
Leu	Thr	Ile	His	Gly	Lys	Asp	His	Glu	Ser	Val	Phe	Thr	Val	Ser	Leu	
	305					310					315					

- 19 -

TGG GAC TGC GAC CGC AAG TTC AGG GTC AAG ATC AGA GGC ATT GAT ATC Trp Asp Cys Asp Arg Lys Phe Arg Val Lys Ile Arg Gly Ile Asp Ile 320 325 330 335	1427
CCC GTC CTG CCT CGG AAC ACC GAC CTC ACA GTT TTT GTA GAG GCA AAC Pro Val Leu Pro Arg Asn Thr Asp Leu Thr Val Phe Val Glu Ala Asn 340 345 350	1475
ATC CAG CAT GGG CAA CAA GTC CTT TGC CAA AGG AGA ACC AGC CCC AAA Ile Gln His Gly Gln Gln Val Leu Cys Gln Arg Arg Thr Ser Pro Lys 355 360 365	1523
CCC TTC ACA GAG GAG GTG CTG TGG AAT GTG TGG CTT GAG TTC AGT ATC Pro Phe Thr Glu Glu Val Leu Trp Asn Val Trp Leu Glu Phe Ser Ile 370 375 380	1571
AAA ATC AAA GAC TTG CCC AAA GGG GCT CTA CTG AAC CTC CAG ATC TAC Lys Ile Lys Asp Leu Pro Lys Gly Ala Leu Leu Asn Leu Gln Ile Tyr 385 390 395	1619
TGC GGT AAA GCT CCA GCA CTG TCC AGC AAG GCC TCT GCA GAG TCC CCC Cys Gly Lys Ala Pro Ala Leu Ser Ser Lys Ala Ser Ala Glu Ser Pro 400 405 410 415	1667
AGT TCT GAG TCC AAG GGC AAA GTT CGG CTT CTC TAT TAT GTG AAC CTG Ser Ser Glu Ser Lys Gly Lys Val Arg Leu Leu Tyr Tyr Val Asn Leu 420 425 430	1715
CTG CTG ATA GAC CAC CGT TTC CTC CTG CGC CGT GGA GAA TAC GTC CTC Leu Leu Ile Asp His Arg Phe Leu Leu Arg Arg Gly Glu Tyr Val Leu 435 440 445	1763
CAC ATG TGG CAG ATA TCT GGG AAG GGA GAA GAC CAA GGA AGC TTC AAT His Met Trp Gln Ile Ser Gly Lys Gly Glu Asp Gln Gly Ser Phe Asn 450 455 460	1811
GCT GAC AAA CTC ACG TCT GCA ACT AAC CCA GAC AAG GAG AAC TCA ATG Ala Asp Lys Leu Thr Ser Ala Thr Asn Pro Asp Lys Glu Asn Ser Met 465 470 475	1859
TCC ATC TCC ATT CTT CTG GAC AAT TAC TGC CAC CCG ATA GCC CTG CCT Ser Ile Ser Ile Leu Leu Asp Asn Tyr Cys His Pro Ile Ala Leu Pro 480 485 490 495	1907
AAG CAT CAG CCC ACC CCT GAC CCG GAA GGG GAC CGG GTT CGA GCA GAA Lys His Gln Pro Thr Pro Asp Pro Glu Gly Asp Arg Val Arg Ala Glu 500 505 510	1955
ATG CCC AAC CAG CTT CGC AAG CAA TTG GAG GCG ATC ATA GCC ACT GAT Met Pro Asn Gln Leu Arg Lys Gln Leu Glu Ala Ile Ile Ala Thr Asp 515 520 525	2003
CCA CTT AAC CCT CTC ACA GCA GAG GAC AAA GAA TTG CTC TGG CAT TTT Pro Leu Asn Pro Leu Thr Ala Glu Asp Lys Glu Leu Leu Trp His Phe 530 535 540	2051
AGA TAC GAA AGC CTT AAG CAC CCA AAA GCA TAT CCT AAG CTA TTT AGT Arg Tyr Glu Ser Leu Lys His Pro Lys Ala Tyr Pro Lys Leu Phe Ser 545 550 555	2099
TCA GTG AAA TGG GGA CAG CAA GAA ATT GTG GCC AAA ACA TAC CAA TTG Ser Val Lys Trp Gly Gln Gln Glu Ile Val Ala Lys Thr Tyr Gln Leu 560 565 570 575	2147
TTG GCC AGA AGG GAA GTC TGG GAT CAA AGT GCT TTG GAT GTT GGG TTA Leu Ala Arg Arg Glu Val Trp Asp Gln Ser Ala Leu Asp Val Gly Leu 580 585 590	2195

- 20 -

ACA ATG CAG CTC CTG GAC TGC AAC TTC TCA GAT GAA AAT GTA AGA GCC Thr Met Gln Leu Leu Asp Cys Asn Phe Ser Asp Glu Asn Val Arg Ala 595 600 605	2243
ATT GCA GTT CAG AAA CTG GAG AGC TTG GAG GAC GAT GAT GTT CTG CAT Ile Ala Val Gln Lys Leu Glu Ser Leu Glu Asp Asp Asp Val Leu His 610 615 620	2291
TAC CTT CTA CAA TTG GTC CAG GCT GTG AAA TTT GAA CCA TAC CAT GAT Tyr Leu Leu Gln Leu Val Gln Ala Val Lys Phe Glu Pro Tyr His Asp 625 630 635	2339
AGC GCC CTT GCC AGA TTT CTG CTG AAG CGT GGT TTA AGA AAC AAA AGA Ser Ala Leu Ala Arg Phe Leu Leu Lys Arg Gly Leu Arg Asn Lys Arg 640 645 650 655	2387
ATT GGT CAC TTT TTG TTT TGG TTC TTG AGA AGT GAG ATA GCC CAG TCC Ile Gly His Phe Leu Phe Trp Phe Leu Arg Ser Glu Ile Ala Gln Ser 660 665 670	2435
AGA CAC TAT CAG CAG AGG TTC GCT GTG ATT CTG GAA GCC TAT CTG AGG Arg His Tyr Gln Gln Arg Phe Ala Val Ile Leu Glu Ala Tyr Leu Arg 675 680 685	2483
GGC TGT GGC ACA GCC ATG CTG CAC GAC TTT ACC CAA CAA GTC CAA GTA Gly Cys Gly Thr Ala Met Leu His Asp Phe Thr Gln Gln Val Gln Val 690 695 700	2531
ATC GAG ATG TTA CAA AAA GTC ACC CTT GAT ATT AAA TCG CTC TCT GCT Ile Glu Met Leu Gln Lys Val Thr Leu Asp Ile Lys Ser Leu Ser Ala 705 710 715	2579
GAA AAG TAT GAC GTC AGT TCC CAA GTT ATT TCA CAA CTT AAA CAA AAG Glu Lys Tyr Asp Val Ser Ser Gln Val Ile Ser Gln Leu Lys Gln Lys 720 725 730 735	2627
CTT GAA AAC CTG CAG AAT TCT CAA CTC CCC GAA AGC TTT AGA GTT CCA Leu Glu Asn Leu Gln Asn Ser Gln Leu Pro Glu Ser Phe Arg Val Pro 740 745 750	2675
TAT GAT CCT GGA CTG AAA GCA GGA GCG CTG GCA ATT GAA AAA TGT AAA Tyr Asp Pro Gly Leu Lys Ala Gly Ala Leu Ala Ile Glu Lys Cys Lys 755 760 765	2723
GTA ATG GCC TCC AAG AAA AAA CCA CTA TGG CTT GAG TTT AAA TGT GCC Val Met Ala Ser Lys Lys Lys Pro Leu Trp Leu Glu Phe Lys Cys Ala 770 775 780	2771
GAT CCT ACA GCC CTA TCA AAT GAA ACA ATT GGA ATT ATC TTT AAA CAT Asp Pro Thr Ala Leu Ser Asn Glu Thr Ile Gly Ile Ile Phe Lys His 785 790 795	2819
GGT GAT GAT CTG CGC CAA GAC ATG CTT ATT TTA CAG ATT CTA CGA ATC Gly Asp Asp Leu Arg Gln Asp Met Leu Ile Leu Gln Ile Leu Arg Ile 800 805 810 815	2867
ATG GAG TCT ATT TGG GAG ACT GAA TCT TTG GAT CTA TGC CTC CTG CCA Met Glu Ser Ile Trp Glu Thr Glu Ser Leu Asp Leu Cys Leu Leu Pro 820 825 830	2915
TAT GGT TGC ATT TCA ACT GGT GAC AAA ATA GGA ATG ATC GAG ATT GTG Tyr Gly Cys Ile Ser Thr Gly Asp Lys Ile Gly Met Ile Glu Ile Val 835 840 845	2963
AAA GAC GCC ACG ACA ATT GCC AAA ATT CAG CAA AGC ACA GTG GGC AAC Lys Asp Ala Thr Thr Ile Ala Lys Ile Gln Gln Ser Thr Val Gly Asn 850 855 860	3011

ACG GGA GCA TTT AAA GAT GAA GTC CTG AAT CAC TGG CTC AAA GAA AAA Thr Gly Ala Phe Lys Asp Glu Val Leu Asn His Trp Leu Lys Glu Lys 865 870 875	3059
TCC CCT ACT GAA GAA AAG TTT CAG GCA GCA GTG GAG AGA TTT GTT TAT Ser Pro Thr Glu Glu Lys Phe Gln Ala Ala Val Glu Arg Phe Val Tyr 880 885 890 895	3107
TCC TGT GCA GGC TAC TGT GTG GCA ACC TTT GTT CTT GGA ATA GGC GAC Ser Cys Ala Gly Tyr Cys Val Ala Thr Phe Val Leu Gly Ile Gly Asp 900 905 910	3155
AGA CAC AAT GAC AAT ATT ATG ATC ACC GAG ACA GGA AAC CTA TTT CAT Arg His Asn Asp Asn Ile Met Ile Thr Glu Thr Gly Asn Leu Phe His 915 920 925	3203
ATT GAC TTC GGG CAC ATT CTT GGG AAT TAC AAA AGT TTC CTG GGC ATT Ile Asp Phe Gly His Ile Leu Gly Asn Tyr Lys Ser Phe Leu Gly Ile 930 935 940	3251
AAT AAA GAG AGA GTG CCA TTT GTG CTA ACC CCT GAC TTC CTC TTT GTG Asn Lys Glu Arg Val Pro Phe Val Leu Thr Pro Asp Phe Leu Phe Val 945 950 955	3299
ATG GGA ACT TCT GGA AAG AAG ACA AGC CCA CAC TTC CAG AAA TTT CAG Met Gly Thr Ser Gly Lys Lys Thr Ser Pro His Phe Gln Lys Phe Gln 960 965 970 975	3347
GAC ATC TGT GTT AAG GCT TAT CTA GCC CTT CGT CAT CAC ACA AAC CTA Asp Ile Cys Val Lys Ala Tyr Leu Ala Leu Arg His His Thr Asn Leu 980 985 990	3395
CTG ATC ATC CTG TTC TCC ATG ATG CTG ATG ACA GGA ATG CCC CAG TTA Leu Ile Ile Leu Phe Ser Met Met Leu Met Thr Gly Met Pro Gln Leu 995 1000 1005	3443
ACA AGC AAA GAA GAC ATT GAA TAT ATC CGG GAT GCC CTC ACA GTG GGG Thr Ser Lys Glu Asp Ile Glu Tyr Ile Arg Asp Ala Leu Thr Val Gly 1010 1015 1020	3491
AAA AAT GAG GAG GAT GCT AAA AAG TAT TTT CTT GAT CAG ATC GAA GTT Lys Asn Glu Glu Asp Ala Lys Lys Tyr Phe Leu Asp Gln Ile Glu Val 1025 1030 1035	3539
TGG CAG AGA CAA AGG ATG GAC TGT GCA GTT TAATTGGTTT CTACATCTTG Trp Gln Arg Gln Arg Met Asp Cys Ala Val 1040 1045	3589
TTCTTGGCAT CAAACAAGGA GAGAAACATT CAGCCTAATA CTTTAGGCTA GAATCAAAAA	3649
CAAGTTAGTG TTCTATGGTT TAAATTAGCA TAGCAATCAT CGAACTTGGA TTTCAAATGC	3709
AATAGACATT GTGAAAGCTG GCATTTTCTG AGTATAGCTC TTTTCCTACC TGAACCTCTC	3769
CCTGGAGAAA AGATGTTGGC ATTGCTGATT GTTTGGTTAA GCAATGTCCA GTGCTAGGAT	3829
TATTTGCAGG TTTGGTTTTT TCTCATTTGT CTGTGGCATT GGAGAATATT CTCGGTTTAA	3889
ACAGACTAAT GACTTCCTTA TTGTCCCTGA TATTTTGGCT ATCTTACTAT TGAGTGCTTC	3949
TGGAAATTCT TTGGAATAAT TGATGACATC TATTTTCATC TGGGTTTAGT CTCAATTTTG	4009
GTTATCTTTG TGTTCCTCAA GCTCTTTAAA GAAAAAGATG TAATCGTTGT AACCTTTGTC	4069
TCATTCCTTA AATGATGCTT CCAAACATCT CCTTAGTGTC TGCAGGTGTT AGTGGTGTGC	4129
TAAAA	4134

- 22 -

(2) INFORMATION FOR SEQ ID NO: 2:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1049 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) TYPE OF MOLECULE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

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Met Glu Leu Ile Pro Ile Glu Phe Val Leu Pro Thr Ser Gln Arg Lys
 1           5           10           15
Cys Lys Ser Pro Glu Thr Ala Leu Leu His Val Ala Gly His Gly Asn
          20           25           30
Val Glu Gln Met Lys Ala Gln Val Trp Leu Arg Ala Leu Glu Thr Ser
          35           40           45
Trp Arg Gly Leu Leu Pro Pro Ala Gly Thr Ala Ser Leu Pro Pro Ala
          50           55           60
Leu Ser Glu Glu Gly Gln Trp Tyr Glu Ile Tyr Asp Lys Tyr Gln Val
          65           70           75           80
Val Gln Thr Leu Asp Cys Leu Arg Tyr Trp Lys Ala Thr His Arg Ser
          85           90           95
Pro Gly Gln Ile His Leu Val Gln Arg His Pro Pro Ser Glu Glu Ser
          100          105          110
Gln Ala Phe Gln Arg Gln Leu Thr Ala Leu Ile Gly Tyr Asp Val Thr
          115          120          125
Asp Val Ser Asn Val His Asp Asp Glu Leu Glu Phe Thr Arg Arg Gly
          130          135          140
Leu Val Thr Pro Arg Met Ala Glu Val Ala Ser Arg Asp Pro Lys Leu
          145          150          155          160
Tyr Ala Met His Pro Trp Val Thr Ser Lys Pro Leu Pro Glu Tyr Leu
          165          170          175
Trp Lys Lys Ile Ala Asn Asn Cys Ile Phe Ile Val Ile His Arg Ser
          180          185          190
Thr Thr Ser Gln Thr Ile Lys Val Ser Pro Asp Asp Thr Pro Gly Ala
          195          200          205
Ile Leu Gln Ser Phe Phe Thr Lys Met Ala Lys Lys Lys Ser Leu Met
          210          215          220
Asp Ile Pro Glu Ser Gln Ser Glu Gln Asp Phe Val Leu Arg Val Cys
          225          230          235          240
Gly Arg Asp Glu Tyr Leu Val Gly Glu Thr Pro Ile Lys Asn Phe Gln
          245          250          255
Trp Val Arg His Cys Leu Lys Asn Gly Glu Glu Ile His Val Val Leu
          260          265          270
Asp Thr Pro Pro Asp Pro Ala Leu Asp Glu Val Arg Lys Glu Glu Trp
          275          280          285
Pro Leu Val Asp Asp Cys Thr Gly Val Thr Gly Tyr His Glu Gln Leu
          290          295          300

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- 23 -

Thr Ile His Gly Lys Asp His Glu Ser Val Phe Thr Val Ser Leu Trp
 305 310 315 320
 Asp Cys Asp Arg Lys Phe Arg Val Lys Ile Arg Gly Ile Asp Ile Pro
 325 330 335
 Val Leu Pro Arg Asn Thr Asp Leu Thr Val Phe Val Glu Ala Asn Ile
 340 345 350
 Gln His Gly Gln Gln Val Leu Cys Gln Arg Arg Thr Ser Pro Lys Pro
 355 360 365
 Phe Thr Glu Glu Val Leu Trp Asn Val Trp Leu Glu Phe Ser Ile Lys
 370 375 380
 Ile Lys Asp Leu Pro Lys Gly Ala Leu Leu Asn Leu Gln Ile Tyr Cys
 385 390 395 400
 Gly Lys Ala Pro Ala Leu Ser Ser Lys Ala Ser Ala Glu Ser Pro Ser
 405 410 415
 Ser Glu Ser Lys Gly Lys Val Arg Leu Leu Tyr Tyr Val Asn Leu Leu
 420 425 430
 Leu Ile Asp His Arg Phe Leu Leu Arg Arg Gly Glu Tyr Val Leu His
 435 440 445
 Met Trp Gln Ile Ser Gly Lys Gly Glu Asp Gln Gly Ser Phe Asn Ala
 450 455 460
 Asp Lys Leu Thr Ser Ala Thr Asn Pro Asp Lys Glu Asn Ser Met Ser
 465 470 475 480
 Ile Ser Ile Leu Leu Asp Asn Tyr Cys His Pro Ile Ala Leu Pro Lys
 485 490 495
 His Gln Pro Thr Pro Asp Pro Glu Gly Asp Arg Val Arg Ala Glu Met
 500 505 510
 Pro Asn Gln Leu Arg Lys Gln Leu Glu Ala Ile Ile Ala Thr Asp Pro
 515 520 525
 Leu Asn Pro Leu Thr Ala Glu Asp Lys Glu Leu Leu Trp His Phe Arg
 530 535 540
 Tyr Glu Ser Leu Lys His Pro Lys Ala Tyr Pro Lys Leu Phe Ser Ser
 545 550 555 560
 Val Lys Trp Gly Gln Gln Glu Ile Val Ala Lys Thr Tyr Gln Leu Leu
 565 570 575
 Ala Arg Arg Glu Val Trp Asp Gln Ser Ala Leu Asp Val Gly Leu Thr
 580 585 590
 Met Gln Leu Leu Asp Cys Asn Phe Ser Asp Glu Asn Val Arg Ala Ile
 595 600 605
 Ala Val Gln Lys Leu Glu Ser Leu Glu Asp Asp Asp Val Leu His Tyr
 610 615 620
 Leu Leu Gln Leu Val Gln Ala Val Lys Phe Glu Pro Tyr His Asp Ser
 625 630 635 640
 Ala Leu Ala Arg Phe Leu Leu Lys Arg Gly Leu Arg Asn Lys Arg Ile
 645 650 655
 Gly His Phe Leu Phe Trp Phe Leu Arg Ser Glu Ile Ala Gln Ser Arg
 660 665 670

- 24 -

His Tyr Gln Gln Arg Phe Ala Val Ile Leu Glu Ala Tyr Leu Arg Gly
 675 680 685
 Cys Gly Thr Ala Met Leu His Asp Phe Thr Gln Gln Val Gln Val Ile
 690 695 700
 Glu Met Leu Gln Lys Val Thr Leu Asp Ile Lys Ser Leu Ser Ala Glu
 705 710 715 720
 Lys Tyr Asp Val Ser Ser Gln Val Ile Ser Gln Leu Lys Gln Lys Leu
 725 730 735
 Glu Asn Leu Gln Asn Ser Gln Leu Pro Glu Ser Phe Arg Val Pro Tyr
 740 745 750
 Asp Pro Gly Leu Lys Ala Gly Ala Leu Ala Ile Glu Lys Cys Lys Val
 755 760 765
 Met Ala Ser Lys Lys Lys Pro Leu Trp Leu Glu Phe Lys Cys Ala Asp
 770 775 780
 Pro Thr Ala Leu Ser Asn Glu Thr Ile Gly Ile Ile Phe Lys His Gly
 785 790 795 800
 Asp Asp Leu Arg Gln Asp Met Leu Ile Leu Gln Ile Leu Arg Ile Met
 805 810 815
 Glu Ser Ile Trp Glu Thr Glu Ser Leu Asp Leu Cys Leu Leu Pro Tyr
 820 825 830
 Gly Cys Ile Ser Thr Gly Asp Lys Ile Gly Met Ile Glu Ile Val Lys
 835 840 845
 Asp Ala Thr Thr Ile Ala Lys Ile Gln Gln Ser Thr Val Gly Asn Thr
 850 855 860
 Gly Ala Phe Lys Asp Glu Val Leu Asn His Trp Leu Lys Glu Lys Ser
 865 870 875 880
 Pro Thr Glu Glu Lys Phe Gln Ala Ala Val Glu Arg Phe Val Tyr Ser
 885 890 895
 Cys Ala Gly Tyr Cys Val Ala Thr Phe Val Leu Gly Ile Gly Asp Arg
 900 905 910
 His Asn Asp Asn Ile Met Ile Thr Glu Thr Gly Asn Leu Phe His Ile
 915 920 925
 Asp Phe Gly His Ile Leu Gly Asn Tyr Lys Ser Phe Leu Gly Ile Asn
 930 935 940
 Lys Glu Arg Val Pro Phe Val Leu Thr Pro Asp Phe Leu Phe Val Met
 945 950 955 960
 Gly Thr Ser Gly Lys Lys Thr Ser Pro His Phe Gln Lys Phe Gln Asp
 965 970 975
 Ile Cys Val Lys Ala Tyr Leu Ala Leu Arg His His Thr Asn Leu Leu
 980 985 990
 Ile Ile Leu Phe Ser Met Met Leu Met Thr Gly Met Pro Gln Leu Thr
 995 1000 1005
 Ser Lys Glu Asp Ile Glu Tyr Ile Arg Asp Ala Leu Thr Val Gly Lys
 1010 1015 1020
 Asn Glu Glu Asp Ala Lys Lys Tyr Phe Leu Asp Gln Ile Glu Val Trp
 1025 1030 1035 1040

- 25 -

Gln Arg Gln Arg Met Asp Cys Ala Val
1045

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4137 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: both
- (D) TOPOLOGY: linear

(ii) TYPE OF MOLECULE: cDNA

(vi) INITIAL ORIGIN:

- (A) ORGANISM: Homo sapiens

(xi) CHARACTERISTICS:

- (A) NAME/KEY: CDS
- (B) LOCATION: 423..3572

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GAATTCGGCA CGAGCACTTC CTTCTCGGCT AGATTATCTG AAACCTGTTGT CGGTTCTTGA	60
GATGATACTA CCACCGAATG TCTGTGTTTC ATTGTCTAGT CCAACCTGTA TTGTGGATAT	120
CTACAACGTT CCGGCAATAG TTTTGCAGGT GCATCACATT TTTGTTTTTG TTTTGGGAGG	180
AAAAGGGAGG GCACGGCAGC CAGGCTTCAT ATTCTACAA GTGCATGCTT CAAGATTACT	240
GTACTTACAG TGTTCCTAAC ATCTTCTCAT AAAAGGGGAA AGCTTCATAG CCTCAACCAT	300
GAAGGAAACC AGTCGCATAG GGCATGGAGC TGGAGAACTA TAAACAGCCC GTGGTGCTGA	360
GAGAGGACAA CTGCCGAAGG CGCCGGAGGA TGAAGCCGCG CAGTGCTGCC AGCCTGTCTT	420
CC ATG GAG CTC ATC CCC ATC GAG TTC GTG CTG CCC ACC AGC CAG CGC	467
Met Glu Leu Ile Pro Ile Glu Phe Val Leu Pro Thr Ser Gln Arg	
1 5 10 15	
AAA TGC AAG AGC CCC GAA ACG GCG CTG CTG CAC GTG GCC GGC CAC GGC	515
Lys Cys Lys Ser Pro Glu Thr Ala Leu Leu His Val Ala Gly His Gly	
20 25 30	
AAC GTG GAG CAG ATG AAG GCC CAG GTG TGG CTG CGA GCG CTG GAG ACC	563
Asn Val Glu Gln Met Lys Ala Gln Val Trp Leu Arg Ala Leu Glu Thr	
35 40 45	
AGC GTG GCG GCG GAC TTC TAC CAC CGG CTG GGA CCG CAT CAC TTC CTC	611
Ser Val Ala Ala Asp Phe Tyr His Arg Leu Gly Pro His His Phe Leu	
50 55 60	
CTG CTC TAT CAG AAG AAG GGG CAG TGG TAC GAG ATC TAC GAC AAG TAC	659
Leu Leu Tyr Gln Lys Lys Gly Gln Trp Tyr Glu Ile Tyr Asp Lys Tyr	
65 70 75	
CAG GTG GTG CAG ACT CTG GAC TGC CTG CGC TAC TGG AAG GCC ACG CAC	707
Gln Val Val Gln Thr Leu Asp Cys Leu Arg Tyr Trp Lys Ala Thr His	
80 85 90 95	
CGG AGC CCG GGC CAG ATC CAC CTG GTG CAG CGG CAC CCG CCC TCC GAG	755
Arg Ser Pro Gly Gln Ile His Leu Val Gln Arg His Pro Pro Ser Glu	
100 105 110	
GAG TCC CAA GCC TTC CAG CGG CAG CTC ACG GCG CTG ATT GGC TAT GAC	803
Glu Ser Gln Ala Phe Gln Arg Gln Leu Thr Ala Leu Ile Gly Tyr Asp	
115 120 125	

- 26 -

GTC	ACT	GAC	GTC	AGC	AAC	GTG	CAC	GAC	GAT	GAG	CTG	GAG	TTC	ACG	CGC	851
Val	Thr	Asp	Val	Ser	Asn	Val	His	Asp	Asp	Glu	Leu	Glu	Phe	Thr	Arg	
	130						135					140				
CGT	GGC	TTG	GTG	ACC	CCG	CGC	ATG	GCG	GAG	GTG	GCC	AGC	CGC	GAC	CCC	899
Arg	Gly	Leu	Val	Thr	Pro	Arg	Met	Ala	Glu	Val	Ala	Ser	Arg	Asp	Pro	
	145						150				155					
AAG	CTC	TAC	GCC	ATG	CAC	CCG	TGG	GTG	ACG	TCC	AAG	CCC	CTC	CCG	GAG	947
Lys	Leu	Tyr	Ala	Met	His	Pro	Trp	Val	Thr	Ser	Lys	Pro	Leu	Pro	Glu	
	160						165			170					175	
TAC	CTG	TGG	AAG	AAG	ATT	GCC	AAC	AAC	TGC	ATC	TTC	ATC	GTC	ATT	CAC	995
Tyr	Leu	Trp	Lys	Lys	Ile	Ala	Asn	Asn	Cys	Ile	Phe	Ile	Val	Ile	His	
					180				185					190		
CGC	AGC	ACC	ACC	AGC	CAG	ACC	ATT	AAG	GTC	TCA	CCC	GAC	GAC	ACC	CCC	1043
Arg	Ser	Thr	Thr	Ser	Gln	Thr	Ile	Lys	Val	Ser	Pro	Asp	Asp	Thr	Pro	
					195			200					205			
GGC	GCC	ATC	CTG	CAG	AGC	TTC	TTC	ACC	AAG	ATG	GCC	AAG	AAG	AAA	TCT	1091
Gly	Ala	Ile	Leu	Gln	Ser	Phe	Phe	Thr	Lys	Met	Ala	Lys	Lys	Lys	Ser	
		210					215					220				
CTG	ATG	GAT	ATT	CCC	GAA	AGC	CAA	AGC	GAA	CAG	GAT	TTT	GTG	CTG	CGC	1139
Leu	Met	Asp	Ile	Pro	Glu	Ser	Gln	Ser	Glu	Gln	Asp	Phe	Val	Leu	Arg	
	225					230					235					
GTC	TGT	GGC	CGG	GAT	GAG	TAC	CTG	GTG	GGC	GAA	ACG	CCC	ATC	AAA	AAC	1187
Val	Cys	Gly	Arg	Asp	Glu	Tyr	Leu	Val	Gly	Glu	Thr	Pro	Ile	Lys	Asn	
	240				245				250						255	
TTC	CAG	TGG	GTG	AGG	CAC	TGC	CTC	AAG	AAC	GGA	GAA	GAG	ATT	CAC	GTG	1235
Phe	Gln	Trp	Val	Arg	His	Cys	Leu	Lys	Asn	Gly	Glu	Glu	Ile	His	Val	
				260				265						270		
GTA	CTG	GAC	ACG	CCT	CCA	GAC	CCG	GCC	CTA	GAC	GAG	GTG	AGG	AAG	GAA	1283
Val	Leu	Asp	Thr	Pro	Pro	Asp	Pro	Ala	Leu	Asp	Glu	Val	Arg	Lys	Glu	
			275					280					285			
GAG	TGG	CCG	CTG	GTG	GAC	GAC	TGC	ACG	GGA	GTC	ACC	GGC	TAC	CAT	GAG	1331
Glu	Trp	Pro	Leu	Val	Asp	Asp	Cys	Thr	Gly	Val	Thr	Gly	Tyr	His	Glu	
	290						295					300				
CAG	CTT	ACC	ATC	CAC	GGC	AAG	GAC	CAC	GAG	AGT	GTG	TTC	ACC	GTG	TCC	1379
Gln	Leu	Thr	Ile	His	Gly	Lys	Asp	His	Glu	Ser	Val	Phe	Thr	Val	Ser	
	305					310					315					
CTG	TGG	GAC	TGC	GAC	CGC	AAG	TTC	AGG	GTC	AAG	ATC	AGA	GGC	ATT	GAT	1427
Leu	Trp	Asp	Cys	Asp	Arg	Lys	Phe	Arg	Val	Lys	Ile	Arg	Gly	Ile	Asp	
	320				325				330						335	
ATC	CCC	GTC	CTG	CCT	CGG	AAC	ACC	GAC	CTC	ACA	GTT	TTT	GTA	GAG	GCA	1475
Ile	Pro	Val	Leu	Pro	Arg	Asn	Thr	Asp	Leu	Thr	Val	Phe	Val	Glu	Ala	
				340					345					350		
AAC	ATC	CAG	CAT	GGG	CAA	CAA	GTC	CTT	TGC	CAA	AGG	AGA	ACC	AGC	CCC	1523
Asn	Ile	Gln	His	Gly	Gln	Gln	Val	Leu	Cys	Gln	Arg	Arg	Thr	Ser	Pro	
			355				360						365			
AAA	CCC	TTC	ACA	GAG	GAG	GTG	CTG	TGG	AAT	GTG	TGG	CTT	GAG	TTC	AGT	1571
Lys	Pro	Phe	Thr	Glu	Glu	Val	Leu	Trp	Asn	Val	Trp	Leu	Glu	Phe	Ser	
		370				375						380				
ATC	AAA	ATC	AAA	GAC	TTG	CCC	AAA	GGG	GCT	CTA	CTG	AAC	CTC	CAG	ATC	1619
Ile	Lys	Ile	Lys	Asp	Leu	Pro	Lys	Gly	Ala	Leu	Leu	Asn	Leu	Gln	Ile	
	385					390					395					
TAC	TGC	GGT	AAA	GCT	CCA	GCA	CTG	TCC	AGC	AAG	GCC	TCT	GCA	GAG	TCC	1667

- 27 -

Tyr 400	Cys	Gly	Lys	Ala	Pro 405	Ala	Leu	Ser	Ser	Lys 410	Ala	Ser	Ala	Glu	Ser 415	
CCC	AGT	TCT	GAG	TCC	AAG	GGC	AAA	GTT	CGG	CTT	CTC	TAT	TAT	GTG	AAC	1715
Pro	Ser	Ser	Glu	Ser	Lys	Gly	Lys	Val	Arg	Leu	Leu	Tyr	Tyr	Val	Asn	
				420					425					430		
CTG	CTG	CTG	ATA	GAC	CAC	CGT	TTC	CTC	CTG	CGC	CGT	GGA	GAA	TAC	GTC	1763
Leu	Leu	Leu	Ile	Asp	His	Arg	Phe	Leu	Leu	Arg	Arg	Gly	Glu	Tyr	Val	
			435					440					445			
CTC	CAC	ATG	TGG	CAG	ATA	TCT	GGG	AAG	GGA	GAA	GAC	CAA	GGA	AGC	TTC	1811
Leu	His	Met	Trp	Gln	Ile	Ser	Gly	Lys	Gly	Glu	Asp	Gln	Gly	Ser	Phe	
		450					455					460				
AAT	GCT	GAC	AAA	CTC	ACG	TCT	GCA	ACT	AAC	CCA	GAC	AAG	GAG	AAC	TCA	1859
Asn	Ala	Asp	Lys	Leu	Thr	Ser	Ala	Thr	Asn	Pro	Asp	Lys	Glu	Asn	Ser	
	465					470					475					
ATG	TCC	ATC	TCC	ATT	CTT	CTG	GAC	AAT	TAC	TGC	CAC	CCG	ATA	GCC	CTG	1907
Met	Ser	Ile	Ser	Ile	Leu	Leu	Asp	Asn	Tyr	Cys	His	Pro	Ile	Ala	Leu	
480					485					490					495	
CCT	AAG	CAT	CAG	CCC	ACC	CCT	GAC	CCG	GAA	GGG	GAC	CGG	GTT	CGA	GCA	1955
Pro	Lys	His	Gln	Pro	Thr	Pro	Asp	Pro	Glu	Gly	Asp	Arg	Val	Arg	Ala	
				500					505					510		
GAA	ATG	CCC	AAC	CAG	CTT	CGC	AAG	CAA	TTG	GAG	GCG	ATC	ATA	GCC	ACT	2003
Glu	Met	Pro	Asn	Gln	Leu	Arg	Lys	Gln	Leu	Glu	Ala	Ile	Ile	Ala	Thr	
			515					520					525			
GAT	CCA	CTT	AAC	CCT	CTC	ACA	GCA	GAG	GAC	AAA	GAA	TTG	CTC	TGG	CAT	2051
Asp	Pro	Leu	Asn	Pro	Leu	Thr	Ala	Glu	Asp	Lys	Glu	Leu	Leu	Trp	His	
		530					535					540				
TTT	AGA	TAC	GAA	AGC	CTT	AAG	CAC	CCA	AAA	GCA	TAT	CCT	AAG	CTA	TTT	2099
Phe	Arg	Tyr	Glu	Ser	Leu	Lys	His	Pro	Lys	Ala	Tyr	Pro	Lys	Leu	Phe	
	545					550					555					
AGT	TCA	GTG	AAA	TGG	GGA	CAG	CAA	GAA	ATT	GTG	GCC	AAA	ACA	TAC	CAA	2147
Ser	Ser	Val	Lys	Trp	Gly	Gln	Gln	Glu	Ile	Val	Ala	Lys	Thr	Tyr	Gln	
560				565					570						575	
TTG	TTG	GCC	AGA	AGG	GAA	GTC	TGG	GAT	CAA	AGT	GCT	TTG	GAT	GTT	GGG	2195
Leu	Leu	Ala	Arg	Arg	Glu	Val	Trp	Asp	Gln	Ser	Ala	Leu	Asp	Val	Gly	
				580					585					590		
TTA	ACA	ATG	CAG	CTC	CTG	GAC	TGC	AAC	TTC	TCA	GAT	GAA	AAT	GTA	AGA	2243
Leu	Thr	Met	Gln	Leu	Leu	Asp	Cys	Asn	Phe	Ser	Asp	Glu	Asn	Val	Arg	
			595					600					605			
GCC	ATT	GCA	GTT	CAG	AAA	CTG	GAG	AGC	TTG	GAG	GAC	GAT	GAT	GTT	CTG	2291
Ala	Ile	Ala	Val	Gln	Lys	Leu	Glu	Ser	Leu	Glu	Asp	Asp	Asp	Val	Leu	
		610					615					620				
CAT	TAC	CTT	CTA	CAA	TTG	GTC	CAG	GCT	GTG	AAA	TTT	GAA	CCA	TAC	CAT	2339
His	Tyr	Leu	Leu	Gln	Leu	Val	Gln	Ala	Val	Lys	Phe	Glu	Pro	Tyr	His	
	625				630						635					
GAT	AGC	GCC	CTT	GCC	AGA	TTT	CTG	CTG	AAG	CGT	GGT	TTA	AGA	AAC	AAA	2387
Asp	Ser	Ala	Leu	Ala	Arg	Phe	Leu	Leu	Lys	Arg	Gly	Leu	Arg	Asn	Lys	
640					645					650					655	
AGA	ATT	GGT	CAC	TTT	TTG	TTT	TGG	TTC	TTG	AGA	AGT	GAG	ATA	GCC	CAG	2435
Arg	Ile	Gly	His	Phe	Leu	Phe	Trp	Phe	Leu	Arg	Ser	Glu	Ile	Ala	Gln	
				660					665					670		
TCC	AGA	CAC	TAT	CAG	CAG	AGG	TTC	GCT	GTG	ATT	CTG	GAA	GCC	TAT	CTG	2483

- 28 -

Ser Arg His Tyr Gln Gln Arg Phe Ala Val Ile Leu Glu Ala Tyr Leu	
675 680 685	
AGG GGC TGT GGC ACA GCC ATG CTG CAC GAC TTT ACC CAA CAA GTC CAA	2531
Arg Gly Cys Gly Thr Ala Met Leu His Asp Phe Thr Gln Gln Val Gln	
690 695 700	
GTA ATC GAG ATG TTA CAA AAA GTC ACC CTT GAT ATT AAA TCG CTC TCT	2579
Val Ile Glu Met Leu Gln Lys Val Thr Leu Asp Ile Lys Ser Leu Ser	
705 710 715	
GCT GAA AAG TAT GAC GTC AGT TCC CAA GTT ATT TCA CAA CTT AAA CAA	2627
Ala Glu Lys Tyr Asp Val Ser Ser Gln Val Ile Ser Gln Leu Lys Gln	
720 725 730 735	
AAG CTT GAA AAC CTG CAG AAT TCT CAA CTC CCC GAA AGC TTT AGA GTT	2675
Lys Leu Glu Asn Leu Gln Asn Ser Gln Leu Pro Glu Ser Phe Arg Val	
740 745 750	
CCA TAT GAT CCT GGA CTG AAA GCA GGA GCG CTG GCA ATT GAA AAA TGT	2723
Pro Tyr Asp Pro Gly Leu Lys Ala Gly Ala Leu Ala Ile Glu Lys Cys	
755 760 765	
AAA GTA ATG GCC TCC AAG AAA AAA CCA CTA TGG CTT GAG TTT AAA TGT	2771
Lys Val Met Ala Ser Lys Lys Lys Pro Leu Trp Leu Glu Phe Lys Cys	
770 775 780	
GCC GAT CCT ACA GCC CTA TCA AAT GAA ACA ATT GGA ATT ATC TTT AAA	2819
Ala Asp Pro Thr Ala Leu Ser Asn Glu Thr Ile Gly Ile Ile Phe Lys	
785 790 795	
CAT GGT GAT GAT CTG CGC CAA GAC ATG CTT ATT TTA CAG ATT CTA CGA	2867
His Gly Asp Asp Leu Arg Gln Asp Met Leu Ile Leu Gln Ile Leu Arg	
800 805 810 815	
ATC ATG GAG TCT ATT TGG GAG ACT GAA TCT TTG GAT CTA TGC CTC CTG	2915
Ile Met Glu Ser Ile Trp Glu Thr Glu Ser Leu Asp Leu Cys Leu Leu	
820 825 830	
CCA TAT GGT TGC ATT TCA ACT GGT GAC AAA ATA GGA ATG ATC GAG ATT	2963
Pro Tyr Gly Cys Ile Ser Thr Gly Asp Lys Ile Gly Met Ile Glu Ile	
835 840 845	
GTG AAA GAC GCC ACG ACA ATT GCC AAA ATT CAG CAA AGC ACA GTG GGC	3011
Val Lys Asp Ala Thr Thr Ile Ala Lys Ile Gln Gln Ser Thr Val Gly	
850 855 860	
AAC ACG GGA GCA TTT AAA GAT GAA GTC CTG AAT CAC TGG CTC AAA GAA	3059
Asn Thr Gly Ala Phe Lys Asp Glu Val Leu Asn His Trp Leu Lys Glu	
865 870 875	
AAA TCC CCT ACT GAA GAA AAG TTT CAG GCA GCA GTG GAG AGA TTT GTT	3107
Lys Ser Pro Thr Glu Glu Lys Phe Gln Ala Ala Val Glu Arg Phe Val	
880 885 890 895	
TAT TCC TGT GCA GGC TAC TGT GTG GCA ACC TTT GTT CTT GGA ATA GGC	3155
Tyr Ser Cys Ala Gly Tyr Cys Val Ala Thr Phe Val Leu Gly Ile Gly	
900 905 910	
GAC AGA CAC AAT GAC AAT ATT ATG ATC ACC GAG ACA GGA AAC CTA TTT	3203
Asp Arg His Asn Asp Asn Ile Met Ile Thr Glu Thr Gly Asn Leu Phe	
915 920 925	
CAT ATT GAC TTC GGG CAC ATT CTT GGG AAT TAC AAA AGT TTC CTG GGC	3251
His Ile Asp Phe Gly His Ile Leu Gly Asn Tyr Lys Ser Phe Leu Gly	
930 935 940	
ATT AAT AAA GAG AGA GTG CCA TTT GTG CTA ACC CCT GAC TTC CTC TTT	3299

- 29 -

Ile	Asn	Lys	Glu	Arg	Val	Pro	Phe	Val	Leu	Thr	Pro	Asp	Phe	Leu	Phe		
945						950					955						
GTG	ATG	GGA	ACT	TCT	GGA	AAG	AAG	ACA	AGC	CCA	CAC	TTC	CAG	AAA	TTT	3347	
Val	Met	Gly	Thr	Ser	Gly	Lys	Lys	Thr	Ser	Pro	His	Phe	Gln	Lys	Phe		
960					965					970					975		
CAG	GAC	ATC	TGT	GTT	AAG	GCT	TAT	CTA	GCC	CTT	CGT	CAT	CAC	ACA	AAC	3395	
Gln	Asp	Ile	Cys	Val	Lys	Ala	Tyr	Leu	Ala	Leu	Arg	His	His	Thr	Asn		
				980					985					990			
CTA	CTG	ATC	ATC	CTG	TTC	TCC	ATG	ATG	CTG	ATG	ACA	GGA	ATG	CCC	CAG	3443	
Leu	Leu	Ile	Ile	Leu	Phe	Ser	Met	Met	Leu	Met	Thr	Gly	Met	Pro	Gln		
			995					1000					1005				
TTA	ACA	AGC	AAA	GAA	GAC	ATT	GAA	TAT	ATC	CGG	GAT	GCC	CTC	ACA	GTG	3491	
Leu	Thr	Ser	Lys	Glu	Asp	Ile	Glu	Tyr	Ile	Arg	Asp	Ala	Leu	Thr	Val		
	1010						1015					1020					
GGG	AAA	AAT	GAG	GAG	GAT	GCT	AAA	AAG	TAT	TTT	CTT	GAT	CAG	ATC	GAA	3539	
Gly	Lys	Asn	Glu	Glu	Asp	Ala	Lys	Lys	Tyr	Phe	Leu	Asp	Gln	Ile	Glu		
	1025					1030					1035						
GTT	TGG	CAG	AGA	CAA	AGG	ATG	GAC	TGT	GCA	GTT	TAATTGGTTT	CTACATCTTG				3592	
Val	Trp	Gln	Arg	Gln	Arg	Met	Asp	Cys	Ala	Val							
1040					1045					1050							
TTCTTGGCAT	CAAACAAGGA	GAGAAACATT	CAGCCTAATA	CTTTAGGCTA	GAATCAAAAA								3652				
CAAGTTAGTG	TTCTATGGTT	TAAATTAGCA	TAGCAATCAT	CGAACTTGGA	TTTCAAATGC								3712				
AATAGACATT	GTGAAAGCTG	GCATTTTCAGA	AGTATAGCTC	TTTTCCTACC	TGAACTCTTC								3772				
CCTGGAGAAA	AGATGTTGGC	ATTGCTGATT	GTTTGGTTAA	GCAATGTCCA	GTGCTAGGAT								3832				
TATTTGCAGG	TTTGGTTTTT	TCTCATTTGT	CTGTGGCATT	GGAGAATATT	CTCGGTTTAA								3892				
ACAGACTAAT	GACTTCCTTA	TTGTCCCTGA	TATTTTGACT	ATCTTACTAT	TGAGTGCTTC								3952				
TGGAAATTCT	TTGGAATAAT	TGATGACATC	TATTTTCATC	TGGGTTTAGT	CTCAATTTTG								4012				
GTTATCTTTG	TGTTCTCAA	GCTCTTTAAA	GAAAAAGATG	TAATCGTTGT	AACCTTTGTC								4072				
TCATTCCTTA	AATGATGCTT	CCAAACATCT	CCTTAGTGTC	TGCAGGTGTT	AGTGGTGTGC								4132				
TAAAA																4137	

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1050 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) TYPE OF MOLECULE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Met	Glu	Leu	Ile	Pro	Ile	Glu	Phe	Val	Leu	Pro	Thr	Ser	Gln	Arg	Lys		
1				5					10					15			
Cys	Lys	Ser	Pro	Glu	Thr	Ala	Leu	Leu	His	Val	Ala	Gly	His	Gly	Asn		
			20				25					30					
Val	Glu	Gln	Met	Lys	Ala	Gln	Val	Trp	Leu	Arg	Ala	Leu	Glu	Thr	Ser		
	35					40					45						

- 30 -

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

- 31 -

Ser Ser Glu Ser Lys Gly Lys Val Arg Leu Leu Tyr Tyr Val Asn Leu
 420 425 430
 Leu Leu Ile Asp His Arg Phe Leu Leu Arg Arg Gly Glu Tyr Val Leu
 435 440 445
 His Met Trp Gln Ile Ser Gly Lys Gly Glu Asp Gln Gly Ser Phe Asn
 450 455 460
 Ala Asp Lys Leu Thr Ser Ala Thr Asn Pro Asp Lys Glu Asn Ser Met
 465 470 475 480
 Ser Ile Ser Ile Leu Leu Asp Asn Tyr Cys His Pro Ile Ala Leu Pro
 485 490 495
 Lys His Gln Pro Thr Pro Asp Pro Glu Gly Asp Arg Val Arg Ala Glu
 500 505 510
 Met Pro Asn Gln Leu Arg Lys Gln Leu Glu Ala Ile Ile Ala Thr Asp
 515 520 525
 Pro Leu Asn Pro Leu Thr Ala Glu Asp Lys Glu Leu Leu Trp His Phe
 530 535 540
 Arg Tyr Glu Ser Leu Lys His Pro Lys Ala Tyr Pro Lys Leu Phe Ser
 545 550 555 560
 Ser Val Lys Trp Gly Gln Gln Glu Ile Val Ala Lys Thr Tyr Gln Leu
 565 570 575
 Leu Ala Arg Arg Glu Val Trp Asp Gln Ser Ala Leu Asp Val Gly Leu
 580 585 590
 Thr Met Gln Leu Leu Asp Cys Asn Phe Ser Asp Glu Asn Val Arg Ala
 595 600 605
 Ile Ala Val Gln Lys Leu Glu Ser Leu Glu Asp Asp Asp Val Leu His
 610 615 620
 Tyr Leu Leu Gln Leu Val Gln Ala Val Lys Phe Glu Pro Tyr His Asp
 625 630 635 640
 Ser Ala Leu Ala Arg Phe Leu Leu Lys Arg Gly Leu Arg Asn Lys Arg
 645 650 655
 Ile Gly His Phe Leu Phe Trp Phe Leu Arg Ser Glu Ile Ala Gln Ser
 660 665 670
 Arg His Tyr Gln Gln Arg Phe Ala Val Ile Leu Glu Ala Tyr Leu Arg
 675 680 685
 Gly Cys Gly Thr Ala Met Leu His Asp Phe Thr Gln Gln Val Gln Val
 690 695 700
 Ile Glu Met Leu Gln Lys Val Thr Leu Asp Ile Lys Ser Leu Ser Ala
 705 710 715 720
 Glu Lys Tyr Asp Val Ser Ser Gln Val Ile Ser Gln Leu Lys Gln Lys
 725 730 735
 Leu Glu Asn Leu Gln Asn Ser Gln Leu Pro Glu Ser Phe Arg Val Pro
 740 745 750
 Tyr Asp Pro Gly Leu Lys Ala Gly Ala Leu Ala Ile Glu Lys Cys Lys
 755 760 765
 Val Met Ala Ser Lys Lys Lys Pro Leu Trp Leu Glu Phe Lys Cys Ala
 770 775 780

- 32 -

Asp Pro Thr Ala Leu Ser Asn Glu Thr Ile Gly Ile Ile Phe Lys His
 785 790 795 800
 Gly Asp Asp Leu Arg Gln Asp Met Leu Ile Leu Gln Ile Leu Arg Ile
 805 810 815
 Met Glu Ser Ile Trp Glu Thr Glu Ser Leu Asp Leu Cys Leu Leu Pro
 820 825 830
 Tyr Gly Cys Ile Ser Thr Gly Asp Lys Ile Gly Met Ile Glu Ile Val
 835 840 845
 Lys Asp Ala Thr Thr Ile Ala Lys Ile Gln Gln Ser Thr Val Gly Asn
 850 855 860
 Thr Gly Ala Phe Lys Asp Glu Val Leu Asn His Trp Leu Lys Glu Lys
 865 870 875 880
 Ser Pro Thr Glu Glu Lys Phe Gln Ala Ala Val Glu Arg Phe Val Tyr
 885 890 895
 Ser Cys Ala Gly Tyr Cys Val Ala Thr Phe Val Leu Gly Ile Gly Asp
 900 905 910
 Arg His Asn Asp Asn Ile Met Ile Thr Glu Thr Gly Asn Leu Phe His
 915 920 925
 Ile Asp Phe Gly His Ile Leu Gly Asn Tyr Lys Ser Phe Leu Gly Ile
 930 935 940
 Asn Lys Glu Arg Val Pro Phe Val Leu Thr Pro Asp Phe Leu Phe Val
 945 950 955 960
 Met Gly Thr Ser Gly Lys Lys Thr Ser Pro His Phe Gln Lys Phe Gln
 965 970 975
 Asp Ile Cys Val Lys Ala Tyr Leu Ala Leu Arg His His Thr Asn Leu
 980 985 990
 Leu Ile Ile Leu Phe Ser Met Met Leu Met Thr Gly Met Pro Gln Leu
 995 1000 1005
 Thr Ser Lys Glu Asp Ile Glu Tyr Ile Arg Asp Ala Leu Thr Val Gly
 1010 1015 1020
 Lys Asn Glu Glu Asp Ala Lys Lys Tyr Phe Leu Asp Gln Ile Glu Val
 1025 1030 1035 1040
 Trp Gln Arg Gln Arg Met Asp Cys Ala Val
 1045 1050

CLAIMS:

1. Protein with phosphatidylinositol-3-kinase activity wherein, it comprises
 - (a) the amino acid sequence shown in SEQ ID NO:2,
 - (b) the amino acid sequence shown in SEQ ID NO:4,
 - or
 - (c) variants of the sequence from (a) having an identity of at least 80% to the amino acid sequence shown in SEQ ID NO:2 or SEQ ID NO:4.
2. Protein as claimed in claim 1 wherein said protein is from humans.
3. Nucleic acid, wherein it codes for the phosphatidylinositol-3-kinase as claimed in claim 1 or 2.
4. Nucleic acid as claimed in claim 3, wherein it is a recombinant DNA molecule.
5. Nucleic acid as claimed in claim 3, wherein it contains
 - (a) the protein-coding sequence shown in SEQ ID NO:1,
 - (b) the protein-coding sequence shown in SEQ ID NO:3,
 - (c) a nucleic acid sequence corresponding to the sequence from (a) or (b) within the scope of the degeneracy of the genetic code, or
 - (d) a sequence which hybridizes with the complement of sequences from (a) or (b) under stringent hybridization conditions that still occur after washing at 55°C in a aqueous low salt buffer comprising 0.2 X SSC with 0.1% SDS and encodes a protein with phosphatidylinositol-3-kinase activity.

6. Nucleic acid, which is a primer or a probe, wherein it contains at least a 20 nucleotide long section of the sequence shown in SEQ ID NO:1 or SEQ ID NO:3, wherein said nucleic acid hybridizes under stringent conditions that still occur after washing with 0.2 x SSC, 0.1% SDS at 62°C to the complement of the nucleic acid according to claim 3, or wherein it contains at least 20 nucleotide long section of the complement of the sequence shown in SEQ ID NO:1 or SEQ ID NO:3, wherein said nucleic acid hybridizes under stringent conditions that still occur after washing with 0.2 x SSC, 0.1% SDS at 62°C to the nucleic acid according to claim 3.
7. Vector, wherein it contains at least one copy of the nucleic acid as claimed in any one of claims 3-5.
8. Vector, wherein it contains at least one copy of the nucleic acid as claimed in claim 6.
9. Cell, wherein it is transformed by the nucleic acid as claimed in any one of claims 3-6 or by the vector as claimed in claim 7 or 8.
10. Use of the protein as claimed in claim 1 or 2 or a fragment of this protein as an immunogen for the production of polyclonal antibodies specifically binding to said protein, wherein said fragment is located within SEQ ID NO:2 or 4.
11. Polyclonal antibody specifically binding to the protein as claimed in claim 1 or 2, wherein it does not exhibit any cross-reaction with other phosphatidylinositol-3-kinases.
12. Polyclonal antibody as claimed in claim 11, wherein it specifically binds a peptide sequence which

corresponds to amino acids 741-745 of the amino acid sequence shown in SEQ ID NO:2 or amino acids 742-746 of the amino acid sequence shown in SEQ ID NO:4.

13. Use of the nucleic acid as claimed in any one of claims 3-5 or the vector as claimed in claim 7 for gene therapy, for treating a disease or disorder associated with the loss of the expression of the protein as claimed in claim 1 or 2.
14. Use of the nucleic acid as claimed in claim 6, or the vector as claimed in claim 8 for the production of therapeutically applicable antisense nucleic acids for the inhibition of the expression of the protein as claimed in claim 1 or 2, wherein said nucleic acid has a nucleotide sequence that specifically binds to the nucleic acid sequence according to SEQ ID NO:3 or encoding SEQ ID NO:4.
15. Pharmaceutical composition, wherein it comprises as the active component the protein as claimed in claim 1 or 2, the polyclonal antibody as claimed in claim 11 or 12, the nucleic acid as claimed in any one of claims 3-6 or the vector as claimed in claim 7 or 8, and pharmaceutically common auxiliary agents, carriers, fillers or diluents.
16. Method for the *in vitro* determination of phosphatidylinositol-3-kinase activity in cells, comprising the step of measuring the level of the expression of a gene coding for the protein as claimed in claim 1 or 2, wherein measuring the expression of the gene is indicative of the level of phosphatidylinositol-3-kinase activity in the cells.
17. Method for the *in vitro* determination of phosphatidylinositol-3-kinase activity in cells, comprising

the step of measuring the concentration of the protein as claimed in claim 1 or 2, wherein measuring the concentration of the protein is indicative of the level of phosphatidylinositol-3-kinase activity in the cells.

18. Method as claimed in claim 16 or 17, wherein said cells are human cells.

1/ 4

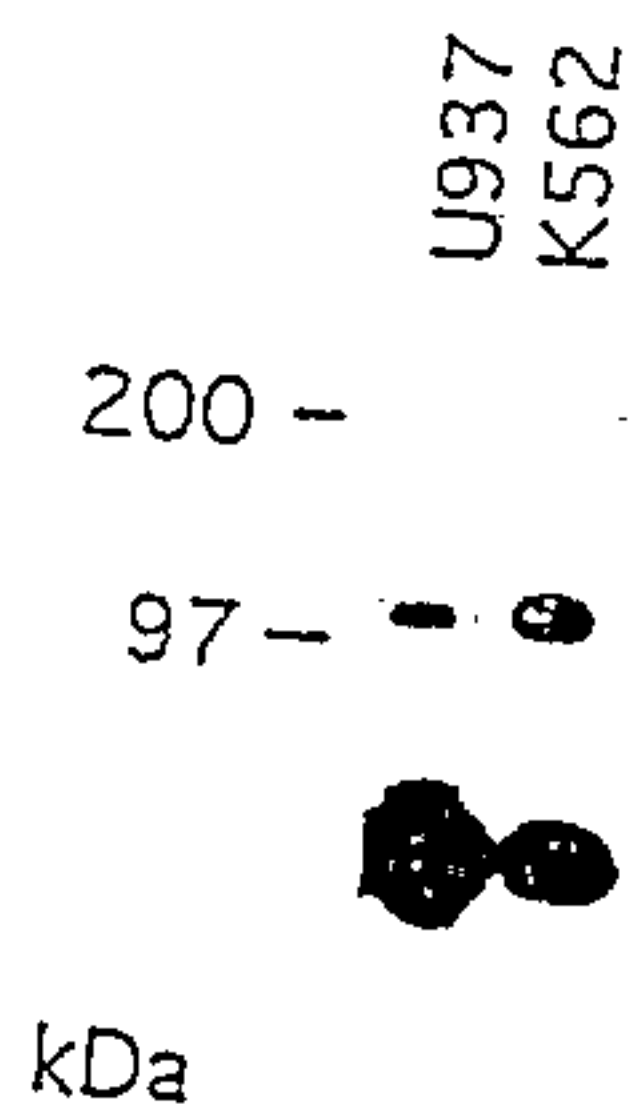


Fig. 1

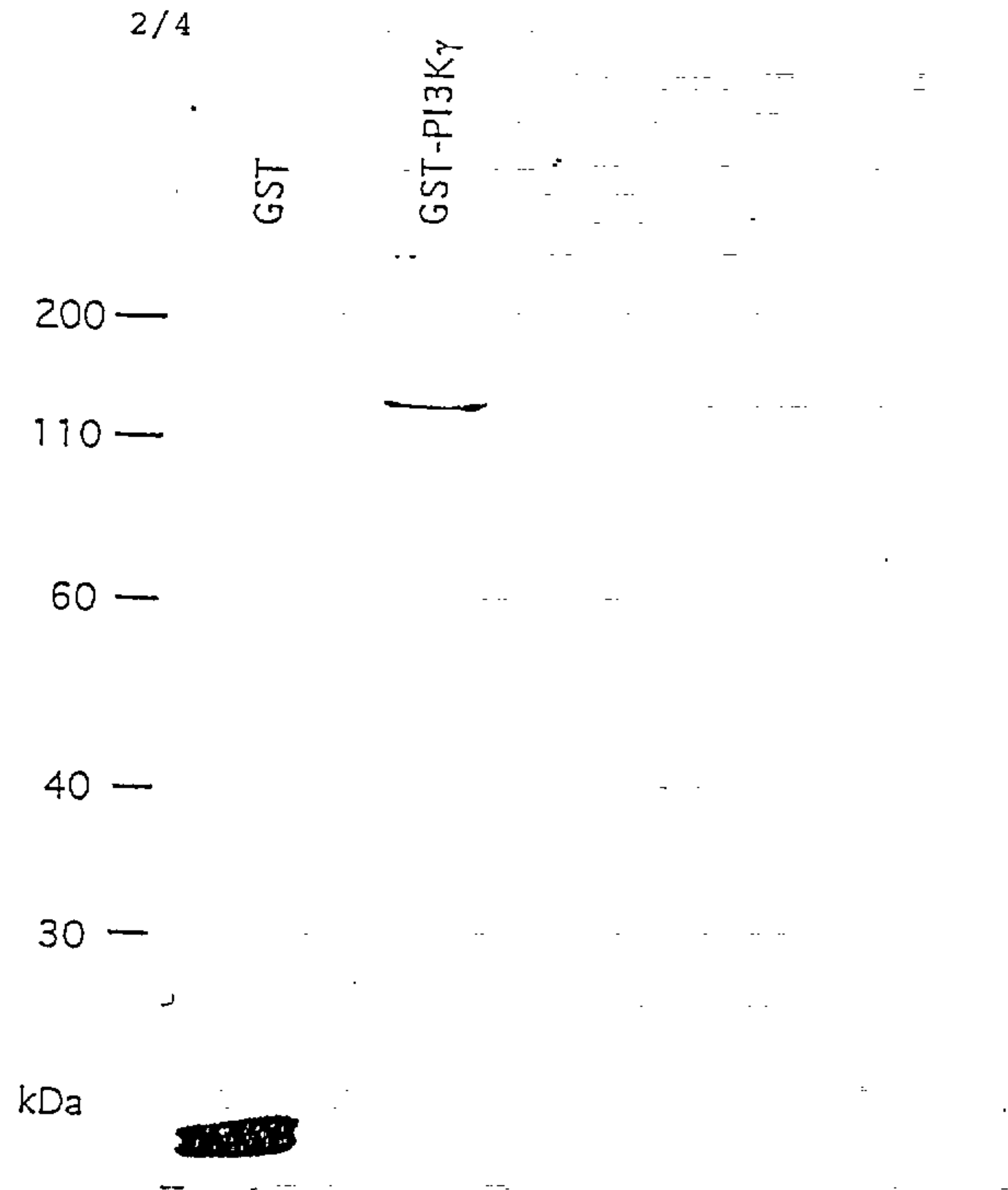


Fig. 2a

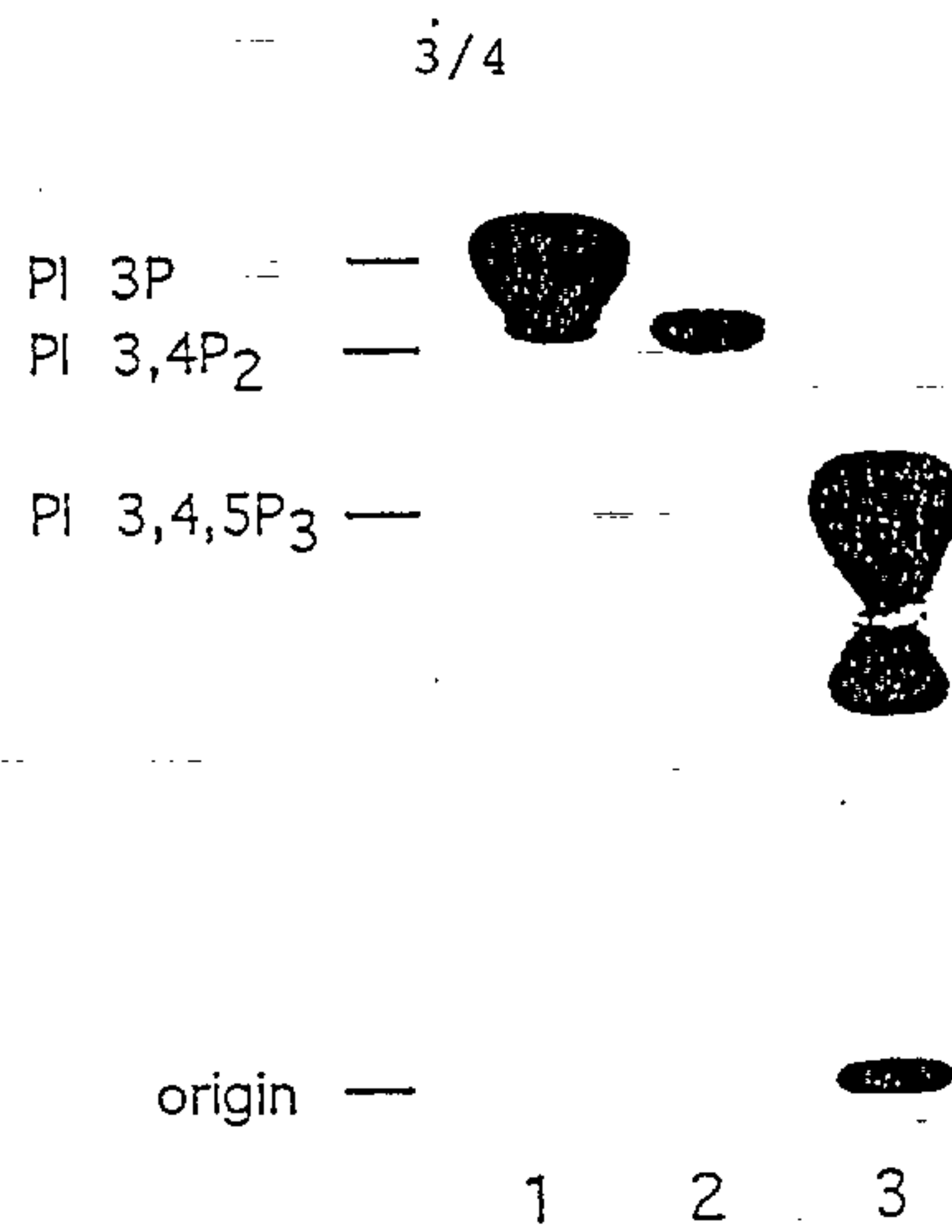


Fig. 2b

4/4

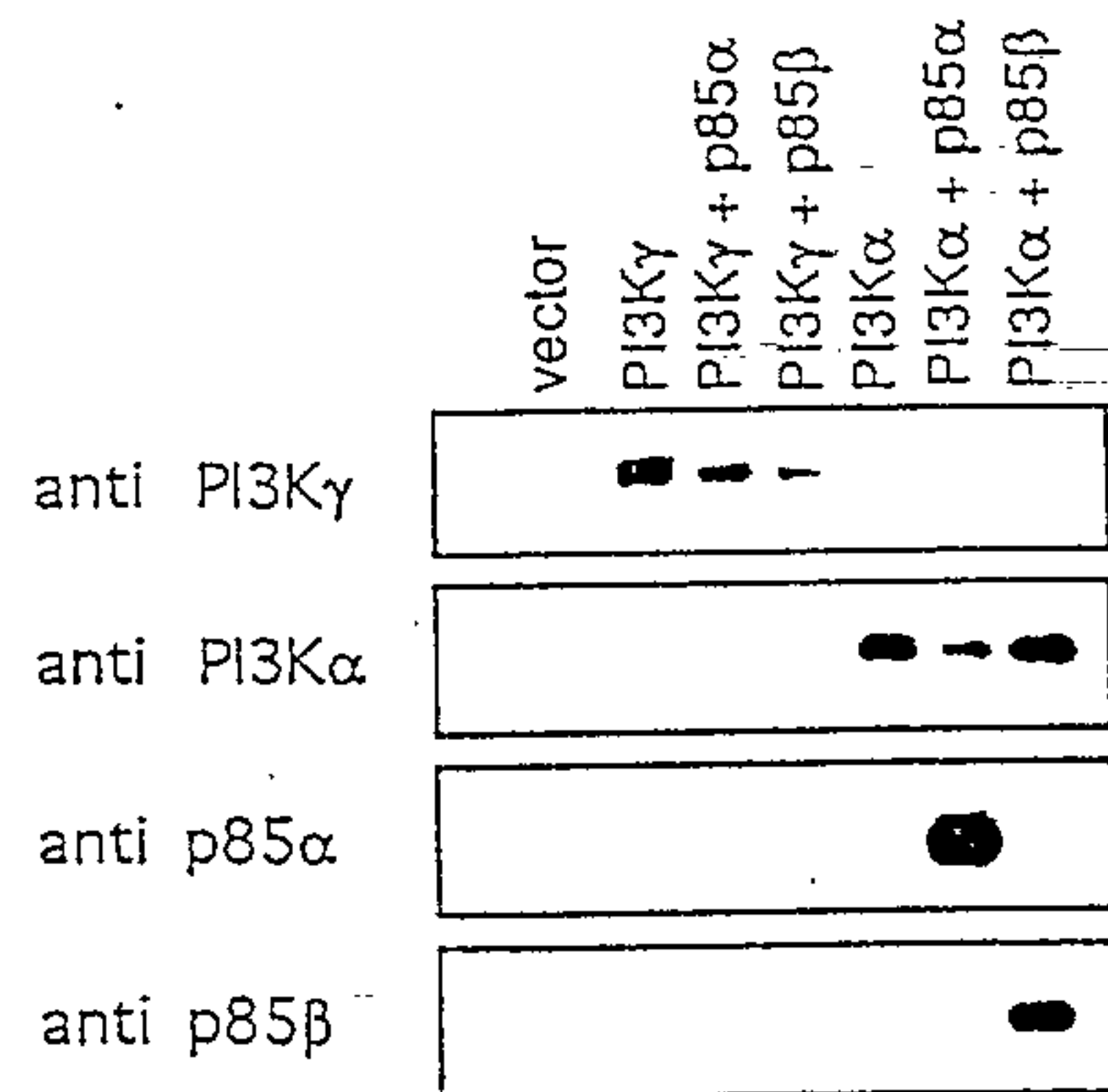


Fig. 3