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(54) NOVEL SH2CONTAINING INOSITOL 5'-PHOSPHATASE ISOFORM THAT PARTNERS WITH THE GRB2 ADAPTER PROTEIN

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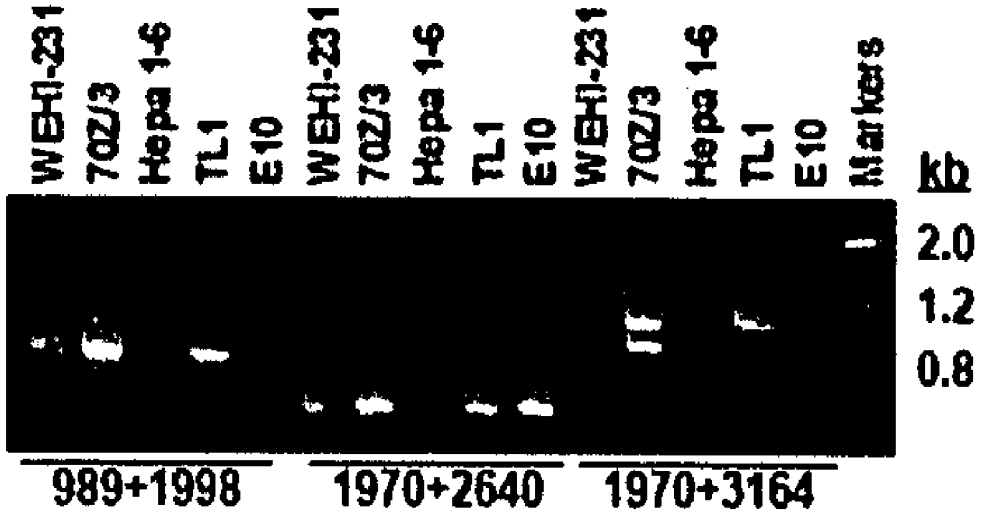
C07H 21/04	(2006.01)

(52) **U.S. Cl.** **424/9.1**; 435/375; 435/377; 435/461; 435/7.21; 536/23.1

(57) **ABSTRACT**

SH2 containing inositol 5'-phosphate (SHIP) modulates the activation of immune cells after recruitment to the membrane by Shc and the cytoplasmic tails of receptors. A novel SHIP isoform of approximately 104 kd expressed in primitive stem cell populations (s-SHIP) is described. It was found that s-SHIP is expressed in totipotent embryonic stem cells to the exclusion of the 145-kd SHIP isoform expressed in differentiated hematopoietic cells. s-SHIP is also expressed in primitive hematopoietic stem cells, but not in lineage-committed hematopoietic cells. In embryoic stem cells, s-SHIP partners with the adapter protein Grb2 without tyrosine phosphorylation and is present constitutively at the cell membrane. It is postulated that s-SHIP modulates the activation threshold of primitive stem cell populations.



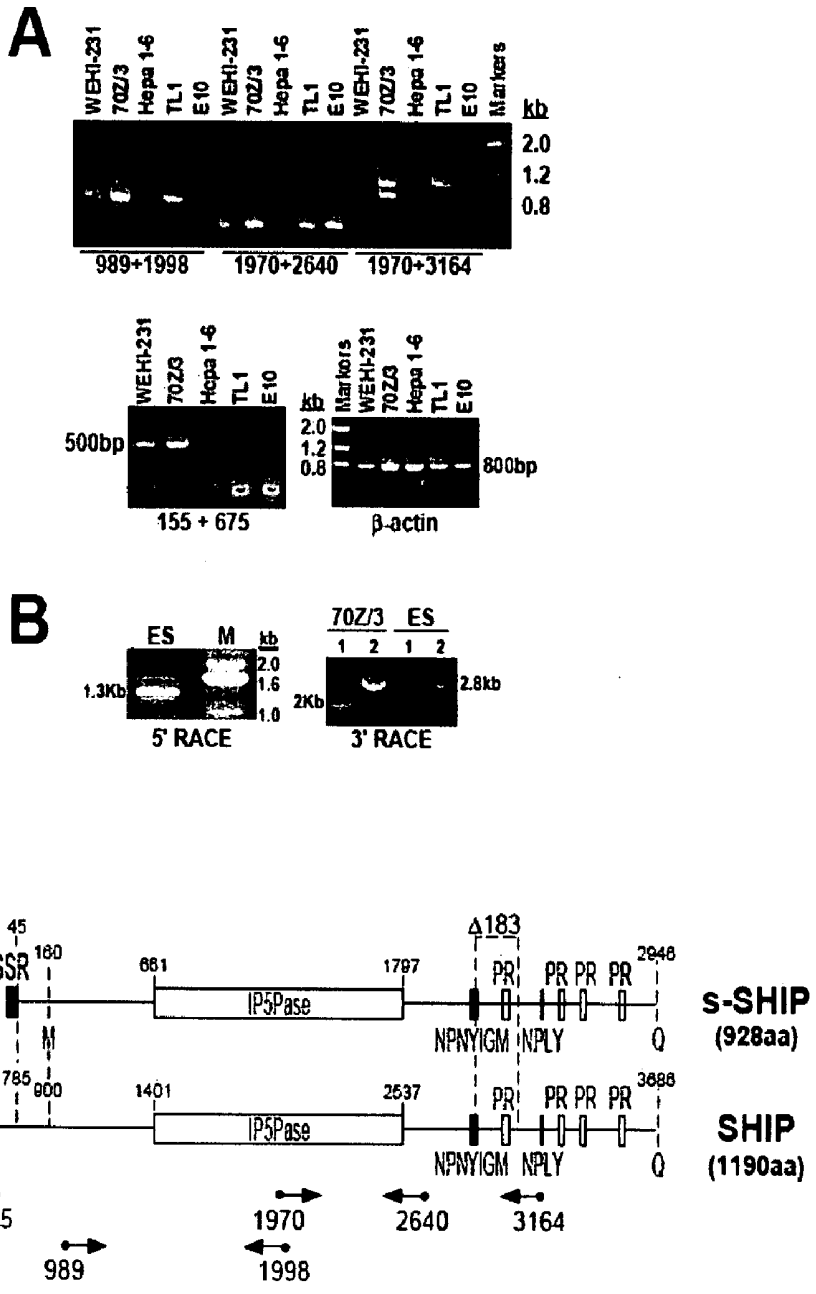

A
WEHI-231
70Z/3
Hepa 1-6
TL1
E10
Markers
kb
2.0
1.2
0.8
989+1998
1970+2640
1970+3164
500bp
155 + 675
β-actin
800bp
B
ES
M
1.3Kb
5' RACE
70Z/3
2Kb
3' RACE
2.8kb
C
SSR
SH2
IP5Pase
PR
NPNYIGM
NPLY
s-SHIP
(928aa)
SHIP
(1190aa)
155
675
989
1970
1998
2640
3164

FIG. 1

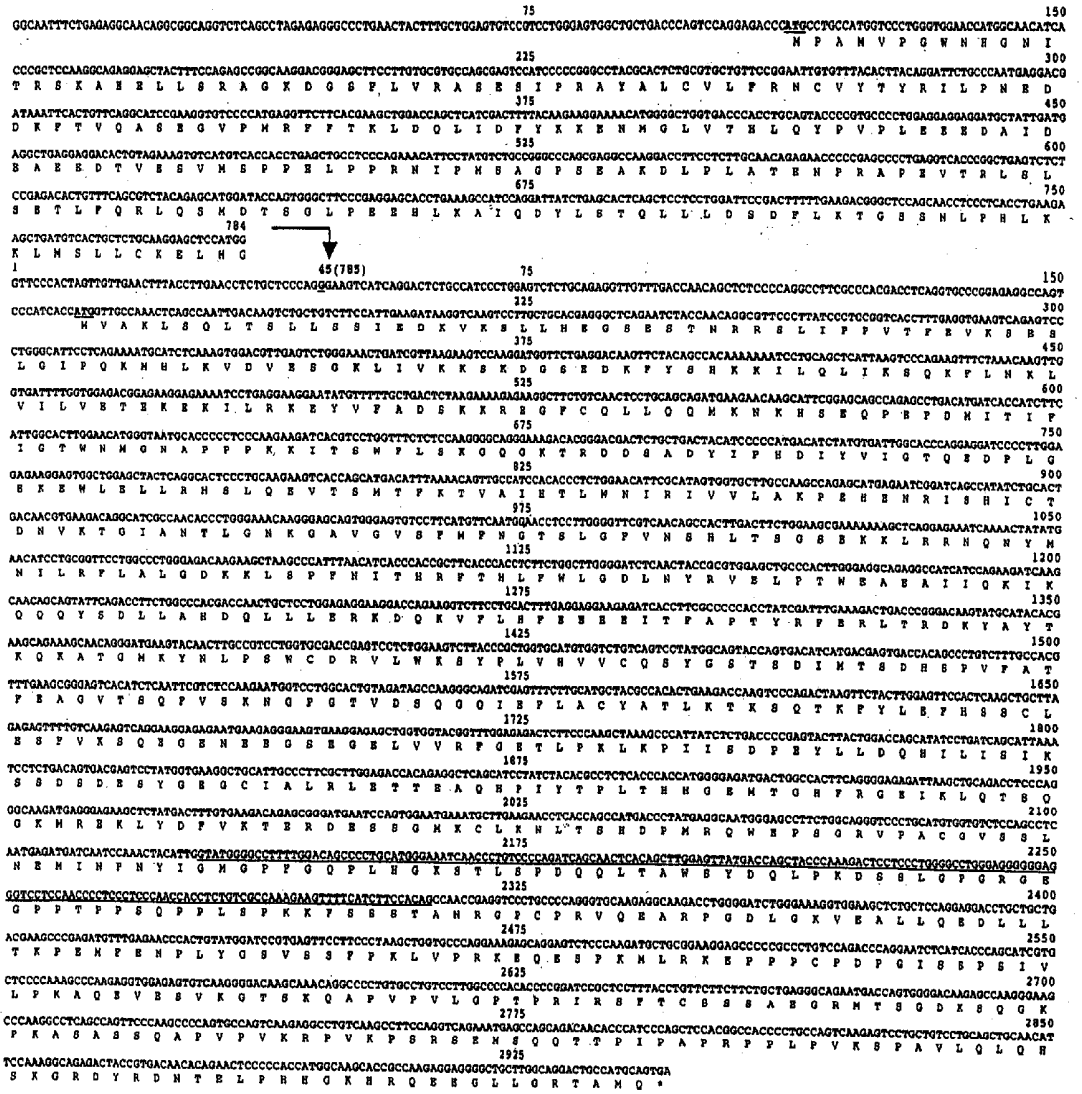


FIG. 2

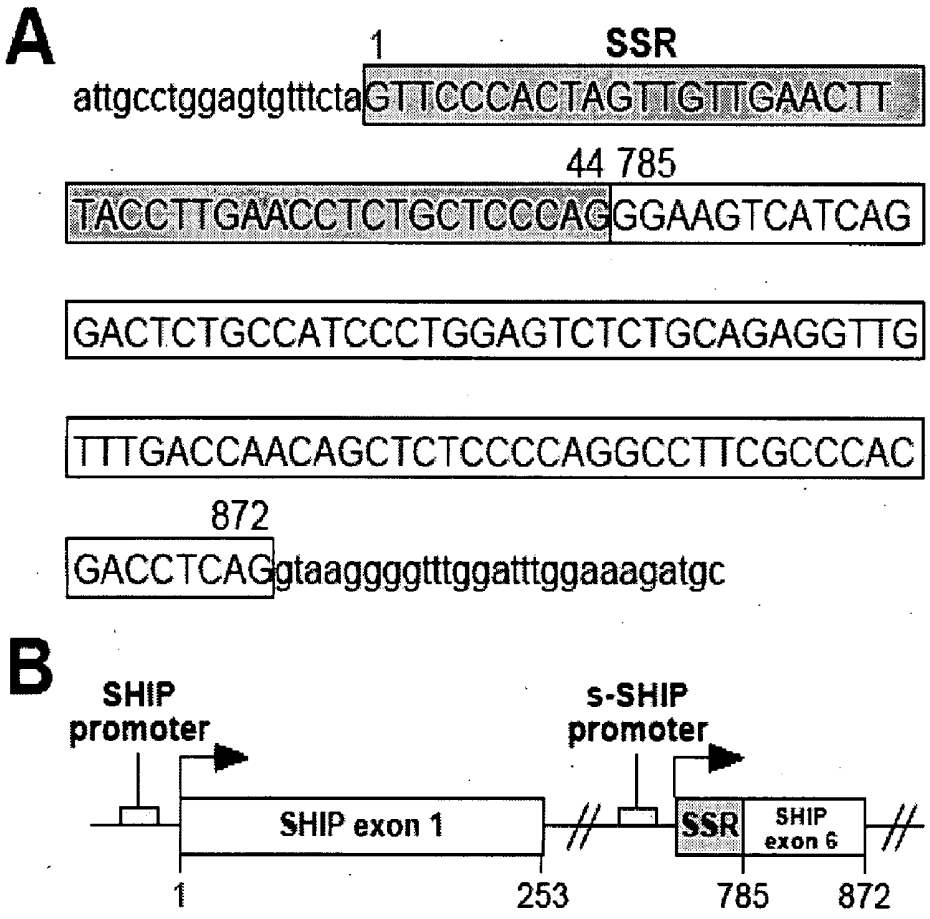

A
1
SSR
attgcctggagtgtttctaGTTCCCACTAGTTGTTGAACTT
44 785
TACCTTGAACCTCTGCTCCCAGGGAAGTCATCAG
GACTCTGCCATCCCTGGAGTCTCTGCAGAGGTTG
TTTGACCAACAGCTCTCCCCAGGCCTTCGCCCAC
872
GACCTCAGgtaaggggtttggatttggaaagatgc
B
SHIP promoter
s-SHIP promoter
SHIP exon 1
SSR
SHIP exon 6
1
253
785
872

FIG. 3

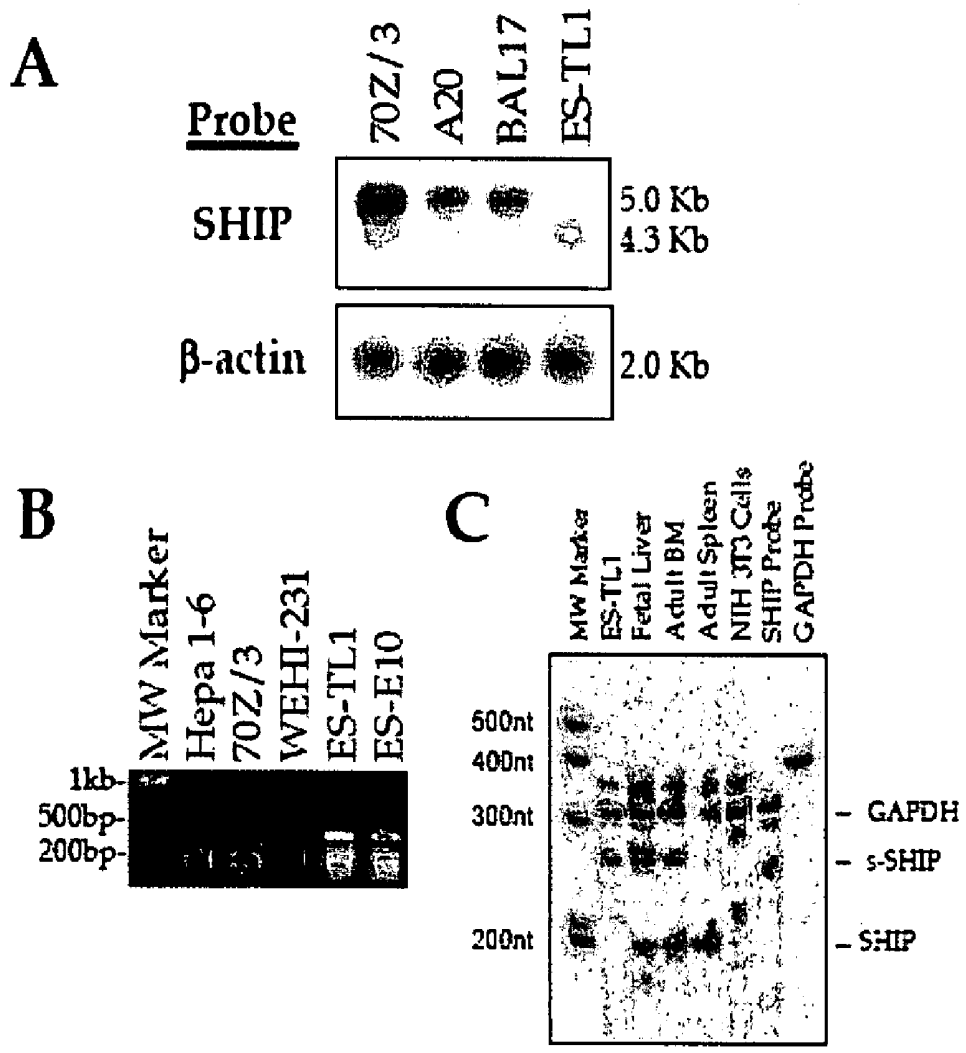

A
Probe
70Z/3
A20
BAL17
ES-TL1
SHIP
5.0 Kb
4.3 Kb
β-actin
2.0 Kb
B
MW Marker
Hepa 1-6
70Z/3
WEHI-231
ES-TL1
ES-E10
1kb-
500bp-
200bp-
C
MW Marker
ES-TL1
Fetal Liver
Adult BM
Adult Spleen
NIH 3T3 Cells
SHIP Probe
GAPDH Probe
500nt
400nt
300nt
200nt
GAPDH
s-SHIP
SHIP

FIG. 4

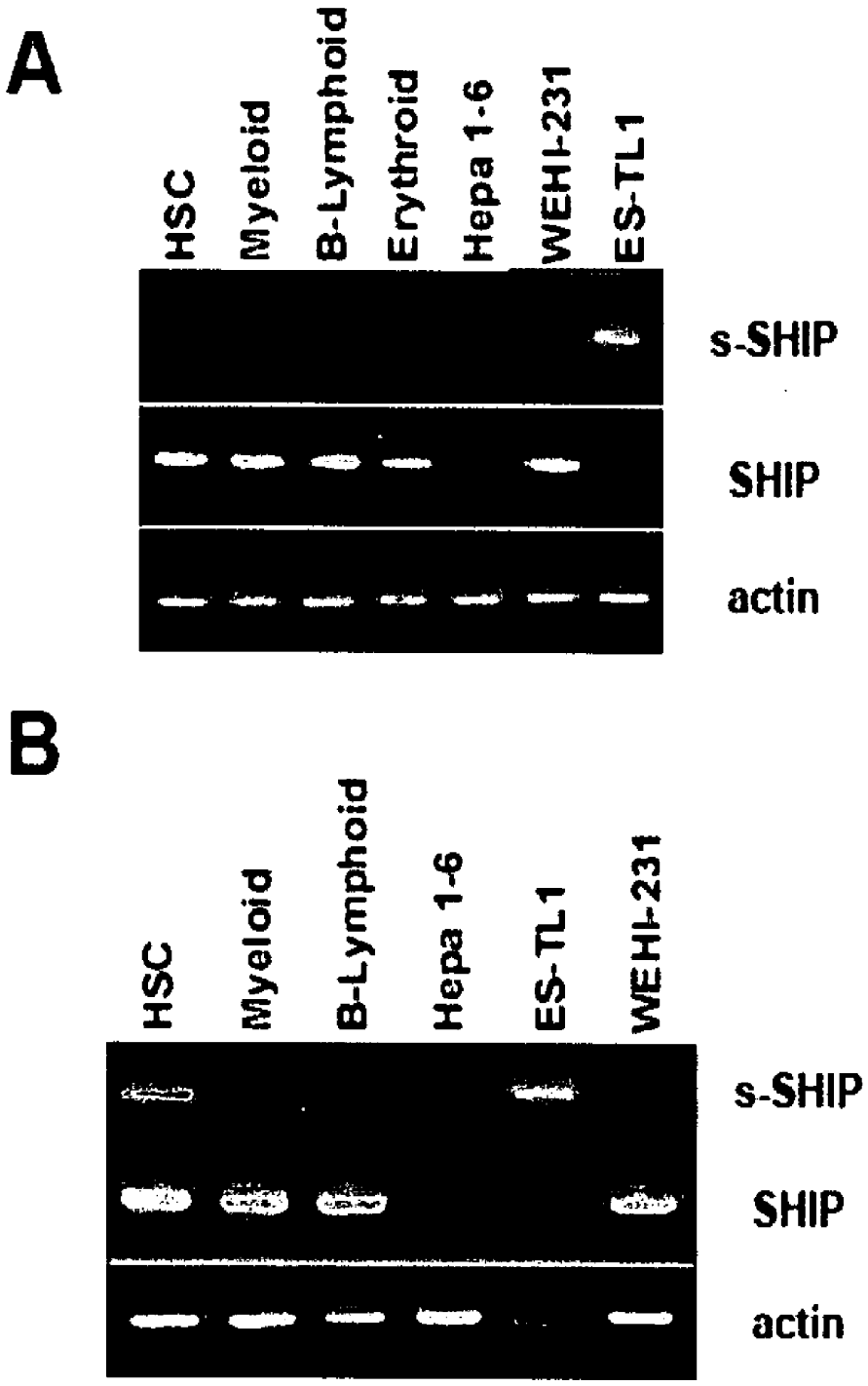

A
HSC
Myeloid
B-Lymphoid
Erythroid
Hepa 1-6
WEHI-231
ES-TL1
s-SHIP
SHIP
actin
B
HSC
Myeloid
B-Lymphoid
Hepa 1-6
ES-TL1
WEHI-231
s-SHIP
SHIP
actin

FIG. 5

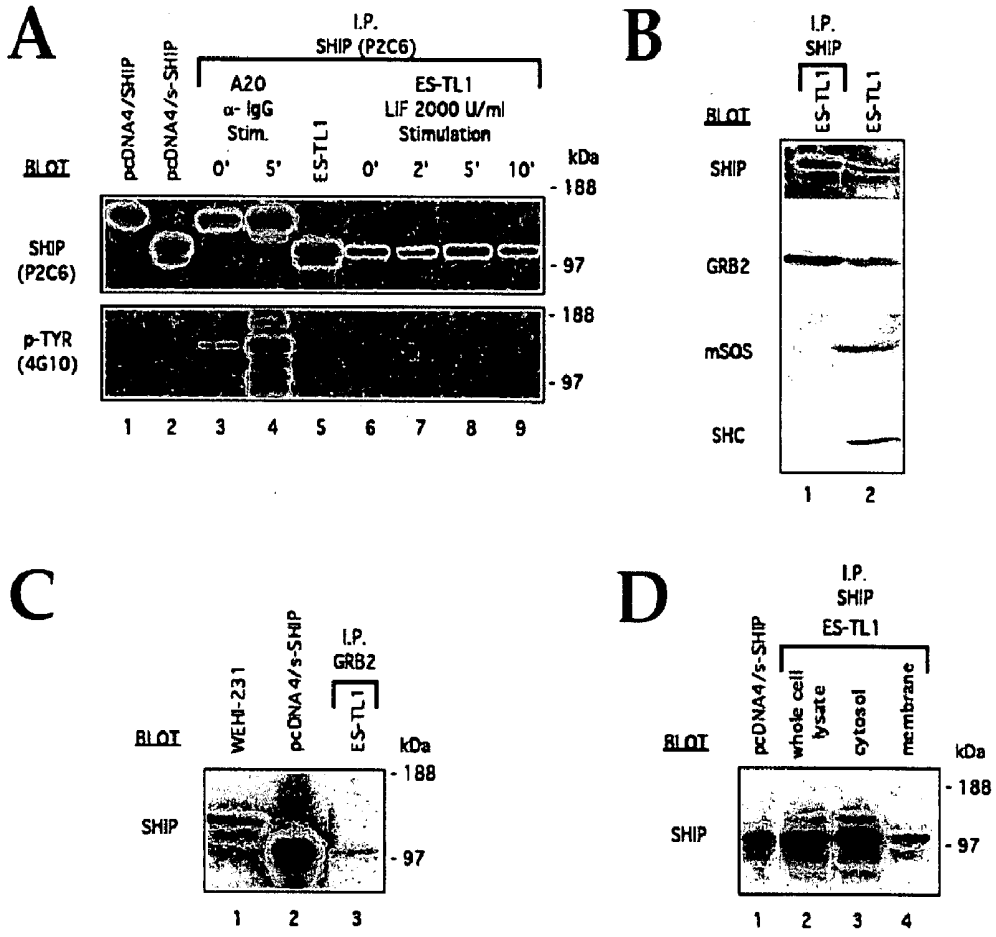

A
I.P.
SHIP (P2C6)
pcDNA4/SHIP
pcDNA4/s-SHIP
A20
α- IgG
Stim.
ES-TL1
ES-TL1
LIF 2000 U/ml
Stimulation
BLOT
0'
5'
0'
2'
5'
10'
kDa
188
97
SHIP
(P2C6)
p-TYR
(4G10)
188
97
1 2 3 4 5 6 7 8 9
B
I.P.
SHIP
ES-TL1
ES-TL1
BLOT
SHIP
GRB2
mSOS
SHC
1 2
C
WEHI-231
pcDNA4/s-SHIP
I.P.
GRB2
ES-TL1
BLOT
kDa
188
SHIP
97
1 2 3
D
I.P.
SHIP
ES-TL1
pcDNA4/s-SHIP
whole cell
lysate
cytosol
membrane
BLOT
kDa
188
SHIP
97
1 2 3 4

FIG. 6

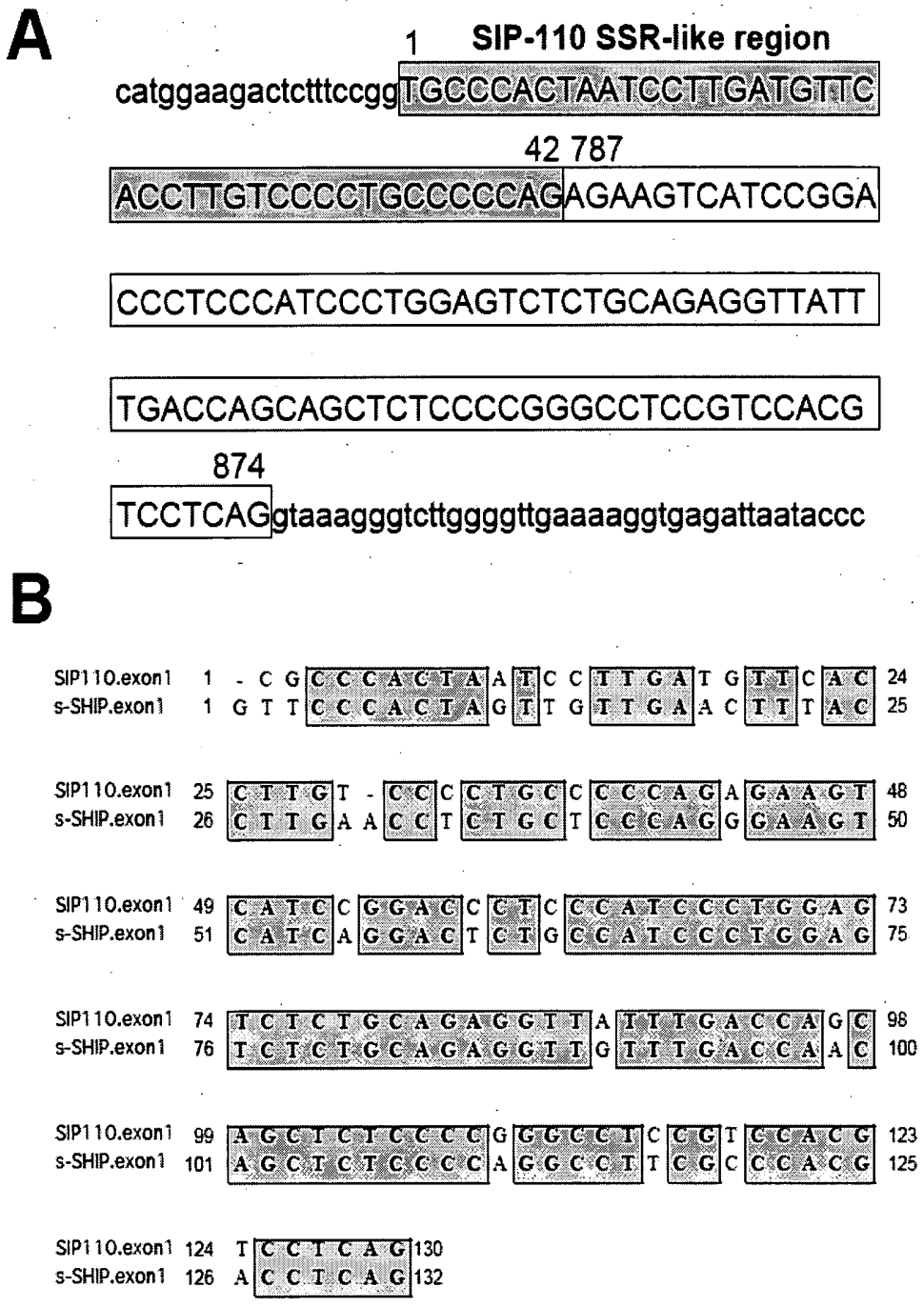
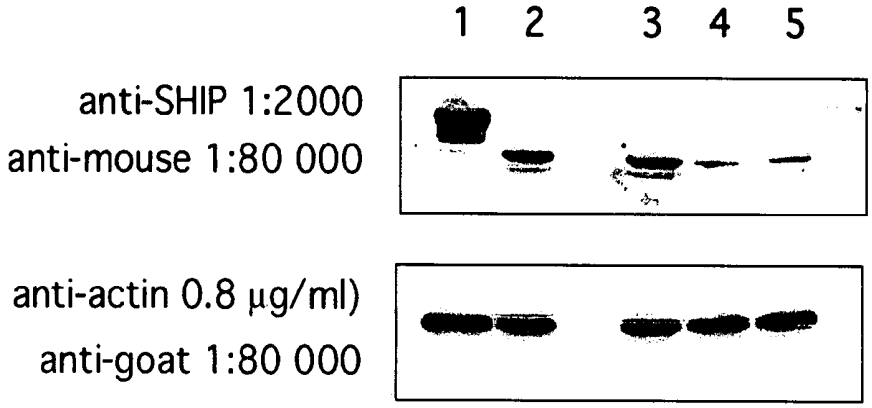

A
1
SIP-110 SSR-like region
catggaagactctttccggTGCCCACTAATCCTTGATGTTC
42 787
ACCTTGTCCCCTGCCCCCAGAGAAGTCATCCGGA
CCCTCCCATCCCTGGAGTCTCTGCAGAGGTTATT
TGACCAGCAGCTCTCCCCGGGCCTCCGTCCACG
874
TCCTCAGgtaaagggtcttggggttgaaaaggtgagattaataccc
B
SIP110.exon1 1 - C G C C C A C T A A T C C T T G A T G T T C 24
s-SHIP.exon1 1 G T T C C C A C T A G T T G T T G A A C T T T A C 25
SIP110.exon1 25 C T T G T - C C C C T G C C C C A G A G A A G T 48
s-SHIP.exon1 26 C T T G A A C C T C T G C T C C C A G G G A A G T 50
SIP110.exon1 49 C A T C C G G A C C T C C C A T C C C T G G A G 73
s-SHIP.exon1 51 C A T C A G G A C T C T G C C A T C C C T G G A G 75
SIP110.exon1 74 T C T C T G C A G A G G T T A T T T G A C C A G C 98
s-SHIP.exon1 76 T C T C T G C A G A G G T T G T T T G A C C A A C 100
SIP110.exon1 99 A G C T C T C C C C G G G C C T C C G T C C A C G 123
s-SHIP.exon1 101 A G C T C T C C C C A G G C C T T C G C C C A C G 125
SIP110.exon1 124 T C C T C A G 130
s-SHIP.exon1 126 A C C T C A G 132

FIG. 7



1) Control SHIP

2) Control sSHIP
(non treated ES cells)

3) ES cell treated with negative control

4) ES cell treated with
shRNA against SHIP

5) ES cell treated with shRNA
against SHIP (EGFP marker)

FIG. 8

NOVEL SH2CONTAINING INOSITOL 5'-PHOSPHATASE ISOFORM THAT PARTNERS WITH THE GRB2 ADAPTER PROTEIN

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application Ser. No. 60/319,583 filed Sep. 30, 2002, the specification

FEDERAL RESEARCH STATEMENT

[0002] Federal Research Statement Paragraph] NIH/NIDDK RO1 DK54767

SUMMARY OF INVENTION

[0003] The present invention is a method of cloning a novel SHIP isoform, s-SHIP, and showing that it is expressed in murine embryonic stem cells and murine hematopoietic stem cells. Because of this it may be expressed in all stem cell types—ES, mesnechymal neural, hepatic, neural, muscle, and the like.

[0004] Its function has been partially characterized and it is recruited to the cell membrane even without an acute stimulation of ES cells, it can access its substrate and modulate PIPS levels that accumulate from P activation in response to basal level growth factor stimulation, even in resting stem cells—thus s-SHIP is likely to influence the proliferation and differentiation of stem cells.

[0005] Advantages of the present invention include: (1) human s-SHIP/SIP1 10 as a marker of stem cells an assay for expression of s-SHIP could be used determine whether a putative human ES cell line is really an ES cell by antibodies or RNA detection of s-SHIP or detection of its enzymatic activity; (2) pharmaceutical modulation of s-SHIP/SIP110 to control the growth and differentiation of human ES cells or other stem cell populations; (3) the human SIP110 cDNA—enforced expression, or inducible expression of s-SHIP could be used to keep human stem cells in an undifferentiated state; (4) the mouse s-SHIP cDNA if mouse cDNA can replace the human cDNA, then enforced expression, or inducible expression of murine s-SHIP, could be used to keep human stem cells in an undifferentiated state; and (5) fluorogenic assays with enzymatic substrates that can be carried out on viable cells to allow PACS sorting of primitive stem cell populations—either embryonic or tissue stem cells.

[0006] The inventive method allows for identifying the presence, and delineation, of embryonic stem cells in a cell sample comprising a mixture of cells, the method comprising the steps of: adding to the sample M-MLV reverse transcriptase to primer pairs selected from the group consisting of s-SHIP, SHIP, and β-actin; and performing nested RT-PCR reactions wherein the presence of embryonic stem cells in the sample is indicated by cells that express s-SHIP mRNA. The method is applied to determine the presence of embryonic stem cells in the sample by the presence of s-SHIP enzymatic activity. Another indicator of the presence of the s-SHIP enzyme is achieved by adding anti-ship monoclonal antibody P2C6 to the sample under conditions, and for a time, suitable for antibody binding and detecting the presence of the antibodies bound to the cells in the sample. Detection can be achieved by labeling the antibodies with a flourochrome and testing by fluorescent activated cell sorting. The inventive method is also applicable for identifying the presence, and delineation, of hematopoietic stem cells in a cell sample comprising a mixture of cells, the method comprising substantially the same steps used for detection in embryonic stem cells. The method is also applicable to identifying subcellular signaling complexes involved in stem cell function co-localization by confocal immunofluorescent microscopy.

[0007] In addition to its diagnostic functionality, the method is also applicable therapeutically. Stem cells can be manipulated, due to s-SHIP"s competition with mSosI, to either induce or retard cellular proliferation and differentiation. For example, one method of inhibiting differentiation of step cells comprises the step of contacting the cells with s-SHIP enzyme whereby the accumulation of the s-SHIP enzyme prevents the accumulation of $PI^{3},^{4},^{5}P_{3}$. Generally, the stem cells are selected from a group consisting of hematopoietic progenitors of mature blood cells, hematopoietic progenitors of lymph cells, and embryonic stem progenitor cells.

[0008] The invention does not only consist of the s-SHIP enzyme, but includes a chemically inducible nucleic acid promoter fragment isolated from the 5" flanking region upstream of the coding region of the SHIP gene.

[0009] This promoter fragment is found in murine and human embryonic, as well as hematopoietic stem cells. By implanting a target cell population with cellular hosts of the nucleotide sequence, the vector cells can be used as a negative regulator of cell activation in populations such as B-Lymphoid, myeloid, and mast cells. Possible unicellular host cells could be a culture or tissue culture of cells selected from the group consisting of, a murine embryonic stem cell, a murine hematopoietic stem cell, a human embryonic stem cell, or a human hematopoietic stem cell.

[0010] The invention also consists of a method for inducing proliferation of stem cells by introducing anti-SHIP shRNA into the cell by electroporation. Additionally a means whereby identification stem cells in a cell sample is possible via detection of s-SHIP by immunofluorescence. This can be accomplished where the cell sample is a mixture of cells, in vivo, or in any situation where the presence of s-SHIP can be indicated. Also a method of identifying subcellular signaling complexes involved in stem cell function co-localization by confocal immunofluorescent microscopy is provided.

[0011] Proliferation of stem cells can also be induced by the introduction of an inhibitor of s-SHIP activity, such as a dominant negative mutant.

BRIEF DESCRIPTION OF DRAWINGS

[0012] For a fuller understanding of the nature and objects of the invention, reference should be made to the following detailed description, taken in connection with the accompanying drawings, in which:

[0013] FIG. **1** is an illustration of how ES cells express e SHIP mRNA species different from that expressed in mature hematopoietic cells.

[0014] FIG. **2** indicates, graphically, the nucleotide sequence of s-SHIP cDNA and the predicted amino acid sequence of its major open reading frame (ORF).

[0015] FIG. 3 shows the organization of the first exon of s-SHIP.

[0016] FIG. 4 graphically indicates the analysis of s-SHIP and SHIP mRNA expression in ES cells and hematopoiesis.

[0017] FIG. 5 blot analysis revealing that HSCs express s-SHIP mRNA.

[0018] FIG. 6 illustrates that ES cells express the 8-SHIP protein isoform that associates with the Grb2 adapter protein.

[0019] FIG. 7 depicts the organization of the first axon of SIP-110, the human homolog of s-SHIP.

[0020] FIG. 8 demonstrates the decrease in s_SHIP expression after electroporation of embryonic stem cells with anti-SHIP shRNA.

BRIEF DESCRIPTION OF SEQUENCES

[0021] Sequence 1 is a mouse s-SHIP sequence of the SHIP isoform.

[0022] Sequence 2 is a mouse s-SHIP sequence of the SHIP isoform.

[0023] Sequence 3 is a human s-SHIP sequence of the SHIP isoform.

[0024] Sequences 4-8 are mouse s-SHIP promoter regions.

[0025] Sequences 9-10 are human S-SHIP promoter regions.

DETAILED DESCRIPTION

[0026] Cell Culture

[0027] The ES cell line, TLI, was obtained from Dr Patricia A. Labosky (University of Pennsylvania, Philadelphia) and was cultured in Dulbecco modified Eagle medium (Gibco-BRL, Grand Island, N.Y.) supplemented with 15% fetal bovine serum (FBS) (Summit Labs, Fort Collins. Colo.), 0.1 mM MEM nonessential amino acids, 2 mM L-glutamine, 50 μ/mL gentamicin, 50μβ-mercaptoethanol (β-ME), and 1000 U/mL leukemia inhibitory factor (LIF) (Gibco-BR.L). The ES cell line, EI0, was derived from TLI. WEHI-23 1, 70Z/3, A20, and BAL7 (B-cell lines) were maintained in RPMI 1640 medium (Mediatech, Herndon, Va.) with 10% FBS, 2 mM L-glutamine, 50 μM β-ME (Gibco-BRL), and antibiotics. Hepa 1-6 and 293T cell lines were maintained in DMEM medium with the same supplements as described for the RPMI medium.

[0028] Reverse Transcription Polymerase Chain Reaction

[0029] Cells were washed once with ice-cold phosphate-buffered saline (PBS) and pelleted. Then cells were lysed, and total RNA was prepared using the RNeasy Mini Kit (Qiagen, Valencia, Calif.) according to the manufacturer"s instructions. Reverse transcription (RT) of total cellular RNA and amplification of cDNA products for specific gene sequences was carried out using Ready-to-Go RT-PCR Beads (Ainersham Pharmacia, Piscataway, N.J.) following the manufacturer"s instructions. In this series of RTpolymerase chain reaction (PCR), 1-μg total RNA and 1-μ each gene-specific primer (10 mM) were placed in a 50 μL reaction volume. In general, PCR conditions were as follows: denaturation for 30 seconds at 94° C., annealing for 30 seconds at a temperature optimal for the primer pair (see below), and a I-minute extension at 72° C. Nested RT-PCR assays to detect mRNAs expressed in sorted cells were carried out as described below.

[0030] Cell Sorts and Nested RT-PCR Assays

[0031] Femurs and tibias from adult (4- to 6-month-old) male C57BL/6 mice were isolated. Adult bone marrow (ABM) was flushed into chilled RPMI 1640 medium. Fetal livers (FLs) (day 14.5 of gestation) were isolated from pregnant female C57BL/6 mice. Cells were teased from the FLs into chilled RPMI. Cell clusters from the ABM and FL preparations were dispersed into single-cell suspensions with transfer pipettes and were passed over 70μ nylon cell strainers. Cell suspensions were pelleted, and red blood cells (RBCs) were lysed for 5 minutes at 4° C. in RBC lysis buffer (163 mM NH. 10 mM KHCO3, 0.13 mM EDTA). After RBC lysis, the cells were washed in PBS, passed over 70 μm strainers, counted, and resuspended in staining media (PBS with 3% FBS and 10 mM HEPES) at 10^7 cells/50 μL. Cells were incubated in Fc Block (Pharmingen, San Diego, 10^7 cells/50 μL staining media and stained with the appropriate panel of fluorochrome-conjugated antimurine antibodies at 1 to 2 μg/10^7 cells/50 μL staining media. Antibodies used were a lineage-fluorescein isothiocyanate panel of Mac-1 (Caltag Laboratories, Burlingame, Calif.), Gr-I, CD3, CD4 (GKI.5), CD8a (53-6.7) B220 (Pharmingen); B220-phycoerythrin (PE), Terl I 9-PE, c-kit-PE, and biotinylated Sca-1 (Pharmingen). Biotinylated Sca-I was revealed with streptavidin-allophycocyanin (APC) (Pharmingen). After staining, the cells were washed and resuspended in staining media (50 μL/10^7 cells) plus propidium iodide (P1) at 1.0μ for dead cell exclusion. HSCs (Sca-1+c-kit+Lin−), B-lymphoid cells (B220+Gr-1−Mac-1−), myeloid cells (Gr-1+Mac-1+B220−), and erythroid cells (Ter119+Lin−) were sorted from ABM and FL using a FACStar flow cytometer (Becton Dickinson, San Jose, Calif.) equipped with an automatic cell deposition unit. ES cells (s-SHIPpositive control), WEHI-231 cells (SHIP-positive control), and Hepa 1-6 cells (negative control) were also prepared in staining media and P1(10^7 cells/50 μL). Fifty viable cells of each population were deposited into separate wells of a 96-well PCR plate containing lysis buffer (0.4% Nonidet P-40, 60 μM dNTP, 25 μM dithiothreitol, 0.5 U/μL RNasin [Promega, Madison, Wis.]) and were lysed for 15 minutes on ice (adapted from Hu et al). RNA was reverse transcribed using multiple primer pairs for β-actin, s-SHIP, and SHIP and 48 U M-MLV reverse transcriptase per reaction in the buffer provided (Gibco-BRL). First-round PCR of35 cycles was performed with addition of 40μ buffered RedTaq DNA polymerase (Sigma, St Louis, Mo.). One-microliter aliquots of the first-round PCR product were further amplified for 35 cycles using fully nested primers for each gene. Aliquots of second-round products were subjected to gel electrophoresis and visualized by ethidium bromide staining. cDNA and genomic cloning To determine the 5" and 3" termini of the s-SHIP cDNA, the inventors performed rapid amplification of cDNA ends (RACE) cloning using the Smart Race cDNA Amplification Kit (Clontech, Palo Alto, Calif.). Touch down PCR amplification conditions were used for 5" and 3" RACE reactions with the following cycling conditions: 30 seconds at 94° C. and 4 minutes at 72° C. for cycles 1 to 5; 30 seconds at 94° C., 30 seconds at 70° C., 4 minutes at 72° C. for cycles 6 to 10; 30. seconds at 94° C., 30 seconds at 68° C., 4 minutes at 72° C. for cycles 11 to 35. Smart Race

products were cloned using the TOPO TA cloning kit (Invitrogen, Carlsbad, Calif.). Sequences derived from the termini of the 5" and 3" RACE clones of s-SHIP were used to design primers that amplify the entire s-SHIP cDNA by RT-PCR. Full-length s-SHIP cDNA5 were obtained by 2 separate RT-PCR amplifications of overlapping fragments that contained either 5" or 3" termini. These 2 fragments were cloned into the pcDNA3 vector (Invitrogen). Genomic sequences were isolated using a mouse GenomeWalker Kit (Clontech). Conditions for touchdown PCR amplification of genomic sequences were as described above. Sequencing of s-SHIP cDNAs and associated genomic clones were carried out at the DNA Sequencing Facility of the University of Pennsylvania Comprehensive Cancer Center.

[0032] Sequence Analysis

[0033] DNA and protein sequences were analyzed with MacVector 7.0 (Oxford Molecular, Madison, Wis.). Sequence alignments and comparisons were performed with the ClustalW algorithm. "The Celera Human Genome Unassembled Fragments database (http://publicstion.celera.com) (Celera Genomics, Rockville, Md.) was accessed to perform BlastN queries of the first 120 nucleotides of human 110-kD signaling inositol polyphosphate 5"-phosphatase (SIP-110) cDNA (GenBank accession number 050040).

[0034] Northern Blot Analysis and Ribonuclease Protection Assay

[0035] PolyA+RNA was prepared as described above. Northern blot analysis of SHIP mRNA expression was as described previously. For ribonuclease protection assay (RPA), the target sequence contained the 44-nucleotide SSR of s-SHIP mRNA and nucleotides 45-247 of s-SHIP (nucleotides 785-987 of SHIP). It was amplified using PCR with primers XHOESHIPI (sense) and ASHIP987 (anti-sense). This PCR product was TA-cloned into pCR2.1-TOPO (Invitrogen) and then subcloned in a reverse orientation downstream of the T3 promoter of the pRRI-amp-18 vector (Ambion, Austin, Tex.). The vector was linearized for s-SHIP/SHIP probe synthesis. Anti-sense RNA probe was synthesized and labeled with 32 using the Maxiscript T7/T3 kit (Ambion) following the manufacturer"s instructions. The probe for mouse GAPDH had 25 times lower specific activity than the s-SHIP/SHIP probe. The 100 nucleotide RNA markers were generated using templates provided by Ambion. RPA assay was performed on 10 μg total RNA for each sample and 20,000 cpm for each probe using the RPAIII kit (Ambion) according to the manufacturer"s instructions. RPA products were visualized by running Quick Point precast gels (6% polyacrylamide denaturing gel; Novex, San Diego, Calif.) and then by autoradiography.

[0036] Transfections

[0037] SHIP cDNA was kindly provided by Dr Larry Rohrschneider. SHIP and s-SHIP cDNA5 were cloned separately into the pcDNA4/HisMaxC expression vector (Invitrogen). These pcDNA4/SHIP and pcDNA4/s-SHIP plasmids were transfected into 293T kidney cells using the FuGENE 6 transfection reagent (Roche Molecular Biochemicals, Indianapolis, Ind.) according to the manufacturer"s instructions.

[0038] Antibodies

[0039] Purified mouse antiSHIP monoclonal antibody, P2C6, was obtained from Drs David Lucas and Larry Rohrschneider. It was used for immunoprecipitation at a concentration of 4 μl/1 mg total protein and for immunoblotting at a dilution of 1:1000. Rabbit antiGrb2 polyclonal antibody (sc-255; Santa Cruz Biotechnology, Santa Cruz, Calif.) was used for immunoprecipitation at a concentration of 2 jig/I mg total protein and for immunoblotting at a dilution of 1:500. Rabbit antiShc polyclonal antibody (06-203; Upstate Biotechnology, Lake Placid, N.Y.) was used for immunoblotting at a concentration of I μg/mL. Rabbit antimSosI polyclonal antibody (06-246; Upstate Biotechnology) was used for immunoblotting at a concentration of I μg/mL. Mouse antiphosphotyrosine monoclonal antibody (4G1 0; 05-321; Upstate Biotechnology) was used for immunoblotting at a concentration of 1 μg/mL.

[0040] Immunoprecipitations and Immunoblots

[0041] Approximately 10^7 cells were washed once with ice-cold PBS and pelleted. Cell pellets were then lysed in 0.5 to 1.0 mL modified RIPA buffer (1% Nonidet P-40, 50 mM Tris-HCl [pH 7.4], 0.25% Na-deoxycholate, 150 mM NaCl, 1 mM EDTA, 1 mM Na3V04, 1 mM phenylmethylsulfonyl fluoride, 10 μg/mL leupeptin, 10 μg/mL pepstatin, 10 μg/mL aprotinin). Lysates were rocked for 30 minutes at 4° C., and cellular debris was removed by centrifugation at 14,000 g for 15 minutes. Total protein concentration of each lysate was determined by spectrophotometry using the BCA Protein Assay Kit (Pierce Chemical, Rockford, Ill.). Lysates were stored at 80° C. Whole cell lysates were subsequently mixed with NUPAGE 4× lithium dodecyl sulfate (LDS) sample buffer and lox sample reducing agent, heated for 10 minutes at 70° C., and loaded Onto NuPAGE 10% or 4% to 12% Bis-Tria 1.0 mm gels (Invitrogen). For immunoprecipitations, equal concentrations of total protein (either 500 μg in 500 μL or 1 mg in 1 mL lysis buffer) were used for each individual experiment. Samples were precleared with 0.25 μg of the appropriate control IgG (normal mouse or rabbit IgG; Santa Cruz Biotechnology) together with 50 μL appropriate agarose bead conjugate (Protein G-Agarose, Fast Flow [immunoprecipitation (I.P.)]; Protein A-Agarose, Fast Flow [1.P.]; Upstate Biotechnology) for 1 hour at 4° C. Precleared samples were transferred to fresh tubes. Four microliters P2C6 antiSHIP monoclonal antibody or 2 μg antiGrb2 polyclonal antibody were added per milligram total protein and were incubated overnight with rocking at 4° C. Fifty microliters appropriate agarose bead conjugate was then added and rocked for 2 hours at 4° C. Agarose bead conjugates were pelleted (14000 g, 5 seconds), washed 3 times with cold PBS, and boiled in NuPAGE 4× LDS sample buffer with IOX sample reducing agent for 5 minutes at 100° C. Beads were pelleted and equal volumes of the immunoprecipitate supernatant were loaded onto NuPAGE 10% or 4% to 12% Bis-Tris gels. Proteins were separated for 50 minutes at 200 V using MOPS sodium dodecyl sulfate running buffer in an XCell II Mini-Cell unit (Protein molecular weights were compared using Novex MultiMark protein standards. Separated proteins were transferred to polyvinylidene difluoride (Bio-Rad Laboratories, Hercules, Calif.) or nitrocellulose [blots] (Millipore, Bedford, Mass.) membranes for 75 minutes at 30 V using the XCell II Blot Module. Immunoblotting was carried out using the enhanced chemiluminescence Western blotting analysis system following the manufacturer"s instructions (Amersham Pharntacia).

[0042] Cell Stimulation

[0043] ES-TLI cells were split into 4 different 100-mm TC plates and grown overnight at 37° C. in ES media supplemented with 1000 U/mL LIF to approximate 80% confluence. LIF-supplemented media was removed, cells were washed twice with PBS, media without LIF was added, and cells were incubated for 5 hours. Cells were washed once with PBS and twice with Hanks balanced salt solution (HBSS; Mediatech). Then they were pre incubated in HBSS at 37° C. for 10 minutes. Cells were stimulated by the addition of HBSS containing 2000 U/ml. LIF and by incubation at 37° C. for either 2, 5, or 10 minutes. A control ES plate (0 minute) containing HBSS without LIF was incubated at 37° C. in parallel for 10 minutes. Stimulations were stopped by the removal of buffer and the addition of 10 μL ice-cold PBS/I mM Na PBSINa was removed, and 10 mL ice-cold modified RIPA buffer was added immediately. Cells were scraped, and cell lysates were processed as described above. A20 cells were grown in RPMI and were washed once with PBS and twice with HBSS. Then 2×10^7 cells were placed in separate 15-mL conicals and were pre-incubated in HBSS at 37° C. for 10 minutes. Cells were spun down, and HBSS was removed. After that, cells were stimulated with I mL HBSS containing 20 μg/mL goat antimouse IgG (Southern Biotechnology Associates, Birmingham, Ala.) and were incubated at 37° C. for 5 minutes. Control A20 cells (0 minute) containing HESS without antimouse IgG were incubated in parallel. Stimulations were stopped by placing the conicals on ice and adding 2 mL ice-cold PBS/Na3V04 Cells were pelleted, supernatant was removed, and 1 mL ice-cold modified RIPA buffer was added. Total protein (1.0 mg in I ml.) of each preparation was used for subsequent immunoprecipitation experiments.

[0044] Membrane and Cytosol Fractionation

[0045] Two confluent 150 mm×25 mm plates of ES-TLI cells cultured in LIF were washed twice with chilled PBS, then collected with a chilled cell scraper. Cells were pelleted by centrifugation at 300 g and resuspended in 2 ml. chilled sonication buffer (20 mM Tris-HCl, pH 8, 137 mM NaCl, 10% glycerol, 2 mM EDTA, 1 mM NaVO4, 1 mM phenylmethylsulfonyl fluoride, 10 μg/mL leupeptin, 10 μg/mL pepstatin, and 10 μg/mL aprotinin). This suspension was sonicated on ice for 20 seconds at 20% full output using a Fisher Model 60 Sonic Dismembrator equipped with a one-eighth inch diameter tip (Fisher Scientific, Pittsburgh, Pa.). Trypan blue dye exclusion and examination by phase-contrast microscopy con firmed that no intact cells remained. The suspension was centrifuged at 500 g for 5 minutes at 4° C. to remove the nuclear fraction. Postnuclear supernatant was centrifuged in Beckman 15×31 mm polycarbonate tubes at 100 000 g for 20 minutes at 4° C. in a Beckman TL-I00 centrifuge equipped with a TLA-100.3 rotor. The supernatant cytosol fraction was removed, and Triton X-100 was added to a final concentration of 1%. The membrane pellet was rinsed once with chilled sonication buffer and then resuspended in chilled sonication buffer plus 1% Triton X-100. Resuspension was achieved by needle probe sonication on ice for 30 seconds at 20% full output, and the resuspended membrane fraction was allowed to solubilize at 4° C. for 45 minutes with frequent gentle vortexing. Insoluble material was removed by centrifugation at 10 000 g for 15 minutes at 4° C. ES-TLI cells from a third 150 mm plate were collected in parallel with the cells collected for fractionation in order to prepare an unfractionated whole cell lysate for comparison purposes. These cells were lysed in 1 mL of chilled sonication buffer/1% Triton X-100, rocked for 45 minutes at 4° C., and centrifuged at 10 000 g for 15 minutes at 4° C. to remove cellular debris. Total protein concentrations of the whole cell lysate, cytosol, and membrane fractions were determined by spectrophotometry using the BCA Protein Assay Kit. Whole cell lysate, cytosol, and membrane fractions were then diluted in sonication buffer/1% Triton X-100 to a final concentration of 1 mg/mL. Fractions were stored at −80° C. and 1 mg total protein (in 1 mL) of each preparation was used for subsequent immunoprecipitation experiments.

[0046] FIG. 1. illustrates how ES cells express e SHIP mRNA species different from that expressed in mature hematopoletic cells. (A) RT-PCR analysis of SHIP expression in ES cells and lineage-committed hematopoiletic cell lines. All primers used in the RT-PCR assays were designed to amplify regions of SHIP mRNA encoded by separate axons; hence, the expected amplification products must arise from amplification of cDNA, not from contaminating genomic DNA. The following cell types were analyzed: B-lymphocyte cell lines 70Z/3 and WEHI-231, hepatoma cell line Hepa 1-6 (negative control), and ES cell lines TL1 and E10. Amplification of β-actin was included 888 control for the RNA isolation and cDNA synthesis steps. PCR products were resolved on a 1% agarose gel and stained with ethidium bromide. (B) RACE cloning of s-SHIP mRNA. PCR products representing the 5" or 3" termini of the s-SHIP mRNA expressed in ES cells were generated by 5" and 3" RACE, respectively. For 3" RACE cloning of SHIP mRNA species in 70Z13 and ES cells, the primers SHIP2766 (sense; lane 1) or SHIP1970 (sense; lane 2) were used. (C) Schematic depiction of the structure of the s-SHIP and SHIP cDNAs. Nucleotide numbering refers to GenBank accession numbers AF184912 and U52044, respectively. Functional do mains and sequence motifs encoded In the s-SHIP and SHIP mRNAs are s-SHIP Region (SSR), Src-homology 2 domain (SH2), proline-rich motifs (PR), and NPXY and YIGM motifs. The internal M83 nucleotide deletion is illustrated. Initial methionine (M) and terminal giutamine (Q) amino acids for each mRNA are indicated, yielding proteins of 928 aa (s-SHIP) and 1191 aa (SHIP). Relative location and orientation of the primers used in the RT-PCR analysis or RACE cloning are indicated below the SHIP cONA. Numbers below the primers (arrows) represent the 5" nucieotide in the primer based on its positioni the SHIP cDNA sequence.

[0047] Results Identification and Characterization of s-SHIP mRNA

[0048] Previous analysis of SHIP expression indicated that its expression is restricted to cells of the hematopoietic system. However, while evaluating other cell types for expression of the SHIP gene, it was found that ES cells express SHIP mRNA. The inventors detected the presence of SHIP mRNA in polyA+RNA isolated from ES cells (TL1) using several different RT-PCR assays that amplify distinct regions of SHIP mRNA (FIG. 1A,C). However, primers that amplify the 5" portion of SHIP mRNA that encodes its SH2 domain failed to amplify the SHIP mRNA species expressed in ES cells, but they yielded the expected product when amplifying mRNA from B-lymphocyte cell lines (70Z/3, WEHI-23I). Furthermore, we found that an ES cell line

(E10) with both SHIP alleles mutated by the insertion of a GFP transgene into exon 1 (J. Wang et al, unpublished data, September 1997) retains expression of SHIP mRNA as detected by several independent RT-PCR assays for SHIP expression (FIG.1A,C). These results indicate that ES cells express a SHIP transcript, which the inventors designate s-SHIP, that differs at its 5" end from the SHIP mRNA previously described in differentiated hematopoietic cells.

[0049] To confirm the presence of a SHIP mRNA species with a different 5" end in ES cells and to determine its sequence, the inventors performed 5" Smart Race cDNA cloning using antisense primers complementary to the SHIP cDNA sequence. The inventors used primers from regions of SHIP that analysis in FIG. 1A indicated were also present in s-SHIP mRNA. Two separate 5" RACE reactions with primers ASHIPI998 and ASHIPI098 yielded a single product of either 1,3 kb (FIG. 1B) or 0.4 kb (data not shown), respectively. Sequence analysis of these 5" RACE products showed that the SHIP mRNA present in ES cells begins with a 44-nucleotide region not previously found in any murine SHIP cDNA identified to date (FIG. 2). The inventors designate this novel 44-nucleotide region the stem-SHIP region (SSR). The complete sequence of these 5" RACE products showed that the SSR forms the 5" end of the s-SHIP mRNA and is fused with the previously identified murine SHIP cDNA sequence beginning at nucleotide 785 and is identical up to nucleotide 1998 (GenBank accession number U52044).

[0050] To determine the sequence of the remainder of the s-SHIP transcript present in ES cells, the inventors performed 2 separate 3" RACE reactions (FIG. 1B) with sense strand specific primers (SHIPI97O and SH1P2766). Cloning and sequencing of these 3" RACE products indicated that s-SHIP mRNA is identical to SHIP mRNA from nucleotide 1970 through the end of the SHIP cDNA. To further confirm the sequence of the s-SHIP cDNA, the inventors obtained full-length s-SHIP cDNA by RT-PCR. Turning to FIG. 2, sequence analysis of the full-length s-SHIP cDNA confirmed that s-SHIP mRNA lacks the SH2 domain but has the 44-nucleotide SSR fused to nucleotide 785 of SHIP. However, like its hematopoietic counter part, s-SHIP mRNA encodes an inositol 5"-phosphatase domain and several protein interaction motifs, including 2 NPXY motifs, a YIGM motif, and 4 proline-rich motifs (FIGS. 1C, 2). As Lucas and Rohrschneider found for SHIP mRNA in hematopoietic cells, s-SHIP mRNA is alternatively spliced to generate a form that lacks a 183-nucleotide region (nucleotides 2129-2311 of s-SHIP [accession number AF184912] corresponding to nucleotides 2869-3051 of SHIP). Forms of s-SHIP mRNA that contain or lack this 183-nucleotide region are present in ES cells, indicated by the RT-PCR reaction, with primers that span this expression arises from an internal promoter in the SHIP gene region (1970+3164 in FIG. 1A). Sequence analysis of these products confirmed that the alternative splice event that results in the Δ83 s-SHIP mRNA (accession number AF1 84913) is identical to that described by Lucas and Rohrschneider for SHIP.

[0051] FIG. 2 indicates the nucleotide sequence of s-SHIP cDNA and the predicted amino acid sequence of its major open reading frame (ORF). The first 784 nucleotides of the SHIP cDNA are provided for comparison above the bold arrow, s-SHIP cDNA sequence is indicated below the bold arrow, starting with the numeral 1 and continuing through nucleotide 2946. Remaining a-SHIP cDNA sequence (nucleotides 2947-4125) is not shown because of size constraints, but it is identical to nucleotides 3687 to 4865 of the SHIP cDNA (data not shown). The number in parentheses (785) at nucleotide 45 of the s-SHIP cDNA indicates the nucleotide in the SHIP cDNA, where identity between the s-SHIP and SHIP cDNAs begins. ATG initiator codons for the SHIP and s-SHIP major ORFs are indicated in bold and underlined, and the termination codon shared by both isoforms is indicated by an asterisk. SH2 (dotted box), SSR (solid box), and Inositol 5 (dashed box) sequences are shown. The nucleotide sequence that encodes the Δ183 nucleotide deletion is underlined. NPXY and proilne-rich motifs are shaded black and gray, respectively.

[0052] FIG. 3 shows the organization of the first exon of s-SHIP. (A) Genomic sequence of the first exon of s-SHIP and adjacent intronic sequence. Uppercase letters represent the nucleotides in the first axon of s-SHIP, and lowercase letters represent the intronic sequence immediately flanking this axon. The 44 nucleotides enclosed in the shaded box indicate the SSR, and the 88 nucleotides in the clear box represent those found in both the s-SHIP and the 145-kd SHIP cDNAs, Numbers 785 and 872 indicate the position of each corresponding nucleotide in the murine 145-kd SHIP cDNA sequence (GenBanic accession number U52044). (B) Schematic representation of the orientation of the predicted promoter regions and first axons of SHIP and s-SHIP relative to each other in the SHIP locus. Arrows indicate the transcriptional start points. The s-SHIP first axon consists of the 44-nucleotide SSR and the adjacent 88-nucleotide SHIP axon 6. Nucleotide numbering refers to the 145-kd SHIP cONA sequence (accession number U52044).

[0053] Genomic Location of the s-SHIP First Exon Indicates its Expression Arises From an Internal Promoter in the SHIP Gene

[0054] To determine whether the 44-nucleotide SSR at the 5" end of the s-SHIP mRNA represents an independent exon or is a part of an existing exon in SHIP, the inventors isolated and sequenced the genomic DNA that spans this region. Sequence analysis of the genomic DNA revealed that the 44-nucleotide SSR is directly adjacent to a sequence that serves as exon 6 (nucleotides 785-872) in the SHIP isoform expressed in lineage-committed hematopoletic cells (FIG. 3). Thus, the 44-nucleotide SSR is not a discrete exon but is part of a larger 132-nucleotide region that serves as exon 1 in s-SHIP.

[0055] Furthermore, because the 132-nucleotide s-SHIP exon 1 is located at an internal site in the SHIP gene, s-SHIP expression must arise from an internal promoter that is 3" to the SH2-encoding exons and 5" to the exons that encode the inositol 5"-phosphatase domain (FIG. 3B). The location of s-SHIP exon 1 requires that its transcription initiate internally in the SHIP genomic locus in a region that serves as an intron for the SHIP mRNA expressed in differentiated hematopoietic cells.

[0056] Embryonic and Hematopoietic Stem Cells Express s-SHIP mRNA

[0057] RT-PCR analysis indicated that s-SHIP is the only SHIP transcript expressed in ES cells (FIG. 1). However, to determine whether s-SHIP is also expressed in the hematopoietic system along with its SH2-encoding counterpart, the

inventors analyzed total polyA+RNA isolated from ES cells and lineage-committed hematopoietic cell lines by Northern blot. This analysis showed that B-lymphocyte cell lines (70Z/3, A20, BAL17) express only the approximately 5 kb SHIP mRNA, whereas the ES cell line TLI expresses only the smaller, approximately 4.3 kb s-SHIP mRNA (FIG. **4**A). In addition, an RT-PCR assay that is specific for s-SHIP expression showed that ES cells (TL1, E10) express s-SHIP, whereas B-lymphocyte cell lines (70Z/3, WEHI-23 I) do not (FIG. **4**B). These results demonstrate that s-SHIP expression is silenced in differentiated hematopoietic cells.

[**0058**] FIG. **4**. Analysis of s-SHIP and SHIP mRNA expression in ES cells and hematopoiesis. (A) Northern Blot analysis of SHIP mRNA species expressed by ES cells (TL1) and lineage-committed hematopoietic cell lines (70ZJ3, A20, BAL17). A full-length SHIP cDNA clone was used to probe the filter. After initial hybridization with the SHIP probe, the filter was stripped and reprobed for β-actin to confirm that comparable amounts of RNA were loaded in each lane. (B) RT-PCR analysis of s-SHIP expression in ES cells (TL 1, E10) and lineage-committed hematopoietic cell lines (70Z/3, WEHI-231). The primer pair ESHIP23 and ASHIPIO98 selectively amplifies s-SHIP mRNA and not SHIP mRNA. Analysis of the hepatoma cell line, Hepa 1-6, serves as a negative control for SHIP. (C) RPA analysis of s-SHIP and SHIP expression in ES cells and hematopoietic development. After annealing and RNase digestion, the s-SHIP/SHIP probe is protected for 247 nucleotides by s-SHIP mRNA and for 203 nucleotides by SHIP mRNA. Thus, a single probe is used to detect the relative abundance of the s-SHIP and SHIP mRNAs. Each RNA sample was incubated with a GAPDH probe as an internal control. Analysis of NIH3T3 cell RNA Is provided as a negative control for both SHIP and s-SHIP mRNA expression.

[**0059**] To further assess the relative ratio of s-SHIP to SHIP mRNA expressed in different cell types and tissues, the inventors developed an RPA that simultaneously detects both s-SHIP and SHIP mRNAs (FIG. **4**C). RPA analysis indicates that s-SHIP is expressed to the exclusion of SHIP in ES cells and that SHIP mRNA is the predominant form in adult spleen. However, in FL and ABM tissues that contain significant numbers of pluripotent HSC the inventors find coexpression of s-SHIP and SHIP mRNA. Interestingly, FL has significantly more s-SHIP than SHIP mRNA, whereas ABM has slightly less s-SHIP than SHIP mRNA. These results suggest that the relative abundance of s-SHIP mRNA in a tissue may correlate to the relative abundance of HSC activity in the tissue. For instance, FL is substantially enriched for primitive HSC activity relative to ABM, whereas the spleen is a poor source of HSC activity.

[**0060**] Focusing now on FIG. **5**, HSCs express s-SHIP mRNA. HSCs and lineage-committed cells were sorted from ASM or day 14.5 FL and analyzed by nested RT-PCR assay for the expression of s-SHIP, SHIP, and β-actin mRNA. In both ABM and FL, s-SHIP mRNA was detected In HSCs (Sca-1+c-kit+Lin−) but not in the myeloid (Gr-1+/MAC-1+), B-lymphoid (B220+), or erythroid (Ter119+) lineages. Hepa 1-6 cells were sorted as the negative control for both s-SHIP and SHIP mRNA expression, and ES-TL1 and WEHI-231 cells were sorted as positive controls for s-SHIP and SHIP mRNA expression, respectively.

[**0061**] To directly assess the possibility that s-SHIP is expressed in HSC, the inventors developed a nested RT-PCR procedure to detect the expression of s-SHIP and SHIP mRNAs. To define the s-SHIP expression pattern in vivo, the inventors sorted HSC (Sca-1+cKit+Lin−) as well as cells of the B-lymphoid (B220+), myeloid (Gr-1+Mac-1), and erythroid (Ter119 lineages from day 14.5 FL or ABM. Fifty cells of each population were deposited into single wells of a 96-well PCR plate containing lysis buffer and dNTPs. RNA was reverse transcribed by adding multiple primer pairs for s-SHIP, SHIP, and β-actin together with M-MLV reverse transcriptase. Nested RT-PCR reactions were performed (see "Materials and methods"). Representative RT-PCR results from multiple independent sorts of ABM and FL are shown in FIG. **5**. The inventors detected s-SHIP mRNA in Sca-1+ cKit+Lin− HSC from both ABM and FL, but not in cells of the B-lymphoid, myeloid, or erythroid lineages. RT-PCR analysis of 50 sorted ES-TL1, WEHI-23 1, and Hepa 1-6 cells served as s-SHIP, SHIP, and negative controls. These results provide further support for the hypothesis that s-SHIP expression is restricted to primitive stem cell populations. The inventors also detected SHIP expression in HSC; thus, it remains to be determined whether the 2 isoforms are coexpressed in all HSC or whether they are discordantly expressed in distinct subsets of HSC.

[**0062**] Embryonic Stem Cells Express a Lower Molecular Weight Isoform of SHIP, Consistent with the Predicted Open-Reading Frame in the s-SHIP cDNA

[**0063**] FIG. **6** illustrates how ES cells express the 8-SHIP protein isoform that associates with the Grb2 adapter protein. (A) Immunoprecipitation and immunoblot detection of s-SHIP in ES cell lysates. Lysate from ES-TL1 cells cultured in LIF was immunoprecipitated with the P2C6 anti-SHIP monoclonal antibody, separated on gels, transferred to membranes, and probed with P2C6, revealing 104-kd and 97-kd proteins (lane 5). No tyrosine phosphorylation of these proteins was detected when they were probed with the 4G10 anti-phosphotyrosine antibody. For comparison, lysates from 293T cells transfected with SHIP cDNA (lane 1) and s-SHIP cDNA (lane 2) were included in the blots. To further assess the tyrosine phosphorylation status of s-SHIP, timed LIF stimulation studies were performed. ES-TL1 cells incubated for 5 hours without LIF were stimulated with 2000 U/mL LIF for 0, 2, 5, or 10 minutes and were rapidly lysed. Equal amounts of total protein were immunoprecipitated with the P2C6 antibody and probed separately with the P2C6 and 4G10 antibodies (lanes 6-9). No tyrosine phosphorylation of s-SHIP was detected at any time point with the 4G10 antibody. For comparison, A20 8-lymphoid cells were stimulated with antiIgG antibody for 0 or 5 minutes, lysed, immunoprecipitated with P2C6, and probed with P2C6 and 4G10 (lanes 3, 4), showing prominent tyrosine phosphorylation of SHIP at 5 minutes. Molecular mass standards are indicated on the right. (B) s-SHIP associates with Grb2 but not Shc in ES cells. ES-TL1 cell lysates were prepared and immunoprecipitated with the P2C8 anti-SHIP monoclonal antibody. Resolved immunoprecipitates were then blotted with antibodies specific for SHIP, Grb2, mSosI, or Shc (lane 1). Whole cell lysates from ES-TL1 cells were also Included to confirm the expression of these proteins in ES cells (lane 2). (C) Grb2 associates with s-SHIP in ES cells. ES-TLI cell lysate was prepared and immunoprecipitated with an antiGrb2 polyclonal antibody. Resolved immunoprecipitate was then blotted with the P2C6 antiSHIP monoclonal antibody (lane 3). For comparison, whole cell lysatea from WEHI-231 cells (lane 1) and 293T cells trans-

fected with s-SHIP cDNA (lane 2) were included. (D) Subcellular localization of s-SHIP protein in ES cells. Whole cell lysate, cytosol, and membrane fractions from ES-TLI cells were prepared as described. One milligram total protein from each fraction was immunoprecipitated with the P2C6 antiSHIP monoclonal antibody, and equal volumes of immunoprecipitate from each preparation were separated on gels, transferred, and blotted with the P2C6 antiSHIP monoclonal antibody (lanes 2-4). For comparison, whole cell lysate from 293T cells transfected with s-SHIP cDNA was induded (lane 1).The major predicted open-reading frame (ORF) in s-SHIP mRNA begins with a Kozak consensus ATO that is 3" to the 44-nucleotide SSR (FIG. **2**). This ATG and its associated ORF of 928 amino acids (an) is predicted to yield a translated product of 104 kd. Immunoprecipitation and blotting with the antiSHIP monoclonal antibody P2C6, a kind gift of Drs. David Lucas and Larry Rohrschneider, revealed a SHIP protein in ES cell lysates with an apparent molecular weight (MW) of approximately 104 kd, consistent with the predicted MW (FIG. **6**A). The P2C6 antibody reacts with a region of SHIP from aa-866 to aa-I020 that, based on the cDNA sequence, should also be present in the s-SHIP isoform. This smaller s-SHIP isoform is not detected in the B-lymphoid cell lines A20 and WEHI-23 1 (FIG. **6**A-C). In addition, the endoge nous s-SHIP protein immunoprecipitated from ES cells comigrated with the translated product of the s-SHIP cDNA when expressed after transfection of a non-ES cell line, 293T (FIG. **6**A). Thus, this approximately 104-kd species represents the s-SHIP protein translated from the s-SHIP mRNA in ES cells, and not the COOH-terminal truncation product of SHIP with a similar MW identified by Damen et al. Furthermore, the inventors found that s-SHIP appeared as a doublet of approximately 104/97 kd in ES cells and in transfected 2931 cells (FIG. **6**A-D). This doublet presumably represents the translation products of 2 different s-SHIP mRNAs (928-aa and 867-an [MW, 97.7 kd], respectively) generated by the alternative 183 nucleotide splice reaction identified in hematopoietic cells that also takes place in ES cells (FIG. **1**A).

[**0064**] s-SHIP Forms a Complex with Grb2 and is Present Constitutively at the Membrane in Embryonic Stem Cells

[**0065**] The SHIP isoform expressed in mature hematopoietic cells is tyrosine phosphorylated on stimulation by growth factor, immune complexes, or BCR engagement. Phosphorylated SHIP is found associated with the adapter protein Shc, which facilitates SHIP recruitment to the plasma membrane, where it can then act on phosphatidylinositol substrates such as P1P3. However, the inventors found that s-SHIP is not tyrosine phosphorylated in either ES cells grown in LIF at steady state or ES cells deprived of LIF for 5 hours and subsequently stimulated with 2× LIF (FIG. **6**A). Furthermore, s-SHIP in ES cells grown in LIF did not associate with Shc (FIG. **6**B). Instead, immunoprecipitation of s-SHIP by the P2C6 anti-SHIP antibody coimmunoprecipitated the adapter protein Grb2. Similarly, immunoprecipitation with a poly clonal antibody specific for Grb2 coimmunoprecipitated s-SHIP (FIG. **6**C). These results demonstrate an in vivo association between s-SHIP and the major adapter protein Grb2 in totipotent stem cells that does not require tyrosine phosphorylation of s-SHIP. s-SHIP does not appear to be associated with either Shc or mSosI in ES cells, suggesting that it may have different preferences for partnering than the SHIP isoform (FIG. **6**B). Immunoblotting of ES cell lysates confirmed that Shc and mSosI are expressed in ES cells. To further assess the potential for s-SHIP to play a signaling role in primitive stem cells, the inventors prepared cytosolic and membrane fractions of ES cells. Immunoprecipitation of s-SHIP from these subcellular fractions (FIG. **6**D) demonstrates the presence of s-SHIP protein in the membrane fraction of ES cells. This membrane localization of s-SHIP and its association with a major adapter protein indicate a role for s-SHIP in signaling pathways active in primitive stem cells,s-SHIP demonstrates significant homology with the human 11O-kd signaling inositol polyphosphate 5"-phosphatase

[**0066**] Clustal W Sequence Analysis revealed that s-SHIP and the human SHIP isoform SIP-110 (GenBank accession number U50040), described by Kavanaugh et al," share 78% nucleotide identity. Of note, Kavanaugh et al predicted a 976-an protein (calculated MW, 109 kd) based on an ATG initiation codon at position 19 of GenBank accession number U50040. This ATG initiation site lacks strong Kozak consensus features. However, a second ATG initiation codon at position 160 displays a strong Kozak consensus sequence of CAnCATGG and would predict a translated protein of 929 aa (calculated MW, 104 kd). This shorter ORF of SIP-I10 shares 88% amino acid identity with the s-SHIP ORF. Nucleotides 43-2786 of human SIP-110 eDNA are identical to nucleotides 787-3537 of human I45-kd SHIP eDNA (GenBank accession number U50041). Reminiscent of s-SHIP nucleotides 1-42 of SIP-110 are not found in the 145-kd SHIP eDNA. Kavanaugh et aP ptup that SIP-110 is a splice variant of the 145-kd SHIP. However, the inventors hypothesized that SIP-110 may represent the human homologue of s-SHIP and may arise by alternative promoter use. To confirm this, the inventors conducted a BlastN query of the first 120 nucleotides of SIP-I10 in the Celera Human Genome-Unassembled Fragments database. The inventors found 2 unassembled and uncharacterized genomic fragments (Celera accession numbers GA_x4N24A5JORM: I 0.262 and GA_x4N24A6F9UD: 1.508) that span the first exon of SIP-110. These genomic fragments revealed that the first 42 nucleotides of SIP-110 are found in the SHIP intronic sequence and are followed directly by an 88-nucleotide sequence representing an internal SHIP exon corresponding to nucleotides 787-874 of 145-kd SHIP (FIG. **7**A). Thus, analogous to s-SHIP, the first exon of SIP-110 is comprised of a 42-nucleotide SSR-like region unique to SIP-110 and an adjacent 88-nucleotide exon shared by both SIP-110 and I45-kd SHIP. The first exons of SIP-110 and s-SHIP show 82% nucleotide identity (FIG. **7**B). These results establish that SIP-110 is the human homologue of s-SHIP.

[**0067**] Discussion

[**0068**] The SHIP protein is a key signaling component that participates in controlling the responses of several different hematopoietic cell types in the adult mouse, 1-3, 13, 16,25. Results provide the first evidence that a SHIP isoform plays a specific role in the biologic composition of stem cell populations, Four lines of evidence support this hypothesis: (1) Totipotent ES cells express the s-SHIP isoform exclusively, (2) s-SHIP partners preferentially with Grb2 in ES cells, (3) s-SHIP is present constitutively in the membrane fraction of ES cells, and (4) s-SHIP expression within the hematopoietic compartment is restricted to fetal and adult hematopoietic stem cells. Results also suggest the evolution

of a transcription control mechanism that promotes the expression of s-SHIP in Stem cell populations.

[0069] The striking discordance between stem cells and mature hematopoietic cells in the expression of s-SHIP mRNA suggests a distinct signaling role for this SHIP isoform in stem cells. The SH2 domain of SHIP allows it to participate in signal transduction pathways in mature hematopoietic cells that involve partnering with Shc or binding to ITM motifs of receptors. The lack of an SH2 domain in s-SHIP may change its binding preferences and, therefore, the pathways with which it interacts. Consistent with this hypothesis, the inventors detected no association of s-SHIP with Shc in ES cells at steady state or after LIF stimulation. The inventors did find an association of s-SHIP with Grb2 in ES cells in the absence of tyrosine phosphorylation. Several groups have shown that SHIP can associate with Grb2 in stimulated hematopoietic cells through an interaction of the SH3 domain of Grb2 and the proline-rich motifs of SHIP. s-SHIP contains these same proline-rich motifs. In addition to SH3 domains, Grb2 contains an SH2 domain that enables its binding to other signal transduction components or receptors at the cell membrane. Grb2, through its SH2 domain, could recruit s-SHIP to tyrosine-phosphorylated receptors that are important in the biologic makeup of ES cells and HSCs. Thus, the absence of an SH2 domain may not preclude s-SHIP from acting at the cell membrane, but it may alter how it is recruited to the cell membrane and which signaling pathways it impacts.

[0070] Membrane recruitment of s-SHIP would enable its inositol 5"-phosphatase domain to access phosphatidylinositols such as PIP3 and to influence proliferation, differentiation, or apoptosis of stem cell populations. Because the association of s-SHIP with Grb2 does not appear to require tyrosine phosphorylation, this complex is likely to be present in quiescent stem cell populations. This preformed complex could rapidly associate with receptors that become tyrosine phosphorylated after basal level growth factor stimulation, enabling s-SHIP to prevent the accumulation of PIP3 to significant levels. In this way, s-SHIP could participate in the process of maintaining a stem cell population in a quiescent state. Furthermore, analogous to the proposal that SHIP interferes with the mSosI/Shc/Grb2 complex of the MAPK pathway in mature cells, one can envision a competition in stem cells between s-SHIP and mSosI for Grb2. The outcome of this competition may influence the decision to remain quiescent or to activate the Ras/MAPK pathway that triggers proliferation and differentiation.

[0071] FIG. **7** depicts the organization of the first axon of SIP-110, the human homolog of s-SHIP. (A) Genomic sequence of the SIP-110 first exon and adjacent intronic sequence as compiled from the Celera Human Genome-Unassembled Fragments database (Celera accession numbers GA_x4N24A5.JORM: 1 0.262 and GA_x4N24A6F9UD:1.508). Uppercase letters represent the nucleotides in the SIP-110 first exon, and lowercase letters represent the intronic sequence immediately flanking this exon. The 42 nucleotides enclosed in the shaded box indicate the SSR-like region, and the 88 nucleotides in the clear box represent those nucleotides found in both the SIP-110 and the human 145-kd SHIP cDNAs. Based on the genomic fragment sequences, position 1 is listed as "T" rather than as the "C" assigned in the SIP-110 cDNA (GenBsnk accession number U50040). Numbers 787 and 874 indicate the position of the corresponding nucleotide in the human 145-kd SHIP cDNA sequence (Gen Bank accession number U50041). (B) Clustal W alignment of the first exon sequences of human SIP-110 and murine s-SHIP. Matching nucleotides are shaded gray. Overall, the first axons of SIP-110 and s-SHIP show 82% nucleotide identity.

[0072] FIG. **8** demonstrates the decrease in s-SHIP expression after electroporation of embryonic stem cells with anti-SHIP shRNA. The electroporation conditions where as follows: 10 μg of protein were loaded into a 4-12% Bis-Tris gel (Invitrogen), 250V, 500 μF, 15 μg of plasmid, and sample was left to rest on ice, in cold PBS, for 30 minutes before being placed in a warm media.

[0073] The identification of a distinct SHIP isoform expressed from an internal site within the SHIP gene suggests the possibility that the recently reported SHIP-null mice may not be absolute nulls for expression from the SHIP locus. 1-3,25,48-50 The mutation strategy used by both groups involved the insertional mutation of the first exon that encodes a portion of the SH2 domain at the amino terminus of the SHIP isoform. This insertional mutation strategy clearly leads to the ablation of the SHIP isoform in mature hematopoietic cells. However, one would not predict that expression of the s-SHIP isoform in the embryo or in HSCs would be affected given that the s-SHIP first exon consists of the terminal 44 nucleotides of intron V, together with exon 6 of SHIP. This region is approximately 27 kb downstream of the 145-kd SHIP promoter. Nevertheless, ablation of SHIP expression by this strategy may lead to the dysregulation of s-SHIP expression by an unknown mechanism. In preliminary experiments, the inventors were unable to detect s-SHIP protein expression from total bone marrow of adult C57BL/6 mice in which the first exon of SHIP was insertionally mutated (data not shown). If it can be determined that s-SHIP expression during embryogenesis and hematopoietic development is intact in these SHIP-null strains, one might predict a novel phenotype in mice designed to be null for both s-SHIP and SHIP.

[0074] Kavanaugh et al" cloned and characterized the human SHIP isoform, SIP-110 that lacks an SH2 domain. They cloned SIP-110 cDNA (GenBank accession number U50040) from a human placenta cDNA expression library based on its affinity for a Grb2 SH3 domain in the absence of tyrosine phosphorylation. The overall structure of SIP-110 was similar to s-SHIP. However, SIP-110 was described as a 976-aa protein with an estimated molecular weight of 110 kd. Although the origin of the first 42 nucleotides of SIP-110 within the human SHIP gene was unknown, it was proposed that SIP-110 results from an alternative splice event. Analysis of the structure and the genomic location of the first exon of SIP-110 confirms that SIP-110 is the human homologue of s-SHIP. Furthermore, the structure and internal location of the SIP-110 first exon within the SHIP gene indicates that SIP-110 arises through alternative promoter use rather than as a splice variant, as was previously proposed. Although there are 2 potential ORFs for SIP-110 that predict proteins of 976 as and 929 as, the distal ATG initiation codon has Kozak consensus features that may favor translation of the 929-aa, 1 04-kd protein, which more closely resembles s-SHIP. Results demonstrate that s-SHIP is expressed in murine HSCs. Because cord blood within placenta is known to be enriched for HSCs, the inventors hypothesize that the SIP-I 10 cDNA isolated by Kavanaugh

et al" may have originated from cord blood HSC cDNA present in the placenta library.

[0075] In vitro studies with recombinant SIP-110 confirmed that it can bind Grb2, but its inositol 5"-phosphatase activity is unaffected by Grb2 binding." Furthermore, SIP-110 did not associate with Shc. These results can be extrapolated to s-SHIP, and they suggest that the purpose of Grb2 binding is not to alter s-SHIP enzymatic activity but rather to direct the subcellular localization of this activity.

[0076] Geier et al similarly found a I 0O-kd isoform of SHIP in both human and murine bone marrow using a polyclonal antibody to an amino acid sequence of marine SHIP (as 670 to as 868) that is also present in s-SHIP. Interestingly, they also found that a 1 00-kd isoform was the most prominent species in human peripheral blood mononuclear cells. Examination of the human ML-1 myeloblastic leukemia cell line revealed the presence of a 100-kd SHIP isoform and a 105-kd isoform and the absence of higher MW isoforms. When these ML-I myeloblasts were induced to differentiate into monocytes in the presence of 12-O-tetradecanoylphorbol-13-acetate, higher MW isoforms (175 kd, 145 kd, and 130 kd) appeared, whereas the lower MW isoforms (105 kd, 100 kd) were no longer detectable. These results with ML-1 cells indicate that as human myeloid cells differentiate, human SHIP expression changes from the lower MW 105-kd and 100-kd isoforms to the higher MW isoforms. This is analogous to what the inventors found with s-SHIP and SHIP isoforms in murine hematopoietic cell development, and it suggests that the lower MW human isoforms characterized by Geier et al represent the SIP-110 identified by Kavanaugh et al." However, it is unclear why in their studies human peripheral blood displayed only the lower MW 100-kd isoform. Wolf et al describe an additional 110-kd SHIP isoform, SHIP, which is the product of an out-of-frame splice event with a deletion of 167 nucleotides in the C-terminal region. This clearly represents a different isoform than s-SHIP. It remains to be determined which SHIP-related proteins, among these several isoforms encoding 100 kd to 110 kd, predominate during different stages of hematopoietic development.

[0077] Recently, Krause et al elegantly demonstrated that a single murine adult bone marrow stem cell can repopulate hematopoietic cells and a diverse array of nonhematopoietic epithelial tissues, including lung, liver, gastrointestinal tract, and skin. Given that s-SHIP is expressed in totipotent ES cells and at least a subset of bone marrow HSCs, this study raises the possibility that s-SHIP expression may serve to further characterize and delineate the pluripotent bone marrow stem cell capable of multi-organ engraftment that Krause et al identified.

[0078] It will be seen that the objects set forth above, and those made apparent from the foregoing description, are efficiently attained and since certain changes may be made in the above construction without departing from the scope of the invention, it is intended that all matters contained in the foregoing description or shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense.

[0079] It is also to be understood that the following claims are intended to cover all of the generic and specific features of the invention herein described, and all statements of the scope of the invention which, as a matter of language, might be the to fall therebetween. Now that the invention has been described,

SEQUENCE LISTING

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<210> SEQ ID NO 1
<211> LENGTH: 4125
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 1

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            20                  25                  30

Cys Thr Cys Thr Gly Cys Thr Cys Cys Cys Ala Gly Gly Gly Ala Ala
        35                  40                  45

Gly Thr Cys Ala Thr Cys Ala Gly Gly Ala Cys Thr Cys Thr Gly Cys
    50                  55                  60

Cys Ala Thr Cys Cys Cys Thr Gly Gly Ala Gly Thr Cys Thr Cys Thr
65                  70                  75                  80

Gly Cys Ala Gly Ala Gly Gly Thr Thr Gly Thr Thr Thr Gly Ala Cys
                85                  90                  95

Cys Ala Ala Cys Ala Gly Cys Thr Cys Thr Cys Cys Cys Cys Ala Gly
            100                 105                 110

Gly Cys Cys Thr Thr Cys Gly Cys Cys Cys Ala Cys Gly Ala Cys Cys
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        115                 120                 125

Thr Cys Ala Gly Gly Thr Gly Cys Cys Cys Gly Gly Ala Gly Ala Gly
    130                 135                 140

Gly Cys Cys Ala Gly Thr Cys Cys Cys Ala Thr Cys Ala Cys Cys Ala
145                 150                 155                 160

Thr Gly Gly Thr Thr Gly Cys Cys Ala Ala Ala Cys Thr Cys Ala Gly
                165                 170                 175

Cys Cys Ala Ala Thr Thr Gly Ala Cys Ala Ala Gly Thr Cys Thr Gly
            180                 185                 190

Cys Thr Gly Thr Cys Thr Thr Cys Cys Ala Thr Thr Gly Ala Ala Gly
        195                 200                 205

Ala Thr Ala Ala Gly Gly Thr Cys Ala Ala Gly Thr Cys Cys Thr Thr
    210                 215                 220

Gly Cys Thr Gly Cys Ala Cys Gly Ala Gly Gly Gly Cys Thr Cys Ala
225                 230                 235                 240

Gly Ala Ala Thr Cys Thr Ala Cys Cys Ala Ala Cys Ala Gly Gly Cys
                245                 250                 255

Gly Thr Thr Cys Cys Cys Thr Thr Ala Thr Cys Cys Cys Thr Cys Cys
            260                 265                 270

Gly Gly Thr Cys Ala Cys Cys Thr Thr Thr Gly Ala Gly Gly Thr Gly
        275                 280                 285

Ala Ala Gly Thr Cys Ala Gly Ala Gly Thr Cys Cys Cys Thr Gly Gly
    290                 295                 300

Gly Cys Ala Thr Thr Cys Cys Thr Cys Ala Gly Ala Ala Ala Ala Thr
305                 310                 315                 320

Gly Cys Ala Thr Cys Thr Cys Ala Ala Ala Gly Thr Gly Gly Ala Cys
                325                 330                 335

Gly Thr Thr Gly Ala Gly Thr Cys Thr Gly Gly Gly Ala Ala Ala Cys
            340                 345                 350

Thr Gly Ala Thr Cys Gly Thr Thr Ala Ala Gly Ala Ala Gly Thr Cys
        355                 360                 365

Cys Ala Ala Gly Gly Ala Thr Gly Gly Thr Thr Cys Thr Gly Ala Gly
    370                 375                 380

Gly Ala Cys Ala Ala Gly Thr Thr Cys Thr Ala Cys Ala Gly Cys Cys
385                 390                 395                 400

Ala Cys Ala Ala Ala Ala Ala Ala Ala Thr Cys Cys Thr Gly Cys Ala
                405                 410                 415

Gly Cys Thr Cys Ala Thr Thr Ala Ala Gly Thr Cys Cys Cys Ala Gly
            420                 425                 430

Ala Ala Gly Thr Thr Thr Cys Thr Ala Ala Ala Cys Ala Ala Gly Thr
        435                 440                 445

Thr Gly Gly Thr Gly Ala Thr Thr Thr Thr Gly Gly Thr Gly Gly Ala
    450                 455                 460

Gly Ala Cys Gly Gly Ala Gly Ala Ala Gly Gly Ala Gly Ala Ala Ala
465                 470                 475                 480

Ala Thr Cys Cys Thr Gly Ala Gly Gly Ala Ala Gly Gly Ala Ala Thr
                485                 490                 495

Ala Thr Gly Thr Thr Thr Thr Thr Gly Cys Thr Gly Ala Cys Thr Cys
            500                 505                 510

Thr Ala Ala Gly Ala Ala Ala Ala Gly Ala Gly Ala Ala Gly Gly Cys
        515                 520                 525
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Thr Thr Cys Thr Gly Thr Cys Ala Ala Cys Thr Cys Cys Thr Gly Cys
    530                 535                 540

Ala Gly Cys Ala Gly Ala Thr Gly Ala Ala Gly Ala Ala Cys Ala Ala
545                 550                 555                 560

Gly Cys Ala Thr Thr Cys Gly Gly Ala Gly Cys Ala Gly Cys Cys Ala
                565                 570                 575

Gly Ala Gly Cys Cys Thr Gly Ala Cys Ala Thr Gly Ala Thr Cys Ala
            580                 585                 590

Cys Cys Ala Thr Cys Thr Thr Cys Ala Thr Thr Gly Gly Cys Ala Cys
        595                 600                 605

Thr Thr Gly Gly Ala Ala Cys Ala Thr Gly Gly Gly Thr Ala Ala Thr
    610                 615                 620

Gly Cys Ala Cys Cys Cys Cys Cys Thr Cys Cys Cys Ala Ala Gly Ala
625                 630                 635                 640

Ala Gly Ala Thr Cys Ala Cys Gly Thr Cys Cys Thr Gly Gly Thr Thr
                645                 650                 655

Thr Cys Thr Cys Thr Cys Cys Ala Ala Gly Gly Gly Gly Cys Ala Gly
            660                 665                 670

Gly Gly Ala Ala Ala Gly Ala Cys Ala Cys Gly Gly Gly Ala Cys Gly
        675                 680                 685

Ala Cys Thr Cys Thr Gly Cys Thr Gly Ala Cys Thr Ala Cys Ala Thr
    690                 695                 700

Cys Cys Cys Cys Cys Ala Thr Gly Ala Cys Ala Thr Cys Thr Ala Thr
705                 710                 715                 720

Gly Thr Gly Ala Thr Thr Gly Gly Cys Ala Cys Cys Cys Ala Gly Gly
                725                 730                 735

Ala Gly Gly Ala Thr Cys Cys Cys Cys Thr Thr Gly Gly Ala Gly Ala
            740                 745                 750

Gly Ala Ala Gly Gly Ala Gly Thr Gly Gly Cys Thr Gly Gly Ala Gly
        755                 760                 765

Cys Thr Ala Cys Thr Cys Ala Gly Gly Cys Ala Cys Thr Cys Cys Cys
    770                 775                 780

Thr Gly Cys Ala Ala Gly Ala Ala Gly Thr Cys Ala Cys Cys Ala Gly
785                 790                 795                 800

Cys Ala Thr Gly Ala Cys Ala Thr Thr Thr Ala Ala Ala Ala Cys Ala
                805                 810                 815

Gly Thr Thr Gly Cys Cys Ala Thr Cys Cys Ala Cys Ala Cys Cys Cys
            820                 825                 830

Thr Cys Thr Gly Gly Ala Ala Cys Ala Thr Thr Cys Gly Cys Ala Thr
        835                 840                 845

Ala Gly Thr Gly Gly Thr Gly Cys Thr Thr Gly Cys Cys Ala Ala Gly
    850                 855                 860

Cys Cys Ala Gly Ala Gly Cys Ala Thr Gly Ala Gly Ala Ala Thr Cys
865                 870                 875                 880

Gly Gly Ala Thr Cys Ala Gly Cys Cys Ala Thr Ala Thr Cys Thr Gly
                885                 890                 895

Cys Ala Cys Thr Gly Ala Cys Ala Ala Cys Gly Thr Gly Ala Ala Gly
            900                 905                 910

Ala Cys Ala Gly Gly Cys Ala Thr Cys Gly Cys Cys Ala Ala Cys Ala
        915                 920                 925
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    930                 935                 940

Ala Gly Cys Ala Gly Thr Gly Gly Gly Ala Gly Thr Gly Thr Cys Cys
945                 950                 955                 960

Thr Thr Cys Ala Thr Gly Thr Thr Cys Ala Ala Thr Gly Gly Ala Ala
                965                 970                 975

Cys Cys Thr Cys Cys Thr Thr Gly Gly Gly Gly Thr Thr Cys Gly Thr
            980                 985                 990

Cys Ala Ala Cys Ala Gly Cys Cys  Ala Cys Thr Thr Gly  Ala Cys Thr
        995                 1000                1005

Thr Cys  Thr Gly Gly Ala Ala  Gly Cys Gly Ala Ala  Ala Ala Ala
    1010                1015                1020

Ala Ala  Gly Cys Thr Cys Ala  Gly Gly Ala Gly Ala  Ala Ala Thr
    1025                1030                1035

Cys Ala  Ala Ala Ala Cys Thr  Ala Thr Ala Thr Gly  Ala Ala Cys
    1040                1045                1050

Ala Thr  Cys Cys Thr Gly Cys  Gly Gly Thr Thr Cys  Cys Thr Gly
    1055                1060                1065

Gly Cys  Cys Cys Thr Gly Gly  Gly Ala Gly Ala Cys  Ala Ala Gly
    1070                1075                1080

Ala Ala  Gly Cys Thr Ala Ala  Gly Cys Cys Cys Ala  Thr Thr Thr
    1085                1090                1095

Ala Ala  Cys Ala Thr Cys Ala  Cys Cys Cys Ala Cys  Cys Gly Cys
    1100                1105                1110

Thr Thr  Cys Ala Cys Cys Cys  Ala Cys Cys Thr Cys  Thr Thr Cys
    1115                1120                1125

Thr Gly  Gly Cys Thr Thr Gly  Gly Gly Gly Ala Thr  Cys Thr Cys
    1130                1135                1140

Ala Ala  Cys Thr Ala Cys Cys  Gly Cys Gly Thr Gly  Gly Ala Gly
    1145                1150                1155

Cys Thr  Gly Cys Cys Cys Ala  Cys Thr Thr Gly Gly  Gly Ala Gly
    1160                1165                1170

Gly Cys  Ala Gly Ala Gly Gly  Cys Cys Ala Thr Cys  Ala Thr Cys
    1175                1180                1185

Cys Ala  Gly Ala Ala Gly Ala  Thr Cys Ala Ala Gly  Cys Ala Ala
    1190                1195                1200

Cys Ala  Gly Cys Ala Gly Thr  Ala Thr Thr Cys Ala  Gly Ala Cys
    1205                1210                1215

Cys Thr  Thr Cys Thr Gly Gly  Cys Cys Cys Ala Cys  Gly Ala Cys
    1220                1225                1230

Cys Ala  Ala Cys Thr Gly Cys  Thr Cys Cys Thr Gly  Gly Ala Gly
    1235                1240                1245

Ala Gly  Gly Ala Ala Gly Gly  Ala Cys Cys Ala Gly  Ala Ala Gly
    1250                1255                1260

Gly Thr  Cys Thr Thr Cys Cys  Thr Gly Cys Ala Cys  Thr Thr Thr
    1265                1270                1275

Gly Ala  Gly Gly Ala Gly Gly  Ala Ala Gly Ala Gly  Ala Thr Cys
    1280                1285                1290

Ala Cys  Cys Thr Thr Cys Gly  Cys Cys Cys Cys Cys  Ala Cys Cys
    1295                1300                1305

Thr Ala  Thr Cys Gly Ala Thr  Thr Thr Gly Ala Ala  Ala Gly Ala
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    1310                1315                1320

Cys Thr  Gly Ala Cys Cys Cys  Gly Gly Gly Ala Cys  Ala Ala Gly
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Thr Ala  Thr Gly Cys Ala Thr  Ala Cys Ala Cys Gly  Ala Ala Gly
    1340                1345                1350

Cys Ala  Gly Ala Ala Ala Gly  Cys Ala Ala Cys Ala  Gly Gly Gly
    1355                1360                1365

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    1370                1375                1380

Cys Cys  Gly Thr Cys Cys Thr  Gly Gly Thr Gly Cys  Gly Ala Cys
    1385                1390                1395

Cys Gly  Ala Gly Thr Cys Cys  Thr Cys Thr Gly Gly  Ala Ala Gly
    1400                1405                1410

Thr Cys  Thr Thr Ala Cys Cys  Cys Gly Cys Thr Gly  Gly Thr Gly
    1415                1420                1425

Cys Ala  Thr Gly Thr Gly Gly  Thr Cys Thr Gly Thr  Cys Ala Gly
    1430                1435                1440

Thr Cys  Cys Thr Ala Thr Gly  Gly Cys Ala Gly Thr  Ala Cys Cys
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Ala Gly  Thr Gly Ala Cys Ala  Thr Cys Ala Thr Gly  Ala Cys Gly
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Ala Gly  Thr Gly Ala Cys Cys  Ala Cys Ala Gly Cys  Cys Cys Thr
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Gly Thr  Cys Thr Thr Thr Gly  Cys Cys Ala Cys Gly  Thr Thr Thr
    1490                1495                1500

Gly Ala  Ala Gly Cys Gly Gly  Gly Ala Gly Thr Cys  Ala Cys Ala
    1505                1510                1515

Thr Cys  Thr Cys Ala Ala Thr  Thr Cys Gly Thr Cys  Thr Cys Cys
    1520                1525                1530

Ala Ala  Gly Ala Ala Thr Gly  Gly Thr Cys Cys Thr  Gly Gly Cys
    1535                1540                1545

Ala Cys  Thr Gly Thr Ala Gly  Ala Thr Ala Gly Cys  Cys Ala Ala
    1550                1555                1560

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    1565                1570                1575

Cys Thr  Thr Gly Cys Ala Thr  Gly Cys Thr Ala Cys  Gly Cys Cys
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Ala Cys  Ala Cys Thr Gly Ala  Ala Gly Ala Cys Cys  Ala Ala Gly
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    1610                1615                1620

Thr Ala  Cys Thr Thr Gly Gly  Ala Gly Thr Thr Cys  Cys Ala Cys
    1625                1630                1635

Thr Cys  Ala Ala Gly Cys Thr  Gly Cys Thr Thr Ala  Gly Ala Gly
    1640                1645                1650

Ala Gly  Thr Thr Thr Thr Gly  Thr Cys Ala Ala Gly  Ala Gly Thr
    1655                1660                1665

Cys Ala  Gly Gly Ala Ala Gly  Gly Ala Gly Ala Gly  Ala Ala Thr
    1670                1675                1680

Gly Ala  Ala Gly Ala Gly Gly  Gly Ala Ala Gly Thr  Gly Ala Ala
    1685                1690                1695
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Cys Gly  Gly Thr Thr Thr Gly  Gly Ala Gly Ala Gly  Ala Cys Thr
    1715                1720                1725

Cys Thr  Thr Cys Cys Cys Ala  Ala Gly Cys Thr Ala  Ala Ala Gly
    1730                1735                1740

Cys Cys  Cys Ala Thr Thr Ala  Thr Cys Thr Cys Thr  Gly Ala Cys
    1745                1750                1755

Cys Cys  Cys Gly Ala Gly Thr  Ala Cys Thr Thr Ala  Cys Thr Gly
    1760                1765                1770

Gly Ala  Cys Cys Ala Gly Cys  Ala Thr Ala Thr Cys  Cys Thr Gly
    1775                1780                1785

Ala Thr  Cys Ala Gly Cys Ala  Thr Thr Ala Ala Ala  Thr Cys Cys
    1790                1795                1800

Thr Cys  Thr Gly Ala Cys Ala  Gly Thr Gly Ala Cys  Gly Ala Gly
    1805                1810                1815

Thr Cys  Cys Thr Ala Thr Gly  Gly Thr Gly Ala Ala  Gly Gly Cys
    1820                1825                1830

Thr Gly  Cys Ala Thr Thr Gly  Cys Cys Cys Thr Thr  Cys Gly Cys
    1835                1840                1845

Thr Thr  Gly Gly Ala Gly Ala  Cys Cys Ala Cys Ala  Gly Ala Gly
    1850                1855                1860

Gly Cys  Thr Cys Ala Gly Cys  Ala Thr Cys Cys Thr  Ala Thr Cys
    1865                1870                1875

Thr Ala  Cys Ala Cys Gly Cys  Cys Thr Cys Thr Cys  Ala Cys Cys
    1880                1885                1890

Cys Ala  Cys Cys Ala Thr Gly  Gly Gly Gly Ala Gly  Ala Thr Gly
    1895                1900                1905

Ala Cys  Thr Gly Gly Cys Cys  Ala Cys Thr Thr Cys  Ala Gly Gly
    1910                1915                1920

Gly Gly  Ala Gly Ala Gly Ala  Thr Thr Ala Ala Gly  Cys Thr Gly
    1925                1930                1935

Cys Ala  Gly Ala Cys Cys Thr  Cys Cys Cys Ala Gly  Gly Gly Cys
    1940                1945                1950

Ala Ala  Gly Ala Thr Gly Ala  Gly Gly Gly Ala Gly  Ala Ala Gly
    1955                1960                1965

Cys Thr  Cys Thr Ala Thr Gly  Ala Cys Thr Thr Thr  Gly Thr Gly
    1970                1975                1980

Ala Ala  Gly Ala Cys Ala Gly  Ala Gly Cys Gly Gly  Gly Ala Thr
    1985                1990                1995

Gly Ala  Ala Thr Cys Cys Ala  Gly Thr Gly Gly Ala  Ala Thr Gly
    2000                2005                2010

Ala Ala  Ala Thr Gly Cys Thr  Thr Gly Ala Ala Gly  Ala Ala Cys
    2015                2020                2025

Cys Thr  Cys Ala Cys Cys Ala  Gly Cys Cys Ala Thr  Gly Ala Cys
    2030                2035                2040

Cys Cys  Thr Ala Thr Gly Ala  Gly Gly Cys Ala Ala  Thr Gly Gly
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Gly Ala  Gly Cys Cys Thr Thr  Cys Thr Gly Gly Cys  Ala Gly Gly
    2060                2065                2070
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Gly Ala  Gly Ala Thr Gly Ala  Thr Cys Ala Ala Thr  Cys Cys Ala
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Ala Ala  Cys Thr Ala Cys Ala  Thr Thr Gly Gly Thr  Ala Thr Gly
    2120                 2125                 2130

Gly Gly  Gly Cys Cys Thr Thr  Thr Thr Gly Gly Ala  Cys Ala Gly
    2135                 2140                 2145

Cys Cys  Cys Cys Thr Gly Cys  Ala Thr Gly Gly Gly  Ala Ala Ala
    2150                 2155                 2160

Thr Cys  Ala Ala Cys Cys Cys  Thr Gly Thr Cys Cys  Cys Cys Ala
    2165                 2170                 2175

Gly Ala  Thr Cys Ala Gly Cys  Ala Ala Cys Thr Cys  Ala Cys Ala
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Gly Cys  Thr Thr Gly Gly Ala  Gly Thr Thr Ala Thr  Gly Ala Cys
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Cys Ala  Gly Cys Thr Ala Cys  Cys Cys Ala Ala Ala  Gly Ala Cys
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Thr Cys  Cys Thr Cys Cys Cys  Thr Gly Gly Gly Gly  Cys Cys Thr
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Cys Cys  Thr Cys Cys Ala Ala  Cys Cys Cys Cys Thr  Cys Cys Cys
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Thr Cys  Cys Cys Ala Ala Cys  Cys Ala Cys Cys Thr  Cys Thr Gly
    2270                 2275                 2280

Thr Cys  Gly Cys Cys Ala Ala  Ala Gly Ala Ala Gly  Thr Thr Thr
    2285                 2290                 2295

Thr Cys  Ala Thr Cys Thr Thr  Cys Cys Ala Cys Ala  Gly Cys Cys
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Ala Ala  Cys Cys Gly Ala Gly  Gly Thr Cys Cys Cys  Thr Gly Cys
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Cys Cys  Cys Ala Gly Gly Gly  Thr Gly Cys Ala Ala  Gly Ala Gly
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Gly Cys  Ala Ala Gly Ala Cys  Cys Thr Gly Gly Gly  Gly Ala Thr
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Cys Thr  Gly Gly Gly Ala Ala  Ala Gly Gly Thr Gly  Gly Ala Ala
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Gly Cys  Thr Cys Thr Gly Cys  Thr Cys Cys Ala Gly  Gly Ala Gly
    2375                 2380                 2385

Gly Ala  Cys Cys Thr Gly Cys  Thr Gly Cys Thr Gly  Ala Cys Gly
    2390                 2395                 2400

Ala Ala  Gly Cys Cys Cys Gly  Ala Gly Ala Thr Gly  Thr Thr Thr
    2405                 2410                 2415

Gly Ala  Gly Ala Ala Cys Cys  Cys Ala Cys Thr Gly  Thr Ala Thr
    2420                 2425                 2430

Gly Gly  Ala Thr Cys Cys Gly  Thr Gly Ala Gly Thr  Thr Cys Cys
    2435                 2440                 2445

Thr Thr  Cys Cys Cys Thr Ala  Ala Gly Cys Thr Gly  Gly Thr Gly
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    2450                2455                2460

Cys Cys  Cys Ala Gly Gly Ala  Ala Ala Gly Ala Gly  Cys Ala Gly
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Gly Ala  Gly Thr Cys Thr Cys  Cys Cys Ala Ala Gly  Ala Thr Gly
    2480                2485                2490

Cys Thr  Gly Cys Gly Gly Ala  Ala Gly Gly Ala Gly  Cys Cys Cys
    2495                2500                2505

Cys Cys  Gly Cys Cys Cys Thr  Gly Thr Cys Cys Ala  Gly Ala Cys
    2510                2515                2520

Cys Cys  Ala Gly Gly Ala Ala  Thr Cys Thr Cys Ala  Thr Cys Ala
    2525                2530                2535

Cys Cys  Cys Ala Gly Cys Ala  Thr Cys Gly Thr Gly  Cys Thr Cys
    2540                2545                2550

Cys Cys  Cys Ala Ala Ala Gly  Cys Cys Cys Ala Ala  Gly Ala Gly
    2555                2560                2565

Gly Thr  Gly Gly Ala Gly Ala  Gly Thr Gly Thr Cys  Ala Ala Gly
    2570                2575                2580

Gly Gly  Gly Ala Cys Ala Ala  Gly Cys Ala Ala Ala  Cys Ala Gly
    2585                2590                2595

Gly Cys  Cys Cys Cys Thr Gly  Thr Gly Cys Cys Thr  Gly Thr Cys
    2600                2605                2610

Cys Thr  Thr Gly Gly Cys Cys  Cys Cys Ala Cys Ala  Cys Cys Cys
    2615                2620                2625

Cys Gly  Gly Ala Thr Cys Cys  Gly Cys Thr Cys Cys  Thr Thr Thr
    2630                2635                2640

Ala Cys  Cys Thr Gly Thr Thr  Cys Thr Thr Cys Thr  Thr Cys Thr
    2645                2650                2655

Gly Cys  Thr Gly Ala Gly Gly  Gly Cys Ala Gly Ala  Ala Thr Gly
    2660                2665                2670

Ala Cys  Cys Ala Gly Thr Gly  Gly Gly Gly Ala Cys  Ala Ala Gly
    2675                2680                2685

Ala Gly  Cys Cys Ala Ala Gly  Gly Gly Ala Ala Gly  Cys Cys Cys
    2690                2695                2700

Ala Ala  Gly Gly Cys Cys Thr  Cys Ala Gly Cys Cys  Ala Gly Thr
    2705                2710                2715

Thr Cys  Cys Cys Ala Ala Gly  Cys Cys Cys Cys Ala  Gly Thr Gly
    2720                2725                2730

Cys Cys  Ala Gly Thr Cys Ala  Ala Gly Ala Gly Gly  Cys Cys Thr
    2735                2740                2745

Gly Thr  Cys Ala Ala Gly Cys  Cys Thr Thr Cys Cys  Ala Gly Gly
    2750                2755                2760

Thr Cys  Ala Gly Ala Ala Ala  Thr Gly Ala Gly Cys  Cys Ala Gly
    2765                2770                2775

Cys Ala  Gly Ala Cys Ala Ala  Cys Ala Cys Cys Cys  Ala Thr Cys
    2780                2785                2790

Cys Cys  Ala Gly Cys Thr Cys  Cys Ala Cys Gly Gly  Cys Cys Ala
    2795                2800                2805

Cys Cys  Cys Cys Thr Gly Cys  Cys Ala Gly Thr Cys  Ala Ala Gly
    2810                2815                2820

Ala Gly  Thr Cys Cys Thr Gly  Cys Thr Gly Thr Cys  Cys Thr Gly
    2825                2830                2835
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Cys Ala  Gly Cys Thr Gly Cys  Ala Ala Cys Ala Thr  Thr Cys Cys
    2840                 2845                 2850

Ala Ala  Ala Gly Gly Cys Ala  Gly Ala Gly Ala Cys  Thr Ala Cys
    2855                 2860                 2865

Cys Gly  Thr Gly Ala Cys Ala  Ala Cys Ala Cys Ala  Gly Ala Ala
    2870                 2875                 2880

Cys Thr  Cys Cys Cys Cys Cys  Ala Cys Cys Ala Thr  Gly Gly Cys
    2885                 2890                 2895

Ala Ala  Gly Cys Ala Cys Cys  Gly Cys Cys Ala Ala  Gly Ala Gly
    2900                 2905                 2910

Gly Ala  Gly Gly Gly Gly Cys  Thr Gly Cys Thr Thr  Gly Gly Cys
    2915                 2920                 2925

Ala Gly  Gly Ala Cys Thr Gly  Cys Cys Ala Thr Gly  Cys Ala Gly
    2930                 2935                 2940

Thr Gly  Ala Gly Cys Thr Gly  Cys Thr Gly Gly Thr  Gly Ala Thr
    2945                 2950                 2955

Cys Gly  Gly Ala Gly Cys Cys  Thr Gly Gly Ala Gly  Gly Ala Ala
    2960                 2965                 2970

Cys Ala  Gly Cys Ala Cys Ala  Ala Ala Gly Cys Ala  Gly Ala Cys
    2975                 2980                 2985

Cys Thr  Gly Cys Gly Cys Cys  Thr Cys Thr Cys Thr  Cys Ala Gly
    2990                 2995                 3000

Gly Ala  Thr Gly Cys Cys Thr  Cys Thr Cys Thr Cys  Ala Gly Gly
    3005                 3010                 3015

Ala Thr  Gly Cys Cys Thr Cys  Thr Thr Gly Gly Ala  Gly Gly Ala
    3020                 3025                 3030

Cys Cys  Thr Cys Cys Thr Gly  Cys Thr Ala Gly Cys  Thr Cys Thr
    3035                 3040                 3045

Thr Cys  Thr Thr Gly Cys Cys  Thr Ala Gly Cys Thr  Thr Cys Ala
    3050                 3055                 3060

Ala Gly  Thr Cys Cys Cys Ala  Gly Gly Cys Thr Gly  Thr Gly Thr
    3065                 3070                 3075

Ala Thr  Thr Thr Thr Thr Thr  Thr Thr Cys Ala Gly  Gly Ala Ala
    3080                 3085                 3090

Ala Cys  Gly Gly Cys Cys Thr  Cys Ala Cys Thr Thr  Cys Thr Cys
    3095                 3100                 3105

Thr Gly  Thr Gly Gly Thr Cys  Cys Ala Ala Gly Ala  Ala Gly Thr
    3110                 3115                 3120

Gly Thr  Gly Cys Thr Gly Cys  Thr Gly Gly Cys Thr  Gly Cys Cys
    3125                 3130                 3135

Ala Cys  Ala Cys Thr Gly Thr  Gly Cys Gly Gly Cys  Ala Gly Ala
    3140                 3145                 3150

Thr Gly  Cys Thr Ala Ala Ala  Gly Cys Thr Gly Gly  Ala Thr Gly
    3155                 3160                 3165

Ala Cys  Ala Ala Ala Cys Gly  Cys Ala Cys Gly Cys  Cys Ala Thr
    3170                 3175                 3180

Ala Cys  Ala Gly Ala Cys Ala  Gly Cys Ala Gly Ala  Cys Ala Gly
    3185                 3190                 3195

Cys Gly  Gly Cys Ala Cys Thr  Gly Gly Gly Thr Cys  Thr Cys Ala
    3200                 3205                 3210
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Gly Ala  Ala Cys Thr Thr Gly  Gly Ala Thr Thr Cys  Cys Thr Gly
    3215                 3220                 3225

Gly Gly  Cys Cys Thr Thr Cys  Thr Thr Cys Cys Ala  Gly Thr Cys
    3230                 3235                 3240

Gly Cys  Cys Gly Thr Thr Thr  Thr Ala Ala Ala Gly  Ala Ala Ala
    3245                 3250                 3255

Gly Gly  Ala Ala Cys Thr Ala  Ala Cys Gly Gly Ala  Gly Cys Thr
    3260                 3265                 3270

Gly Cys  Thr Cys Ala Thr Cys  Cys Gly Ala Gly Gly  Gly Thr Gly
    3275                 3280                 3285

Ala Ala  Gly Ala Thr Ala Thr  Ala Ala Ala Thr Ala  Ala Thr Ala
    3290                 3295                 3300

Ala Thr  Ala Thr Thr Ala Thr  Thr Ala Ala Thr Ala  Ala Thr Ala
    3305                 3310                 3315

Ala Thr  Ala Ala Cys Ala Gly  Thr Cys Ala Gly Gly  Thr Gly Cys
    3320                 3325                 3330

Cys Ala  Thr Gly Thr Gly Cys  Thr Gly Thr Gly Thr  Thr Ala Ala
    3335                 3340                 3345

Gly Thr  Gly Cys Thr Thr Thr  Ala Thr Gly Ala Ala  Cys Ala Thr
    3350                 3355                 3360

Thr Thr  Gly Thr Cys Gly Gly  Gly Cys Thr Gly Gly  Cys Cys Thr
    3365                 3370                 3375

Cys Cys  Ala Gly Thr Gly Cys  Thr Gly Ala Gly Gly  Thr Gly Cys
    3380                 3385                 3390

Cys Ala  Gly Thr Cys Ala Gly  Cys Cys Thr Gly Ala  Ala Cys Cys
    3395                 3400                 3405

Cys Thr  Ala Thr Gly Cys Cys  Cys Ala Gly Gly Cys  Cys Cys Ala
    3410                 3415                 3420

Cys Thr  Ala Ala Thr Cys Cys  Cys Ala Ala Ala Thr  Gly Gly Thr
    3425                 3430                 3435

Gly Gly  Gly Thr Cys Cys Thr  Gly Ala Gly Ala Thr  Gly Thr Thr
    3440                 3445                 3450

Thr Thr  Thr Ala Ala Ala Ala  Ala Gly Cys Ala Thr  Thr Ala Ala
    3455                 3460                 3465

Ala Gly  Ala Ala Ala Ala Cys  Cys Ala Thr Cys Gly  Gly Thr Cys
    3470                 3475                 3480

Thr Cys  Thr Thr Ala Gly Ala  Gly Cys Thr Ala Ala  Cys Cys Gly
    3485                 3490                 3495

Gly Cys  Cys Gly Gly Gly Cys  Thr Cys Thr Ala Cys  Thr Gly Cys
    3500                 3505                 3510

Ala Gly  Gly Gly Ala Cys Cys  Cys Gly Ala Ala Cys  Ala Gly Thr
    3515                 3520                 3525

Cys Thr  Gly Cys Ala Thr Gly  Gly Cys Thr Ala Ala  Gly Thr Gly
    3530                 3535                 3540

Gly Cys  Ala Cys Ala Ala Gly  Gly Ala Gly Cys Cys  Thr Gly Gly
    3545                 3550                 3555

Cys Cys  Cys Thr Gly Thr Cys  Cys Ala Gly Cys Thr  Thr Cys Ala
    3560                 3565                 3570

Gly Ala  Gly Ala Thr Cys Cys  Ala Ala Gly Cys Thr  Gly Cys Thr
    3575                 3580                 3585

Thr Thr  Thr Thr Gly Cys Thr  Gly Gly Gly Gly Thr  Thr Cys Thr
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    3590                3595                3600

Gly Thr  Cys Ala Cys Ala Gly  Gly Cys Cys Thr Gly  Ala Thr Cys
    3605                3610                3615

Cys Thr  Cys Thr Thr Gly Gly  Thr Thr Thr Thr Thr  Ala Thr Gly
    3620                3625                3630

Gly Gly  Gly Thr Thr Thr Cys  Ala Ala Gly Thr Cys  Thr Gly Cys
    3635                3640                3645

Cys Ala  Gly Ala Gly Thr Cys  Ala Gly Ala Ala Ala  Thr Cys Ala
    3650                3655                3660

Gly Cys  Thr Cys Thr Ala Ala  Cys Thr Cys Gly Cys  Cys Ala Gly
    3665                3670                3675

Thr Gly  Ala Ala Gly Ala Gly  Ala Thr Cys Thr Gly  Gly Cys Cys
    3680                3685                3690

Thr Thr  Ala Ala Cys Thr Thr  Ala Ala Gly Cys Cys  Ala Gly Cys
    3695                3700                3705

Cys Ala  Cys Gly Thr Cys Ala  Gly Gly Cys Cys Cys  Cys Thr Gly
    3710                3715                3720

Cys Thr  Gly Ala Gly Cys Cys  Thr Ala Thr Gly Gly  Ala Cys Cys
    3725                3730                3735

Ala Ala  Thr Ala Ala Ala Thr  Ala Cys Thr Cys Cys  Cys Cys Gly
    3740                3745                3750

Thr Gly  Cys Cys Ala Cys Thr  Gly Gly Ala Gly Gly  Thr Gly Gly
    3755                3760                3765

Gly Cys  Ala Gly Cys Thr Ala  Thr Cys Ala Cys Cys  Ala Thr Ala
    3770                3775                3780

Cys Cys  Cys Thr Gly Ala Gly  Thr Thr Gly Gly Gly  Cys Cys Ala
    3785                3790                3795

Ala Gly  Cys Cys Cys Ala Cys  Cys Cys Cys Ala Cys  Cys Cys Cys
    3800                3805                3810

Thr Ala  Cys Cys Cys Thr Gly  Cys Ala Ala Cys Ala  Thr Thr Thr
    3815                3820                3825

Cys Thr  Gly Ala Thr Gly Thr  Trp Cys Thr Gly Ala  Gly Gly Ala
    3830                3835                3840

Ala Gly  Ala Gly Thr Cys Thr  Cys Cys Ala Cys Cys  Ala Thr Ala
    3845                3850                3855

Gly Thr  Cys Cys Cys Cys Ala  Ala Gly Gly Gly Cys  Thr Gly Ala
    3860                3865                3870

Gly Thr  Thr Cys Thr Cys Cys  Ala Gly Cys Cys Thr  Gly Cys Thr
    3875                3880                3885

Ala Thr  Cys Ala Gly Gly Gly  Ala Ala Gly Gly Thr  Gly Ala Gly
    3890                3895                3900

Cys Ala  Thr Thr Gly Gly Thr  Cys Cys Cys Ala Gly  Gly Cys Thr
    3905                3910                3915

Cys Thr  Cys Ala Ala Ala Ala  Thr Ala Gly Thr Gly  Cys Ala Gly
    3920                3925                3930

Cys Cys  Thr Cys Thr Thr Cys  Thr Thr Cys Cys Cys  Ala Ala Gly
    3935                3940                3945

Cys Thr  Cys Thr Gly Gly Gly  Gly Thr Gly Cys Ala  Cys Cys Cys
    3950                3955                3960

Thr Gly  Thr Gly Thr Cys Cys  Thr Thr Gly Gly Thr  Thr Ala Cys
    3965                3970                3975
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```
Cys Ala  Gly Gly Ala Gly Ala  Cys Thr Ala Gly Gly  Gly Thr Thr
    3980                 3985                 3990

Gly Thr  Gly Ala Thr Ala Thr  Cys Thr Thr Thr Thr  Cys Thr Thr
    3995                 4000                 4005

Gly Thr  Cys Thr Thr Gly Cys  Thr Thr Thr Thr Thr  Gly Ala Thr
    4010                 4015                 4020

Ala Thr  Ala Thr Cys Ala Gly  Gly Ala Thr Thr Ala  Ala Thr Gly
    4025                 4030                 4035

Thr Ala  Gly Gly Ala Ala Ala  Cys Cys Ala Gly Ala  Cys Cys Thr
    4040                 4045                 4050

Ala Gly  Ala Thr Thr Ala Thr  Thr Cys Ala Gly Gly  Ala Gly Ala
    4055                 4060                 4065

Gly Thr  Ala Gly Gly Thr Ala  Thr Ala Thr Cys Cys  Cys Cys Thr
    4070                 4075                 4080

Gly Thr  Gly Thr Thr Thr Cys  Cys Cys Ala Gly Thr  Cys Thr Gly
    4085                 4090                 4095

Ala Gly  Thr Gly Ala Cys Cys  Ala Ala Thr Ala Ala  Ala Ala Thr
    4100                 4105                 4110

Thr Gly  Thr Gly Cys Cys Thr  Thr Thr Cys Thr Ala
    4115                 4120                 4125


<210> SEQ ID NO 2
<211> LENGTH: 3942
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 2

Gly Thr Thr Cys Cys Cys Ala Cys Thr Ala Gly Thr Thr Gly Thr Thr
1               5                  10                  15

Gly Ala Ala Cys Thr Thr Thr Ala Cys Cys Thr Thr Gly Ala Ala Cys
            20                  25                  30

Cys Thr Cys Thr Gly Cys Thr Cys Cys Cys Ala Gly Gly Gly Ala Ala
        35                  40                  45

Gly Thr Cys Ala Thr Cys Ala Gly Gly Ala Cys Thr Cys Thr Gly Cys
    50                  55                  60

Cys Ala Thr Cys Cys Cys Thr Gly Gly Ala Gly Thr Cys Thr Cys Thr
65                  70                  75                  80

Gly Cys Ala Gly Ala Gly Gly Thr Thr Gly Thr Thr Thr Gly Ala Cys
                85                  90                  95

Cys Ala Ala Cys Ala Gly Cys Thr Cys Thr Cys Cys Cys Cys Ala Gly
            100                 105                 110

Gly Cys Cys Thr Thr Cys Gly Cys Cys Cys Ala Cys Gly Ala Cys Cys
        115                 120                 125

Thr Cys Ala Gly Gly Thr Gly Cys Cys Cys Gly Gly Ala Gly Ala Gly
    130                 135                 140

Gly Cys Cys Ala Gly Thr Cys Cys Cys Ala Thr Cys Ala Cys Cys Ala
145                 150                 155                 160

Thr Gly Gly Thr Thr Gly Cys Cys Ala Ala Ala Cys Thr Cys Ala Gly
                165                 170                 175

Cys Cys Ala Ala Thr Thr Gly Ala Cys Ala Ala Gly Thr Cys Thr Gly
            180                 185                 190

Cys Thr Gly Thr Cys Thr Thr Cys Cys Ala Thr Thr Gly Ala Ala Gly
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        195                 200                 205

Ala Thr Ala Ala Gly Gly Thr Cys Ala Ala Gly Thr Cys Cys Thr Thr
    210                 215                 220

Gly Cys Thr Gly Cys Ala Cys Gly Ala Gly Gly Gly Cys Thr Cys Ala
225                 230                 235                 240

Gly Ala Ala Thr Cys Thr Ala Cys Cys Ala Ala Cys Ala Gly Gly Cys
                245                 250                 255

Gly Thr Thr Cys Cys Cys Thr Thr Ala Thr Cys Cys Cys Thr Cys Cys
            260                 265                 270

Gly Gly Thr Cys Ala Cys Cys Thr Thr Thr Gly Ala Gly Gly Thr Gly
        275                 280                 285

Ala Ala Gly Thr Cys Ala Gly Ala Gly Thr Cys Cys Cys Thr Gly Gly
    290                 295                 300

Gly Cys Ala Thr Thr Cys Cys Thr Cys Ala Gly Ala Ala Ala Ala Thr
305                 310                 315                 320

Gly Cys Ala Thr Cys Thr Cys Ala Ala Ala Gly Thr Gly Gly Ala Cys
                325                 330                 335

Gly Thr Thr Gly Ala Gly Thr Cys Thr Gly Gly Gly Ala Ala Ala Cys
            340                 345                 350

Thr Gly Ala Thr Cys Gly Thr Thr Ala Ala Gly Ala Ala Gly Thr Cys
        355                 360                 365

Cys Ala Ala Gly Gly Ala Thr Gly Gly Thr Thr Cys Thr Gly Ala Gly
    370                 375                 380

Gly Ala Cys Ala Ala Gly Thr Thr Cys Thr Ala Cys Ala Gly Cys Cys
385                 390                 395                 400

Ala Cys Ala Ala Ala Ala Ala Ala Ala Thr Cys Cys Thr Gly Cys Ala
                405                 410                 415

Gly Cys Thr Cys Ala Thr Thr Ala Ala Gly Thr Cys Cys Cys Ala Gly
            420                 425                 430

Ala Ala Gly Thr Thr Thr Cys Thr Ala Ala Ala Cys Ala Ala Gly Thr
        435                 440                 445

Thr Gly Gly Thr Gly Ala Thr Thr Thr Thr Gly Gly Thr Gly Gly Ala
    450                 455                 460

Gly Ala Cys Gly Gly Ala Gly Ala Ala Gly Gly Ala Gly Ala Ala Ala
465                 470                 475                 480

Ala Thr Cys Cys Thr Gly Ala Gly Gly Ala Ala Gly Gly Ala Ala Thr
                485                 490                 495

Ala Thr Gly Thr Thr Thr Thr Thr Gly Cys Thr Gly Ala Cys Thr Cys
            500                 505                 510

Thr Ala Ala Gly Ala Ala Ala Ala Gly Ala Gly Ala Ala Gly Gly Cys
        515                 520                 525

Thr Thr Cys Thr Gly Thr Cys Ala Ala Cys Thr Cys Cys Thr Gly Cys
    530                 535                 540

Ala Gly Cys Ala Gly Ala Thr Gly Ala Ala Gly Ala Ala Cys Ala Ala
545                 550                 555                 560

Gly Cys Ala Thr Thr Cys Gly Gly Ala Gly Cys Ala Gly Cys Cys Ala
                565                 570                 575

Gly Ala Gly Cys Cys Thr Gly Ala Cys Ala Thr Gly Ala Thr Cys Ala
            580                 585                 590

Cys Cys Ala Thr Cys Thr Thr Cys Ala Thr Thr Gly Gly Cys Ala Cys
        595                 600                 605
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Thr Thr Gly Gly Ala Ala Cys Ala Thr Gly Gly Gly Thr Ala Ala Thr
    610                 615                 620

Gly Cys Ala Cys Cys Cys Cys Cys Thr Cys Cys Cys Ala Ala Gly Ala
625                 630                 635                 640

Ala Gly Ala Thr Cys Ala Cys Gly Thr Cys Cys Thr Gly Gly Thr Thr
                645                 650                 655

Thr Cys Thr Cys Thr Cys Cys Ala Ala Gly Gly Gly Gly Cys Ala Gly
            660                 665                 670

Gly Gly Ala Ala Ala Gly Ala Cys Ala Cys Gly Gly Gly Ala Cys Gly
        675                 680                 685

Ala Cys Thr Cys Thr Gly Cys Thr Gly Ala Cys Thr Ala Cys Ala Thr
    690                 695                 700

Cys Cys Cys Cys Cys Ala Thr Gly Ala Cys Ala Thr Cys Thr Ala Thr
705                 710                 715                 720

Gly Thr Gly Ala Thr Thr Gly Gly Cys Ala Cys Cys Cys Ala Gly Gly
                725                 730                 735

Ala Gly Gly Ala Thr Cys Cys Cys Cys Thr Thr Gly Gly Ala Gly Ala
            740                 745                 750

Gly Ala Ala Gly Gly Ala Gly Thr Gly Gly Cys Thr Gly Gly Ala Gly
        755                 760                 765

Cys Thr Ala Cys Thr Cys Ala Gly Gly Cys Ala Cys Thr Cys Cys Cys
    770                 775                 780

Thr Gly Cys Ala Ala Gly Ala Ala Gly Thr Cys Ala Cys Cys Ala Gly
785                 790                 795                 800

Cys Ala Thr Gly Ala Cys Ala Thr Thr Thr Ala Ala Ala Ala Cys Ala
                805                 810                 815

Gly Thr Thr Gly Cys Cys Ala Thr Cys Cys Ala Cys Ala Cys Cys Cys
            820                 825                 830

Thr Cys Thr Gly Gly Ala Ala Cys Ala Thr Thr Cys Gly Cys Ala Thr
        835                 840                 845

Ala Gly Thr Gly Gly Thr Gly Cys Thr Thr Gly Cys Cys Ala Ala Gly
    850                 855                 860

Cys Cys Ala Gly Ala Gly Cys Ala Thr Gly Ala Gly Ala Ala Thr Cys
865                 870                 875                 880

Gly Gly Ala Thr Cys Ala Gly Cys Cys Ala Thr Ala Thr Cys Thr Gly
                885                 890                 895

Cys Ala Cys Thr Gly Ala Cys Ala Ala Cys Gly Thr Gly Ala Ala Gly
            900                 905                 910

Ala Cys Ala Gly Gly Cys Ala Thr Cys Gly Cys Cys Ala Ala Cys Ala
        915                 920                 925

Cys Cys Cys Thr Gly Gly Gly Ala Ala Ala Cys Ala Ala Gly Gly Gly
    930                 935                 940

Ala Gly Cys Ala Gly Thr Gly Gly Gly Ala Gly Thr Gly Thr Cys Cys
945                 950                 955                 960

Thr Thr Cys Ala Thr Gly Thr Thr Cys Ala Ala Thr Gly Gly Ala Ala
                965                 970                 975

Cys Cys Thr Cys Cys Thr Thr Gly Gly Gly Gly Thr Thr Cys Gly Thr
            980                 985                 990

Cys Ala Ala Cys Ala Gly Cys Cys  Ala Cys Thr Thr Gly  Ala Cys Thr
        995                 1000                1005
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```
Thr Cys  Thr Gly Gly Ala Ala  Gly Cys Gly Ala Ala  Ala Ala Ala
    1010                1015                1020

Ala Ala  Gly Cys Thr Cys Ala  Gly Gly Ala Gly Ala  Ala Ala Thr
    1025                1030                1035

Cys Ala  Ala Ala Ala Cys Thr  Ala Thr Ala Thr Gly  Ala Ala Cys
    1040                1045                1050

Ala Thr  Cys Cys Thr Gly Cys  Gly Gly Thr Thr Cys  Cys Thr Gly
    1055                1060                1065

Gly Cys  Cys Cys Thr Gly Gly  Gly Ala Gly Ala Cys  Ala Ala Gly
    1070                1075                1080

Ala Ala  Gly Cys Thr Ala Ala  Gly Cys Cys Cys Ala  Thr Thr Thr
    1085                1090                1095

Ala Ala  Cys Ala Thr Cys Ala  Cys Cys Cys Ala Cys  Cys Gly Cys
    1100                1105                1110

Thr Thr  Cys Ala Cys Cys Cys  Ala Cys Cys Thr Cys  Thr Thr Cys
    1115                1120                1125

Thr Gly  Gly Cys Thr Thr Gly  Gly Gly Gly Ala Thr  Cys Thr Cys
    1130                1135                1140

Ala Ala  Cys Thr Ala Cys Cys  Gly Cys Gly Thr Gly  Gly Ala Gly
    1145                1150                1155

Cys Thr  Gly Cys Cys Cys Ala  Cys Thr Thr Gly Gly  Gly Ala Gly
    1160                1165                1170

Gly Cys  Ala Gly Ala Gly Gly  Cys Cys Ala Thr Cys  Ala Thr Cys
    1175                1180                1185

Cys Ala  Gly Ala Ala Gly Ala  Thr Cys Ala Ala Gly  Cys Ala Ala
    1190                1195                1200

Cys Ala  Gly Cys Ala Gly Thr  Ala Thr Thr Cys Ala  Gly Ala Cys
    1205                1210                1215

Cys Thr  Thr Cys Thr Gly Gly  Cys Cys Cys Ala Cys  Gly Ala Cys
    1220                1225                1230

Cys Ala  Ala Cys Thr Gly Cys  Thr Cys Cys Thr Gly  Gly Ala Gly
    1235                1240                1245

Ala Gly  Gly Ala Ala Gly Gly  Ala Cys Cys Ala Gly  Ala Ala Gly
    1250                1255                1260

Gly Thr  Cys Thr Thr Cys Cys  Thr Gly Cys Ala Cys  Thr Thr Thr
    1265                1270                1275

Gly Ala  Gly Gly Ala Gly Gly  Ala Ala Gly Ala Gly  Ala Thr Cys
    1280                1285                1290

Ala Cys  Cys Thr Thr Cys Gly  Cys Cys Cys Cys Cys  Ala Cys Cys
    1295                1300                1305

Thr Ala  Thr Cys Gly Ala Thr  Thr Thr Gly Ala Ala  Ala Gly Ala
    1310                1315                1320

Cys Thr  Gly Ala Cys Cys Cys  Gly Gly Gly Ala Cys  Ala Ala Gly
    1325                1330                1335

Thr Ala  Thr Gly Cys Ala Thr  Ala Cys Ala Cys Gly  Ala Ala Gly
    1340                1345                1350

Cys Ala  Gly Ala Ala Ala Gly  Cys Ala Ala Cys Ala  Gly Gly Gly
    1355                1360                1365

Ala Thr  Gly Ala Ala Gly Thr  Ala Cys Ala Ala Cys  Thr Thr Gly
    1370                1375                1380

Cys Cys  Gly Thr Cys Cys Thr  Gly Gly Thr Gly Cys  Gly Ala Cys
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    1385                1390                1395

Cys Gly  Ala Gly Thr Cys Cys  Thr Cys Thr Gly Gly  Ala Ala Gly
    1400                1405                1410

Thr Cys  Thr Thr Ala Cys Cys  Cys Gly Cys Thr Gly  Gly Thr Gly
    1415                1420                1425

Cys Ala  Thr Gly Thr Gly Gly  Thr Cys Thr Gly Thr  Cys Ala Gly
    1430                1435                1440

Thr Cys  Cys Thr Ala Thr Gly  Gly Cys Ala Gly Thr  Ala Cys Cys
    1445                1450                1455

Ala Gly  Thr Gly Ala Cys Ala  Thr Cys Ala Thr Gly  Ala Cys Gly
    1460                1465                1470

Ala Gly  Thr Gly Ala Cys Cys  Ala Cys Ala Gly Cys  Cys Cys Thr
    1475                1480                1485

Gly Thr  Cys Thr Thr Thr Gly  Cys Cys Ala Cys Gly  Thr Thr Thr
    1490                1495                1500

Gly Ala  Ala Gly Cys Gly Gly  Gly Ala Gly Thr Cys  Ala Cys Ala
    1505                1510                1515

Thr Cys  Thr Cys Ala Ala Thr  Thr Cys Gly Thr Cys  Thr Cys Cys
    1520                1525                1530

Ala Ala  Gly Ala Ala Thr Gly  Gly Thr Cys Cys Thr  Gly Gly Cys
    1535                1540                1545

Ala Cys  Thr Gly Thr Ala Gly  Ala Thr Ala Gly Cys  Cys Ala Ala
    1550                1555                1560

Gly Gly  Gly Cys Ala Gly Ala  Thr Cys Gly Ala Gly  Thr Thr Thr
    1565                1570                1575

Cys Thr  Thr Gly Cys Ala Thr  Gly Cys Thr Ala Cys  Gly Cys Cys
    1580                1585                1590

Ala Cys  Ala Cys Thr Gly Ala  Ala Gly Ala Cys Cys  Ala Ala Gly
    1595                1600                1605

Thr Cys  Cys Cys Ala Gly Ala  Cys Thr Ala Ala Gly  Thr Thr Cys
    1610                1615                1620

Thr Ala  Cys Thr Thr Gly Gly  Ala Gly Thr Thr Cys  Cys Ala Cys
    1625                1630                1635

Thr Cys  Ala Ala Gly Cys Thr  Gly Cys Thr Thr Ala  Gly Ala Gly
    1640                1645                1650

Ala Gly  Thr Thr Thr Thr Gly  Thr Cys Ala Ala Gly  Ala Gly Thr
    1655                1660                1665

Cys Ala  Gly Gly Ala Ala Gly  Gly Ala Gly Ala Gly  Ala Ala Thr
    1670                1675                1680

Gly Ala  Ala Gly Ala Gly Gly  Gly Ala Ala Gly Thr  Gly Ala Ala
    1685                1690                1695

Gly Gly  Ala Gly Ala Gly Cys  Thr Gly Gly Thr Gly  Gly Thr Ala
    1700                1705                1710

Cys Gly  Gly Thr Thr Thr Gly  Gly Ala Gly Ala Gly  Ala Cys Thr
    1715                1720                1725

Cys Thr  Thr Cys Cys Cys Ala  Ala Gly Cys Thr Ala  Ala Ala Gly
    1730                1735                1740

Cys Cys  Cys Ala Thr Thr Ala  Thr Cys Thr Cys Thr  Gly Ala Cys
    1745                1750                1755

Cys Cys  Cys Gly Ala Gly Thr  Ala Cys Thr Thr Ala  Cys Thr Gly
    1760                1765                1770
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```
Gly Ala  Cys Cys Ala Gly Cys  Ala Thr Ala Thr Cys  Cys Thr Gly
    1775                1780                1785

Ala Thr  Cys Ala Gly Cys Ala  Thr Thr Ala Ala Ala  Thr Cys Cys
    1790                1795                1800

Thr Cys  Thr Gly Ala Cys Ala  Gly Thr Gly Ala Cys  Gly Ala Gly
    1805                1810                1815

Thr Cys  Cys Thr Ala Thr Gly  Gly Thr Gly Ala Ala  Gly Gly Cys
    1820                1825                1830

Thr Gly  Cys Ala Thr Thr Gly  Cys Cys Cys Thr Thr  Cys Gly Cys
    1835                1840                1845

Thr Thr  Gly Gly Ala Gly Ala  Cys Cys Ala Cys Ala  Gly Ala Gly
    1850                1855                1860

Gly Cys  Thr Cys Ala Gly Cys  Ala Thr Cys Cys Thr  Ala Thr Cys
    1865                1870                1875

Thr Ala  Cys Ala Cys Gly Cys  Cys Thr Cys Thr Cys  Ala Cys Cys
    1880                1885                1890

Cys Ala  Cys Cys Ala Thr Gly  Gly Gly Gly Ala Gly  Ala Thr Gly
    1895                1900                1905

Ala Cys  Thr Gly Gly Cys Cys  Ala Cys Thr Thr Cys  Ala Gly Gly
    1910                1915                1920

Gly Gly  Ala Gly Ala Gly Ala  Thr Thr Ala Ala Gly  Cys Thr Gly
    1925                1930                1935

Cys Ala  Gly Ala Cys Cys Thr  Cys Cys Cys Ala Gly  Gly Gly Cys
    1940                1945                1950

Ala Ala  Gly Ala Thr Gly Ala  Gly Gly Gly Ala Gly  Ala Ala Gly
    1955                1960                1965

Cys Thr  Cys Thr Ala Thr Gly  Ala Cys Thr Thr Thr  Gly Thr Gly
    1970                1975                1980

Ala Ala  Gly Ala Cys Ala Gly  Ala Gly Cys Gly Gly  Gly Ala Thr
    1985                1990                1995

Gly Ala  Ala Thr Cys Cys Ala  Gly Thr Gly Gly Ala  Ala Thr Gly
    2000                2005                2010

Ala Ala  Ala Thr Gly Cys Thr  Thr Gly Ala Ala Gly  Ala Ala Cys
    2015                2020                2025

Cys Thr  Cys Ala Cys Cys Ala  Gly Cys Cys Ala Thr  Gly Ala Cys
    2030                2035                2040

Cys Cys  Thr Ala Thr Gly Ala  Gly Gly Cys Ala Ala  Thr Gly Gly
    2045                2050                2055

Gly Ala  Gly Cys Cys Thr Thr  Cys Thr Gly Gly Cys  Ala Gly Gly
    2060                2065                2070

Gly Thr  Cys Cys Cys Thr Gly  Cys Ala Thr Gly Thr  Gly Gly Thr
    2075                2080                2085

Gly Thr  Cys Thr Cys Cys Ala  Gly Cys Cys Thr Cys  Ala Ala Thr
    2090                2095                2100

Gly Ala  Gly Ala Thr Gly Ala  Thr Cys Ala Ala Thr  Cys Cys Ala
    2105                2110                2115

Ala Ala  Cys Thr Ala Cys Ala  Thr Thr Gly Cys Cys  Ala Ala Cys
    2120                2125                2130

Cys Gly  Ala Gly Gly Thr Cys  Cys Cys Thr Gly Cys  Cys Cys Cys
    2135                2140                2145
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-continued

```
Ala Gly  Gly Gly Thr Gly Cys  Ala Ala Gly Ala Gly  Gly Cys Ala
    2150                 2155                 2160

Ala Gly  Ala Cys Cys Thr Gly  Gly Gly Gly Ala Thr  Cys Thr Gly
    2165                 2170                 2175

Gly Gly  Ala Ala Ala Gly Gly  Thr Gly Gly Ala Ala  Gly Cys Thr
    2180                 2185                 2190

Cys Thr  Gly Cys Thr Cys Cys  Ala Gly Gly Ala Gly  Gly Ala Cys
    2195                 2200                 2205

Cys Thr  Gly Cys Thr Gly Cys  Thr Gly Ala Cys Gly  Ala Ala Gly
    2210                 2215                 2220

Cys Cys  Cys Gly Ala Gly Ala  Thr Gly Thr Thr Thr  Gly Ala Gly
    2225                 2230                 2235

Ala Ala  Cys Cys Cys Ala Cys  Thr Gly Thr Ala Thr  Gly Gly Ala
    2240                 2245                 2250

Thr Cys  Cys Gly Thr Gly Ala  Gly Thr Thr Cys Cys  Thr Thr Cys
    2255                 2260                 2265

Cys Cys  Thr Ala Ala Gly Cys  Thr Gly Gly Thr Gly  Cys Cys Cys
    2270                 2275                 2280

Ala Gly  Gly Ala Ala Ala Gly  Ala Gly Cys Ala Gly  Gly Ala Gly
    2285                 2290                 2295

Thr Cys  Thr Cys Cys Cys Ala  Ala Gly Ala Thr Gly  Cys Thr Gly
    2300                 2305                 2310

Cys Gly  Gly Ala Ala Gly Gly  Ala Gly Cys Cys Cys  Cys Cys Gly
    2315                 2320                 2325

Cys Cys  Cys Thr Gly Thr Cys  Cys Ala Gly Ala Cys  Cys Cys Ala
    2330                 2335                 2340

Gly Gly  Ala Ala Thr Cys Thr  Cys Ala Thr Cys Ala  Cys Cys Cys
    2345                 2350                 2355

Ala Gly  Cys Ala Thr Cys Gly  Thr Gly Cys Thr Cys  Cys Cys Cys
    2360                 2365                 2370

Ala Ala  Ala Gly Cys Cys Cys  Ala Ala Gly Ala Gly  Gly Thr Gly
    2375                 2380                 2385

Gly Ala  Gly Ala Gly Thr Gly  Thr Cys Ala Ala Gly  Gly Gly Gly
    2390                 2395                 2400

Ala Cys  Ala Ala Gly Cys Ala  Ala Ala Cys Ala Gly  Gly Cys Cys
    2405                 2410                 2415

Cys Cys  Thr Gly Thr Gly Cys  Cys Thr Gly Thr Cys  Cys Thr Thr
    2420                 2425                 2430

Gly Gly  Cys Cys Cys Cys Ala  Cys Ala Cys Cys Cys  Cys Gly Gly
    2435                 2440                 2445

Ala Thr  Cys Cys Gly Cys Thr  Cys Cys Thr Thr Thr  Ala Cys Cys
    2450                 2455                 2460

Thr Gly  Thr Thr Cys Thr Thr  Cys Thr Thr Cys Thr  Gly Cys Thr
    2465                 2470                 2475

Gly Ala  Gly Gly Gly Cys Ala  Gly Ala Ala Thr Gly  Ala Cys Cys
    2480                 2485                 2490

Ala Gly  Thr Gly Gly Gly Gly  Ala Cys Ala Ala Gly  Ala Gly Cys
    2495                 2500                 2505

Cys Ala  Ala Gly Gly Gly Ala  Ala Gly Cys Cys Cys  Ala Ala Gly
    2510                 2515                 2520

Gly Cys  Cys Thr Cys Ala Gly  Cys Cys Ala Gly Thr  Thr Cys Cys
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    2525                2530                2535

Cys Ala  Ala Gly Cys Cys Cys  Cys Ala Gly Thr Gly  Cys Cys Ala
    2540                2545                2550

Gly Thr  Cys Ala Ala Gly Ala  Gly Gly Cys Cys Thr  Gly Thr Cys
    2555                2560                2565

Ala Ala  Gly Cys Cys Thr Thr  Cys Cys Ala Gly Gly  Thr Cys Ala
    2570                2575                2580

Gly Ala  Ala Ala Thr Gly Ala  Gly Cys Cys Ala Gly  Cys Ala Gly
    2585                2590                2595

Ala Cys  Ala Ala Cys Ala Cys  Cys Cys Ala Thr Cys  Cys Cys Ala
    2600                2605                2610

Gly Cys  Thr Cys Cys Ala Cys  Gly Gly Cys Cys Ala  Cys Cys Cys
    2615                2620                2625

Cys Thr  Gly Cys Cys Ala Gly  Thr Cys Ala Ala Gly  Ala Gly Thr
    2630                2635                2640

Cys Cys  Thr Gly Cys Thr Gly  Thr Cys Cys Thr Gly  Cys Ala Gly
    2645                2650                2655

Cys Thr  Gly Cys Ala Ala Cys  Ala Thr Thr Cys Cys  Ala Ala Ala
    2660                2665                2670

Gly Gly  Cys Ala Gly Ala Gly  Ala Cys Thr Ala Cys  Cys Gly Thr
    2675                2680                2685

Gly Ala  Cys Ala Ala Cys Ala  Cys Ala Gly Ala Ala  Cys Thr Cys
    2690                2695                2700

Cys Cys  Cys Cys Ala Cys Cys  Ala Thr Gly Gly Cys  Ala Ala Gly
    2705                2710                2715

Cys Ala  Cys Cys Gly Cys Cys  Ala Ala Gly Ala Gly  Gly Ala Gly
    2720                2725                2730

Gly Gly  Gly Cys Thr Gly Cys  Thr Thr Gly Gly Cys  Ala Gly Gly
    2735                2740                2745

Ala Cys  Thr Gly Cys Cys Ala  Thr Gly Cys Ala Gly  Thr Gly Ala
    2750                2755                2760

Gly Cys  Thr Gly Cys Thr Gly  Gly Thr Gly Ala Thr  Cys Gly Gly
    2765                2770                2775

Ala Gly  Cys Cys Thr Gly Gly  Ala Gly Gly Ala Ala  Cys Ala Gly
    2780                2785                2790

Cys Ala  Cys Ala Ala Ala Gly  Cys Ala Gly Ala Cys  Cys Thr Gly
    2795                2800                2805

Cys Gly  Cys Cys Thr Cys Thr  Cys Thr Cys Ala Gly  Gly Ala Thr
    2810                2815                2820

Gly Cys  Cys Thr Cys Thr Cys  Thr Cys Ala Gly Gly  Ala Thr Gly
    2825                2830                2835

Cys Cys  Thr Cys Thr Thr Gly  Gly Ala Gly Gly Ala  Cys Cys Thr
    2840                2845                2850

Cys Cys  Thr Gly Cys Thr Ala  Gly Cys Thr Cys Thr  Thr Cys Thr
    2855                2860                2865

Thr Gly  Cys Cys Thr Ala Gly  Cys Thr Thr Cys Ala  Ala Gly Thr
    2870                2875                2880

Cys Cys  Cys Ala Gly Gly Cys  Thr Gly Thr Gly Thr  Ala Thr Thr
    2885                2890                2895

Thr Thr  Thr Thr Thr Thr Cys  Ala Gly Gly Ala Ala  Ala Cys Gly
    2900                2905                2910
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Gly Cys  Cys Thr Cys Ala Cys  Thr Thr Cys Thr Cys  Thr Gly Thr
    2915                 2920                 2925

Gly Gly  Thr Cys Cys Ala Ala  Gly Ala Ala Gly Thr  Gly Thr Gly
    2930                 2935                 2940

Cys Thr  Gly Cys Thr Gly Gly  Cys Thr Gly Cys Cys  Ala Cys Ala
    2945                 2950                 2955

Cys Thr  Gly Thr Gly Cys Gly  Gly Cys Ala Gly Ala  Thr Gly Cys
    2960                 2965                 2970

Thr Ala  Ala Ala Gly Cys Thr  Gly Gly Ala Thr Gly  Ala Cys Ala
    2975                 2980                 2985

Ala Ala  Cys Gly Cys Ala Cys  Gly Cys Cys Ala Thr  Ala Cys Ala
    2990                 2995                 3000

Gly Ala  Cys Ala Gly Cys Ala  Gly Ala Cys Ala Gly  Cys Gly Gly
    3005                 3010                 3015

Cys Ala  Cys Thr Gly Gly Gly  Thr Cys Thr Cys Ala  Gly Ala Ala
    3020                 3025                 3030

Cys Thr  Thr Gly Gly Ala Thr  Thr Cys Cys Thr Gly  Gly Gly Cys
    3035                 3040                 3045

Cys Thr  Thr Cys Thr Thr Cys  Cys Ala Gly Thr Cys  Gly Cys Cys
    3050                 3055                 3060

Gly Thr  Thr Thr Thr Ala Ala  Ala Gly Ala Ala Ala  Gly Gly Ala
    3065                 3070                 3075

Ala Cys  Thr Ala Ala Cys Gly  Gly Ala Gly Cys Thr  Gly Cys Thr
    3080                 3085                 3090

Cys Ala  Thr Cys Cys Gly Ala  Gly Gly Gly Thr Gly  Ala Ala Gly
    3095                 3100                 3105

Ala Thr  Ala Thr Ala Ala Ala  Thr Ala Ala Thr Ala  Ala Thr Ala
    3110                 3115                 3120

Thr Thr  Ala Thr Thr Ala Ala  Thr Ala Ala Thr Ala  Ala Thr Ala
    3125                 3130                 3135

Ala Cys  Ala Gly Thr Cys Ala  Gly Gly Thr Gly Cys  Cys Ala Thr
    3140                 3145                 3150

Gly Thr  Gly Cys Thr Gly Thr  Gly Thr Thr Ala Ala  Gly Thr Gly
    3155                 3160                 3165

Cys Thr  Thr Thr Ala Thr Gly  Ala Ala Cys Ala Thr  Thr Thr Gly
    3170                 3175                 3180

Thr Cys  Gly Gly Gly Cys Thr  Gly Gly Cys Cys Thr  Cys Cys Ala
    3185                 3190                 3195

Gly Thr  Gly Cys Thr Gly Ala  Gly Gly Thr Gly Cys  Cys Ala Gly
    3200                 3205                 3210

Thr Cys  Ala Gly Cys Cys Thr  Gly Ala Ala Cys Cys  Cys Thr Ala
    3215                 3220                 3225

Thr Gly  Cys Cys Cys Ala Gly  Gly Cys Cys Cys Ala  Cys Thr Ala
    3230                 3235                 3240

Ala Thr  Cys Cys Cys Ala Ala  Ala Thr Gly Gly Thr  Gly Gly Gly
    3245                 3250                 3255

Thr Cys  Cys Thr Gly Ala Gly  Ala Thr Gly Thr Thr  Thr Thr Thr
    3260                 3265                 3270

Ala Ala  Ala Ala Ala Gly Cys  Ala Thr Thr Ala Ala  Ala Gly Ala
    3275                 3280                 3285
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```
Ala Ala  Ala Cys Cys Ala Thr  Cys Gly Gly Thr Cys  Thr Cys Thr
    3290                 3295                 3300

Thr Ala  Gly Ala Gly Cys Thr  Ala Ala Cys Cys Gly  Gly Cys Cys
    3305                 3310                 3315

Gly Gly  Gly Cys Thr Cys Thr  Ala Cys Thr Gly Cys  Ala Gly Gly
    3320                 3325                 3330

Gly Ala  Cys Cys Cys Gly Ala  Ala Cys Ala Gly Thr  Cys Thr Gly
    3335                 3340                 3345

Cys Ala  Thr Gly Gly Cys Thr  Ala Ala Gly Thr Gly  Gly Cys Ala
    3350                 3355                 3360

Cys Ala  Ala Gly Gly Ala Gly  Cys Cys Thr Gly Gly  Cys Cys Cys
    3365                 3370                 3375

Thr Gly  Thr Cys Cys Ala Gly  Cys Thr Thr Cys Ala  Gly Ala Gly
    3380                 3385                 3390

Ala Thr  Cys Cys Ala Ala Gly  Cys Thr Gly Cys Thr  Thr Thr Thr
    3395                 3400                 3405

Thr Gly  Cys Thr Gly Gly Gly  Gly Thr Thr Cys Thr  Gly Thr Cys
    3410                 3415                 3420

Ala Cys  Ala Gly Gly Cys Cys  Thr Gly Ala Thr Cys  Cys Thr Cys
    3425                 3430                 3435

Thr Thr  Gly Gly Thr Thr Thr  Thr Thr Ala Thr Gly  Gly Gly Gly
    3440                 3445                 3450

Thr Thr  Thr Cys Ala Ala Gly  Thr Cys Thr Gly Cys  Cys Ala Gly
    3455                 3460                 3465

Ala Gly  Thr Cys Ala Gly Ala  Ala Ala Thr Cys Ala  Gly Cys Thr
    3470                 3475                 3480

Cys Thr  Ala Ala Cys Thr Cys  Gly Cys Cys Ala Gly  Thr Gly Ala
    3485                 3490                 3495

Ala Gly  Ala Gly Ala Thr Cys  Thr Gly Gly Cys Cys  Thr Thr Ala
    3500                 3505                 3510

Ala Cys  Thr Thr Ala Ala Gly  Cys Cys Ala Gly Cys  Cys Ala Cys
    3515                 3520                 3525

Gly Thr  Cys Ala Gly Gly Cys  Cys Cys Cys Thr Gly  Cys Thr Gly
    3530                 3535                 3540

Ala Gly  Cys Cys Thr Ala Thr  Gly Gly Ala Cys Cys  Ala Ala Thr
    3545                 3550                 3555

Ala Ala  Ala Thr Ala Cys Thr  Cys Cys Cys Cys Gly  Thr Gly Cys
    3560                 3565                 3570

Cys Ala  Cys Thr Gly Gly Ala  Gly Gly Thr Gly Gly  Gly Cys Ala
    3575                 3580                 3585

Gly Cys  Thr Ala Thr Cys Ala  Cys Cys Ala Thr Ala  Cys Cys Cys
    3590                 3595                 3600

Thr Gly  Ala Gly Thr Thr Gly  Gly Gly Cys Cys Ala  Ala Gly Cys
    3605                 3610                 3615

Cys Cys  Ala Cys Cys Cys Cys  Ala Cys Cys Cys Cys  Thr Ala Cys
    3620                 3625                 3630

Cys Cys  Thr Gly Cys Ala Ala  Cys Ala Thr Thr Thr  Cys Thr Gly
    3635                 3640                 3645

Ala Thr  Gly Thr Trp Cys Thr  Gly Ala Gly Gly Ala  Ala Gly Ala
    3650                 3655                 3660

Gly Thr  Cys Thr Cys Cys Ala  Cys Cys Ala Thr Ala  Gly Thr Cys
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    3665                3670                3675

Cys Cys  Cys Ala Ala Gly Gly  Gly Cys Thr Gly Ala  Gly Thr Thr
    3680                3685                3690

Cys Thr  Cys Cys Ala Gly Cys  Cys Thr Gly Cys Thr  Ala Thr Cys
    3695                3700                3705

Ala Gly  Gly Gly Ala Ala Gly  Gly Thr Gly Ala Gly  Cys Ala Thr
    3710                3715                3720

Thr Gly  Gly Thr Cys Cys Cys  Ala Gly Gly Cys Thr  Cys Thr Cys
    3725                3730                3735

Ala Ala  Ala Ala Thr Ala Gly  Thr Gly Cys Ala Gly  Cys Cys Thr
    3740                3745                3750

Cys Thr  Thr Cys Thr Thr Cys  Cys Cys Ala Ala Gly  Cys Thr Cys
    3755                3760                3765

Thr Gly  Gly Gly Gly Thr Gly  Cys Ala Cys Cys Cys  Thr Gly Thr
    3770                3775                3780

Gly Thr  Cys Cys Thr Thr Gly  Gly Thr Thr Ala Cys  Cys Ala Gly
    3785                3790                3795

Gly Ala  Gly Ala Cys Thr Ala  Gly Gly Gly Thr Thr  Gly Thr Gly
    3800                3805                3810

Ala Thr  Ala Thr Cys Thr Thr  Thr Thr Cys Thr Thr  Gly Thr Cys
    3815                3820                3825

Thr Thr  Gly Cys Thr Thr Thr  Thr Thr Gly Ala Thr  Ala Thr Ala
    3830                3835                3840

Thr Cys  Ala Gly Gly Ala Thr  Thr Ala Ala Thr Gly  Thr Ala Gly
    3845                3850                3855

Gly Ala  Ala Ala Cys Cys Ala  Gly Ala Cys Cys Thr  Ala Gly Ala
    3860                3865                3870

Thr Thr  Ala Thr Thr Cys Ala  Gly Gly Ala Gly Ala  Gly Thr Ala
    3875                3880                3885

Gly Gly  Thr Ala Thr Ala Thr  Cys Cys Cys Cys Thr  Gly Thr Gly
    3890                3895                3900

Thr Thr  Thr Cys Cys Cys Ala  Gly Thr Cys Thr Gly  Ala Gly Thr
    3905                3910                3915

Gly Ala  Cys Cys Ala Ala Thr  Ala Ala Ala Ala Thr  Thr Gly Thr
    3920                3925                3930

Gly Cys  Cys Thr Thr Thr Cys  Thr Ala
    3935                3940


<210> SEQ ID NO 3
<211> LENGTH: 4147
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

Cys Gly Cys Cys Cys Ala Cys Thr Ala Ala Thr Cys Cys Thr Thr Gly
1               5                  10                  15

Ala Thr Gly Thr Thr Cys Ala Cys Cys Thr Thr Gly Thr Cys Cys Cys
            20                  25                  30

Cys Thr Gly Cys Cys Cys Cys Cys Ala Gly Ala Gly Ala Ala Gly Thr
        35                  40                  45

Cys Ala Thr Cys Cys Gly Gly Ala Cys Cys Cys Thr Cys Cys Cys Ala
    50                  55                  60
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Thr Cys Cys Cys Thr Gly Gly Ala Gly Thr Cys Thr Cys Thr Gly Cys
65                  70                  75                  80

Ala Gly Ala Gly Gly Thr Thr Ala Thr Thr Thr Gly Ala Cys Cys Ala
                85                  90                  95

Gly Cys Ala Gly Cys Thr Cys Thr Cys Cys Cys Cys Gly Gly Gly Cys
            100                 105                 110

Cys Thr Cys Cys Gly Thr Cys Cys Ala Cys Gly Thr Cys Cys Thr Cys
        115                 120                 125

Ala Gly Gly Thr Thr Cys Cys Thr Gly Gly Thr Gly Ala Gly Gly Cys
    130                 135                 140

Cys Ala Ala Thr Cys Cys Cys Ala Thr Cys Ala Ala Cys Ala Thr Gly
145                 150                 155                 160

Gly Thr Gly Thr Cys Cys Ala Ala Gly Cys Thr Cys Ala Gly Cys Cys
                165                 170                 175

Ala Ala Cys Thr Gly Ala Cys Ala Ala Gly Cys Cys Thr Gly Thr Thr
            180                 185                 190

Gly Thr Cys Ala Thr Cys Cys Ala Thr Thr Gly Ala Ala Gly Ala Cys
        195                 200                 205

Ala Ala Gly Gly Thr Cys Ala Ala Gly Gly Cys Cys Thr Thr Gly Cys
    210                 215                 220

Thr Gly Cys Ala Cys Gly Ala Gly Gly Gly Thr Cys Cys Thr Gly Ala
225                 230                 235                 240

Gly Thr Cys Thr Cys Cys Gly Cys Ala Cys Cys Gly Gly Cys Cys Cys
                245                 250                 255

Thr Cys Cys Cys Thr Thr Ala Thr Cys Cys Cys Thr Cys Cys Ala Gly
            260                 265                 270

Thr Cys Ala Cys Cys Thr Thr Thr Gly Ala Gly Gly Thr Gly Ala Ala
        275                 280                 285

Gly Gly Cys Ala Gly Ala Gly Thr Cys Thr Cys Thr Gly Gly Gly Gly
    290                 295                 300

Ala Thr Thr Cys Cys Thr Cys Ala Gly Ala Ala Ala Ala Thr Gly Cys
305                 310                 315                 320

Ala Gly Cys Thr Cys Ala Ala Ala Gly Thr Cys Gly Ala Cys Gly Thr
                325                 330                 335

Thr Gly Ala Gly Thr Cys Thr Gly Gly Gly Ala Ala Ala Cys Thr Gly
            340                 345                 350

Ala Thr Cys Ala Thr Thr Ala Ala Gly Ala Ala Gly Thr Cys Cys Ala
        355                 360                 365

Ala Gly Gly Ala Thr Gly Gly Thr Thr Cys Thr Gly Ala Gly Gly Ala
    370                 375                 380

Cys Ala Ala Gly Thr Thr Cys Thr Ala Cys Ala Gly Cys Cys Ala Cys
385                 390                 395                 400

Ala Ala Gly Ala Ala Ala Ala Thr Cys Cys Thr Gly Cys Ala Gly Cys
                405                 410                 415

Thr Cys Ala Thr Thr Ala Ala Gly Thr Cys Ala Cys Ala Gly Ala Ala
            420                 425                 430

Ala Thr Thr Thr Cys Thr Gly Ala Ala Thr Ala Ala Gly Thr Thr Gly
        435                 440                 445

Gly Thr Gly Ala Thr Cys Thr Thr Gly Gly Thr Gly Gly Ala Ala Ala
    450                 455                 460

Cys Ala Gly Ala Gly Ala Ala Gly Gly Ala Gly Ala Ala Gly Ala Thr
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465                 470                 475                 480

Cys Cys Thr Gly Cys Gly Gly Ala Ala Gly Gly Ala Ala Thr Ala Thr
                485                 490                 495

Gly Thr Thr Thr Thr Thr Gly Cys Thr Gly Ala Cys Thr Cys Cys Ala
            500                 505                 510

Ala Ala Ala Ala Gly Ala Gly Ala Gly Ala Ala Gly Gly Cys Thr Thr
        515                 520                 525

Cys Thr Gly Cys Cys Ala Gly Cys Thr Cys Cys Thr Gly Cys Ala Gly
    530                 535                 540

Cys Ala Gly Ala Thr Gly Ala Ala Gly Ala Ala Cys Ala Ala Gly Cys
545                 550                 555                 560

Ala Cys Thr Cys Ala Gly Ala Gly Cys Ala Gly Cys Cys Gly Gly Ala
                565                 570                 575

Gly Cys Cys Cys Gly Ala Cys Ala Thr Gly Ala Thr Cys Ala Cys Cys
            580                 585                 590

Ala Thr Cys Thr Thr Cys Ala Thr Cys Gly Gly Cys Ala Cys Cys Thr
        595                 600                 605

Gly Gly Ala Ala Cys Ala Thr Gly Gly Gly Thr Ala Ala Cys Gly Cys
    610                 615                 620

Cys Cys Cys Cys Cys Cys Thr Cys Cys Cys Ala Ala Gly Ala Ala Gly
625                 630                 635                 640

Ala Thr Cys Ala Cys Gly Thr Cys Cys Thr Gly Gly Thr Thr Thr Cys
                645                 650                 655

Thr Cys Thr Cys Cys Ala Ala Gly Gly Gly Gly Cys Ala Gly Gly Gly
            660                 665                 670

Ala Ala Ala Gly Ala Cys Gly Cys Gly Gly Gly Ala Cys Gly Ala Cys
        675                 680                 685

Thr Cys Thr Gly Cys Gly Gly Ala Cys Thr Ala Cys Ala Thr Cys Cys
    690                 695                 700

Cys Cys Cys Ala Thr Gly Ala Cys Ala Thr Thr Thr Ala Cys Gly Thr
705                 710                 715                 720

Gly Ala Thr Cys Gly Gly Cys Ala Cys Cys Cys Ala Ala Gly Ala Gly
                725                 730                 735

Gly Ala Cys Cys Cys Cys Cys Thr Gly Ala Gly Thr Gly Ala Gly Ala
            740                 745                 750

Ala Gly Gly Ala Gly Thr Gly Gly Cys Thr Gly Gly Ala Gly Ala Thr
        755                 760                 765

Cys Cys Thr Cys Ala Ala Ala Cys Ala Cys Thr Cys Cys Cys Thr Gly
    770                 775                 780

Cys Ala Ala Gly Ala Ala Ala Thr Cys Ala Cys Cys Ala Gly Thr Gly
785                 790                 795                 800

Thr Gly Ala Cys Thr Thr Thr Thr Ala Ala Ala Ala Cys Ala Gly Thr
                805                 810                 815

Cys Gly Cys Cys Ala Thr Cys Cys Ala Cys Ala Cys Gly Cys Thr Cys
            820                 825                 830

Thr Gly Gly Ala Ala Cys Ala Thr Cys Cys Gly Cys Ala Thr Cys Gly
        835                 840                 845

Thr Gly Gly Thr Gly Cys Thr Gly Gly Cys Cys Ala Ala Gly Cys Cys
    850                 855                 860

Thr Gly Ala Gly Cys Ala Cys Gly Ala Gly Ala Ala Cys Cys Gly Gly
865                 870                 875                 880
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Ala Thr Cys Ala Gly Cys Cys Ala Cys Ala Thr Cys Thr Gly Thr Ala
                885                 890                 895

Cys Thr Gly Ala Cys Ala Ala Cys Gly Thr Gly Ala Ala Gly Ala Cys
            900                 905                 910

Ala Gly Gly Cys Ala Thr Thr Gly Cys Ala Ala Ala Cys Ala Cys Ala
        915                 920                 925

Cys Thr Gly Gly Gly Gly Ala Ala Cys Ala Ala Gly Gly Gly Ala Gly
    930                 935                 940

Cys Cys Gly Thr Gly Gly Gly Gly Gly Thr Gly Thr Cys Gly Thr Thr
945                 950                 955                 960

Cys Ala Thr Gly Thr Thr Cys Ala Ala Thr Gly Gly Ala Ala Cys Cys
                965                 970                 975

Thr Cys Cys Thr Thr Ala Gly Gly Gly Thr Thr Cys Gly Thr Cys Ala
            980                 985                 990

Ala Cys Ala Gly Cys Cys Ala Cys  Thr Thr Gly Ala Cys  Thr Thr Cys
        995                 1000                1005

Ala Gly  Gly Ala Ala Gly Thr  Gly Ala Ala Ala Ala  Gly Ala Ala
    1010                1015                1020

Ala Cys  Thr Cys Ala Gly Gly  Cys Gly Ala Ala Ala  Cys Cys Ala
    1025                1030                1035

Ala Ala  Ala Cys Thr Ala Thr  Ala Thr Gly Ala Ala  Cys Ala Thr
    1040                1045                1050

Thr Cys  Thr Cys Cys Gly Gly  Thr Thr Cys Cys Thr  Gly Gly Cys
    1055                1060                1065

Cys Cys  Thr Gly Gly Gly Cys  Gly Ala Cys Ala Ala  Gly Ala Ala
    1070                1075                1080

Gly Cys  Thr Gly Ala Gly Thr  Cys Cys Cys Thr Thr  Thr Ala Ala
    1085                1090                1095

Cys Ala  Thr Cys Ala Cys Thr  Cys Ala Cys Cys Gly  Cys Thr Thr
    1100                1105                1110

Cys Ala  Cys Gly Cys Ala Cys  Cys Thr Cys Thr Thr  Cys Thr Gly
    1115                1120                1125

Gly Thr  Thr Thr Gly Gly Gly  Gly Ala Thr Cys Thr  Thr Ala Ala
    1130                1135                1140

Cys Thr  Ala Cys Cys Gly Thr  Gly Thr Gly Gly Ala  Thr Cys Thr
    1145                1150                1155

Gly Cys  Cys Thr Ala Cys Cys  Thr Gly Gly Gly Ala  Gly Gly Cys
    1160                1165                1170

Ala Gly  Ala Ala Ala Cys Cys  Ala Thr Cys Ala Thr  Cys Cys Ala
    1175                1180                1185

Gly Ala  Ala Ala Ala Thr Cys  Ala Ala Gly Cys Ala  Gly Cys Ala
    1190                1195                1200

Gly Cys  Ala Gly Thr Ala Cys  Gly Cys Ala Gly Ala  Cys Cys Thr
    1205                1210                1215

Cys Cys  Thr Gly Thr Cys Cys  Cys Ala Cys Gly Ala  Cys Cys Ala
    1220                1225                1230

Gly Cys  Thr Gly Cys Thr Cys  Ala Cys Ala Gly Ala  Gly Ala Gly
    1235                1240                1245

Gly Ala  Gly Gly Gly Ala Gly  Cys Ala Gly Ala Ala  Gly Gly Thr
    1250                1255                1260
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Cys Thr  Thr Cys Cys Thr Ala  Cys Ala Cys Thr Thr  Cys Gly Ala
    1265                1270                1275

Gly Gly  Ala Gly Gly Ala Ala  Gly Ala Ala Ala Thr  Cys Ala Cys
    1280                1285                1290

Gly Thr  Thr Thr Gly Cys Cys  Cys Cys Ala Ala Cys  Cys Thr Ala
    1295                1300                1305

Cys Cys  Gly Thr Thr Thr Thr  Gly Ala Gly Ala Gly  Ala Cys Thr
    1310                1315                1320

Gly Ala  Cys Thr Cys Gly Gly  Gly Ala Cys Ala Ala  Ala Thr Ala
    1325                1330                1335

Cys Gly  Cys Cys Thr Ala Cys  Ala Cys Cys Ala Ala  Gly Cys Ala
    1340                1345                1350

Gly Ala  Ala Ala Gly Cys Gly  Ala Cys Ala Gly Gly  Gly Ala Thr
    1355                1360                1365

Gly Ala  Ala Gly Thr Ala Cys  Ala Ala Cys Thr Thr  Gly Cys Cys
    1370                1375                1380

Thr Thr  Cys Cys Thr Gly Gly  Thr Gly Thr Gly Ala  Cys Cys Gly
    1385                1390                1395

Ala Gly  Thr Cys Cys Thr Cys  Thr Gly Gly Ala Ala  Gly Thr Cys
    1400                1405                1410

Thr Thr  Ala Thr Cys Cys Cys  Cys Thr Gly Gly Thr  Gly Cys Ala
    1415                1420                1425

Cys Gly  Thr Gly Gly Thr Gly  Thr Gly Thr Cys Ala  Gly Thr Cys
    1430                1435                1440

Thr Thr  Ala Thr Gly Gly Cys  Ala Gly Thr Ala Cys  Cys Ala Gly
    1445                1450                1455

Cys Gly  Ala Cys Ala Thr Cys  Ala Thr Gly Ala Cys  Gly Ala Gly
    1460                1465                1470

Thr Gly  Ala Cys Cys Ala Cys  Ala Gly Cys Cys Cys  Thr Gly Thr
    1475                1480                1485

Cys Thr  Thr Thr Gly Cys Cys  Ala Cys Ala Thr Thr  Thr Gly Ala
    1490                1495                1500

Gly Gly  Cys Ala Gly Gly Ala  Gly Thr Cys Ala Cys  Thr Thr Cys
    1505                1510                1515

Cys Cys  Ala Gly Thr Thr Thr  Gly Thr Cys Thr Cys  Cys Ala Ala
    1520                1525                1530

Gly Ala  Ala Cys Gly Gly Thr  Cys Cys Cys Gly Gly  Gly Ala Cys
    1535                1540                1545

Thr Gly  Thr Thr Gly Ala Cys  Ala Gly Cys Cys Ala  Ala Gly Gly
    1550                1555                1560

Ala Cys  Ala Gly Ala Thr Thr  Gly Ala Gly Thr Thr  Thr Cys Thr
    1565                1570                1575

Cys Ala  Gly Gly Thr Gly Cys  Thr Ala Thr Gly Cys  Cys Ala Cys
    1580                1585                1590

Ala Thr  Thr Gly Ala Ala Gly  Ala Cys Cys Ala Ala  Gly Thr Cys
    1595                1600                1605

Cys Cys  Ala Gly Ala Cys Cys  Ala Ala Ala Thr Thr  Cys Thr Ala
    1610                1615                1620

Cys Cys  Thr Gly Gly Ala Gly  Thr Thr Cys Cys Ala  Cys Thr Cys
    1625                1630                1635

Gly Ala  Gly Cys Thr Gly Cys  Thr Thr Gly Gly Ala  Gly Ala Gly
```

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```
    1640                1645                1650

Thr Thr  Thr Thr Gly Thr Cys  Ala Ala Gly Ala Gly  Thr Cys Ala
    1655                1660                1665

Gly Gly  Ala Ala Gly Gly Ala  Gly Ala Ala Ala Ala  Thr Gly Ala
    1670                1675                1680

Ala Gly  Ala Ala Gly Gly Ala  Ala Gly Thr Gly Ala  Gly Gly Gly
    1685                1690                1695

Gly Gly  Ala Gly Cys Thr Gly  Gly Thr Gly Gly Thr  Gly Ala Ala
    1700                1705                1710

Gly Thr  Thr Thr Gly Gly Thr  Gly Ala Gly Ala Cys  Thr Cys Thr
    1715                1720                1725

Thr Cys  Cys Ala Ala Ala Gly  Cys Thr Gly Ala Ala  Gly Cys Cys
    1730                1735                1740

Cys Ala  Thr Thr Ala Thr Cys  Thr Cys Thr Gly Ala  Cys Cys Cys
    1745                1750                1755

Thr Gly  Ala Gly Thr Ala Cys  Cys Thr Gly Cys Thr  Ala Gly Ala
    1760                1765                1770

Cys Cys  Ala Gly Cys Ala Cys  Ala Thr Cys Cys Thr  Cys Ala Thr
    1775                1780                1785

Cys Ala  Gly Cys Ala Thr Cys  Ala Ala Gly Thr Cys  Cys Thr Cys
    1790                1795                1800

Thr Gly  Ala Cys Ala Gly Cys  Gly Ala Cys Gly Ala  Ala Thr Cys
    1805                1810                1815

Cys Thr  Ala Thr Gly Gly Cys  Gly Ala Gly Gly Gly  Cys Thr Gly
    1820                1825                1830

Cys Ala  Thr Thr Gly Cys Cys  Cys Thr Thr Cys Gly  Gly Thr Thr
    1835                1840                1845

Ala Gly  Ala Gly Gly Cys Cys  Ala Cys Ala Gly Ala  Ala Ala Cys
    1850                1855                1860

Gly Cys  Ala Gly Cys Thr Gly  Cys Cys Cys Ala Thr  Cys Thr Ala
    1865                1870                1875

Cys Ala  Cys Gly Cys Cys Thr  Cys Thr Cys Ala Cys  Cys Cys Ala
    1880                1885                1890

Cys Cys  Ala Thr Gly Gly Gly  Gly Ala Gly Thr Thr  Gly Ala Cys
    1895                1900                1905

Ala Gly  Gly Cys Cys Ala Cys  Thr Thr Cys Cys Ala  Gly Gly Gly
    1910                1915                1920

Gly Gly  Ala Gly Ala Thr Cys  Ala Ala Gly Cys Thr  Gly Cys Ala
    1925                1930                1935

Gly Ala  Cys Cys Thr Cys Thr  Cys Ala Gly Gly Gly  Cys Ala Ala
    1940                1945                1950

Gly Ala  Cys Gly Ala Gly Gly  Gly Ala Gly Ala Ala  Gly Cys Thr
    1955                1960                1965

Cys Thr  Ala Thr Gly Ala Cys  Thr Thr Thr Gly Thr  Gly Ala Ala
    1970                1975                1980

Gly Ala  Cys Gly Gly Ala Gly  Cys Gly Thr Gly Ala  Thr Gly Ala
    1985                1990                1995

Ala Thr  Cys Cys Ala Gly Thr  Gly Gly Gly Cys Cys  Ala Ala Ala
    2000                2005                2010

Gly Ala  Cys Cys Cys Thr Gly  Ala Ala Gly Ala Gly  Cys Cys Thr
    2015                2020                2025
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```
Cys Ala  Cys Cys Ala Gly Cys  Cys Ala Cys Gly Ala  Cys Cys Cys
    2030                2035                2040

Cys Ala  Thr Gly Ala Ala Gly  Cys Ala Gly Thr Gly  Gly Gly Ala
    2045                2050                2055

Ala Gly  Thr Cys Ala Cys Thr  Ala Gly Cys Ala Gly  Gly Gly Cys
    2060                2065                2070

Cys Cys  Cys Thr Cys Cys Gly  Thr Gly Cys Ala Gly  Thr Gly Gly
    2075                2080                2085

Cys Thr  Cys Cys Ala Gly Cys  Ala Thr Cys Ala Cys  Thr Gly Ala
    2090                2095                2100

Ala Ala  Thr Cys Ala Thr Cys  Ala Ala Cys Cys Cys  Cys Ala Ala
    2105                2110                2115

Cys Thr  Ala Cys Ala Thr Gly  Gly Gly Ala Gly Thr  Gly Gly Gly
    2120                2125                2130

Gly Cys  Cys Cys Thr Thr Thr  Gly Gly Gly Cys Cys  Ala Cys Cys
    2135                2140                2145

Ala Ala  Thr Gly Cys Cys Cys  Cys Thr Gly Cys Ala  Cys Gly Thr
    2150                2155                2160

Gly Ala  Ala Gly Cys Ala Gly  Ala Cys Cys Thr Thr  Gly Thr Cys
    2165                2170                2175

Cys Cys  Cys Thr Gly Ala Cys  Cys Ala Gly Cys Ala  Gly Cys Cys
    2180                2185                2190

Cys Ala  Cys Ala Gly Cys Cys  Thr Gly Gly Ala Gly  Cys Thr Ala
    2195                2200                2205

Cys Gly  Ala Cys Cys Ala Gly  Cys Cys Gly Cys Cys  Cys Ala Ala
    2210                2215                2220

Gly Gly  Ala Cys Thr Cys Cys  Cys Cys Gly Cys Thr  Gly Gly Gly
    2225                2230                2235

Gly Cys  Cys Cys Thr Gly Cys  Ala Gly Gly Gly Gly  Ala Gly Ala
    2240                2245                2250

Ala Ala  Gly Thr Cys Cys Thr  Cys Cys Gly Ala Cys  Ala Cys Cys
    2255                2260                2265

Thr Cys  Cys Cys Gly Gly Cys  Cys Ala Gly Cys Cys  Gly Cys Cys
    2270                2275                2280

Cys Ala  Thr Ala Thr Cys Ala  Cys Cys Cys Ala Ala  Gly Ala Ala
    2285                2290                2295

Gly Thr  Thr Thr Thr Thr Ala  Cys Cys Cys Thr Cys  Ala Ala Cys
    2300                2305                2310

Ala Gly  Cys Ala Ala Ala Cys  Cys Gly Gly Gly Gly  Thr Cys Thr
    2315                2320                2325

Cys Cys  Cys Thr Cys Cys Cys  Ala Gly Gly Ala Cys  Ala Cys Ala
    2330                2335                2340

Gly Gly  Ala Gly Thr Cys Ala  Ala Gly Gly Cys Cys  Cys Ala Gly
    2345                2350                2355

Thr Gly  Ala Cys Cys Thr Gly  Gly Gly Gly Ala Ala  Gly Ala Ala
    2360                2365                2370

Cys Gly  Cys Ala Gly Gly Gly  Gly Ala Cys Ala Cys  Gly Cys Thr
    2375                2380                2385

Gly Cys  Cys Thr Cys Ala Gly  Gly Ala Gly Gly Ala  Cys Cys Thr
    2390                2395                2400
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```
Gly Cys  Cys Gly Cys Thr Gly  Ala Cys Gly Ala Ala  Gly Cys Cys
    2405                2410                2415

Cys Gly  Ala Gly Ala Thr Gly  Thr Thr Thr Gly Ala  Gly Ala Ala
    2420                2425                2430

Cys Cys  Cys Cys Cys Thr Gly  Thr Ala Thr Gly Gly  Gly Thr Cys
    2435                2440                2445

Cys Cys  Thr Gly Ala Gly Thr  Thr Cys Cys Thr Thr  Cys Cys Cys
    2450                2455                2460

Thr Ala  Ala Gly Cys Cys Thr  Gly Cys Thr Cys Cys  Cys Ala Gly
    2465                2470                2475

Gly Ala  Ala Gly Gly Ala Cys  Cys Ala Gly Gly Ala  Ala Thr Cys
    2480                2485                2490

Cys Cys  Cys Cys Ala Ala Ala  Ala Thr Gly Cys Cys  Gly Cys Gly
    2495                2500                2505

Gly Ala  Ala Gly Gly Ala Ala  Cys Cys Cys Cys Cys  Gly Cys Cys
    2510                2515                2520

Cys Thr  Gly Cys Cys Cys Gly  Gly Ala Ala Cys Cys  Cys Gly Gly
    2525                2530                2535

Cys Ala  Thr Cys Thr Thr Gly  Thr Cys Gly Cys Cys  Cys Ala Gly
    2540                2545                2550

Cys Ala  Thr Cys Gly Thr Gly  Cys Thr Cys Ala Cys  Cys Ala Ala
    2555                2560                2565

Ala Gly  Cys Cys Cys Ala Gly  Gly Ala Gly Gly Cys  Thr Gly Ala
    2570                2575                2580

Thr Cys  Gly Cys Gly Gly Cys  Gly Ala Gly Gly Gly  Gly Cys Cys
    2585                2590                2595

Cys Gly  Gly Cys Ala Ala Gly  Cys Ala Gly Gly Thr  Gly Cys Cys
    2600                2605                2610

Cys Gly  Cys Gly Cys Cys Cys  Cys Gly Gly Cys Thr  Gly Cys Gly
    2615                2620                2625

Cys Thr  Cys Cys Thr Thr Cys  Ala Cys Gly Thr Gly  Cys Thr Cys
    2630                2635                2640

Ala Thr  Cys Cys Thr Cys Thr  Gly Cys Cys Gly Ala  Gly Gly Gly
    2645                2650                2655

Cys Ala  Gly Gly Gly Cys Gly  Gly Cys Cys Gly Gly  Cys Gly Gly
    2660                2665                2670

Gly Gly  Ala Cys Ala Ala Gly  Ala Gly Cys Cys Ala  Ala Gly Gly
    2675                2680                2685

Gly Ala  Ala Gly Cys Cys Cys  Ala Ala Gly Ala Cys  Cys Cys Cys
    2690                2695                2700

Gly Gly  Thr Cys Ala Gly Cys  Thr Cys Cys Cys Ala  Gly Gly Cys
    2705                2710                2715

Cys Cys  Cys Gly Gly Thr Gly  Cys Cys Gly Gly Cys  Cys Ala Ala
    2720                2725                2730

Gly Ala  Gly Gly Cys Cys Cys  Ala Thr Cys Ala Ala  Gly Cys Cys
    2735                2740                2745

Thr Thr  Cys Cys Ala Gly Ala  Thr Cys Gly Gly Ala  Ala Ala Thr
    2750                2755                2760

Cys Ala  Ala Cys Cys Ala Gly  Cys Ala Gly Ala Cys  Cys Cys Cys
    2765                2770                2775

Gly Cys  Cys Cys Ala Cys Cys  Cys Cys Gly Ala Cys  Gly Cys Cys
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    2780                2785                2790

Gly Cys  Gly Gly Cys Cys Gly  Cys Cys Gly Cys Thr  Gly Cys Cys
    2795                2800                2805

Ala Gly  Thr Cys Ala Ala Gly  Ala Gly Cys Cys Cys  Gly Gly Cys
    2810                2815                2820

Gly Gly  Thr Gly Cys Thr Gly  Cys Ala Cys Cys Thr  Cys Cys Ala
    2825                2830                2835

Gly Cys  Ala Cys Thr Cys Cys  Ala Ala Gly Gly Gly  Cys Cys Gly
    2840                2845                2850

Cys Gly  Ala Cys Thr Ala Cys  Cys Gly Cys Gly Ala  Cys Ala Ala
    2855                2860                2865

Cys Ala  Cys Cys Gly Ala Gly  Cys Thr Cys Cys Cys  Gly Cys Ala
    2870                2875                2880

Thr Cys  Ala Cys Gly Gly Cys  Ala Ala Gly Cys Ala  Cys Cys Gly
    2885                2890                2895

Gly Cys  Cys Gly Gly Ala Gly  Gly Ala Gly Gly Gly  Gly Cys Cys
    2900                2905                2910

Ala Cys  Cys Ala Gly Gly Gly  Cys Cys Thr Cys Thr  Ala Gly Gly
    2915                2920                2925

Cys Ala  Gly Gly Ala Cys Thr  Gly Cys Cys Ala Thr  Gly Cys Ala
    2930                2935                2940

Gly Thr  Gly Ala Ala Gly Cys  Cys Cys Thr Cys Ala  Gly Thr Gly
    2945                2950                2955

Ala Gly  Cys Thr Gly Cys Cys  Ala Cys Thr Gly Ala  Gly Thr Cys
    2960                2965                2970

Gly Gly  Gly Ala Gly Cys Cys  Cys Ala Gly Ala Gly  Gly Ala Ala
    2975                2980                2985

Cys Gly  Gly Cys Gly Thr Gly  Ala Ala Gly Cys Cys  Ala Cys Thr
    2990                2995                3000

Gly Gly  Ala Cys Cys Cys Thr  Cys Thr Cys Cys Cys  Gly Gly Gly
    3005                3010                3015

Ala Cys  Cys Thr Cys Cys Thr  Gly Cys Thr Gly Gly  Cys Thr Cys
    3020                3025                3030

Cys Thr  Cys Cys Thr Gly Cys  Cys Cys Ala Gly Cys  Thr Thr Cys
    3035                3040                3045

Cys Thr  Ala Thr Gly Cys Ala  Ala Gly Gly Cys Thr  Thr Thr Gly
    3050                3055                3060

Thr Gly  Thr Thr Thr Thr Cys  Ala Gly Gly Ala Ala  Ala Gly Gly
    3065                3070                3075

Gly Cys  Cys Thr Ala Gly Cys  Thr Thr Cys Thr Gly  Thr Gly Thr
    3080                3085                3090

Gly Gly  Cys Cys Cys Ala Cys  Ala Gly Ala Gly Thr  Thr Cys Ala
    3095                3100                3105

Cys Thr  Gly Cys Cys Thr Gly  Thr Gly Ala Gly Ala  Cys Thr Thr
    3110                3115                3120

Ala Gly  Cys Ala Cys Cys Ala  Ala Gly Thr Gly Cys  Thr Gly Ala
    3125                3130                3135

Gly Gly  Cys Thr Gly Gly Ala  Ala Gly Ala Ala Ala  Ala Ala Cys
    3140                3145                3150

Gly Cys  Ala Cys Ala Cys Cys  Ala Gly Ala Cys Gly  Gly Gly Cys
    3155                3160                3165
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Ala Ala  Cys Ala Ala Ala Cys  Ala Gly Thr Cys Thr  Gly Gly Gly
    3170                 3175                 3180

Thr Cys  Cys Cys Cys Ala Gly  Cys Thr Cys Gly Cys  Thr Cys Thr
    3185                 3190                 3195

Thr Gly  Gly Thr Ala Cys Thr  Thr Gly Gly Gly Ala  Cys Cys Cys
    3200                 3205                 3210

Cys Ala  Gly Thr Gly Cys Cys  Thr Cys Gly Thr Thr  Gly Ala Gly
    3215                 3220                 3225

Gly Gly  Cys Gly Cys Cys Ala  Thr Thr Cys Thr Gly  Ala Ala Gly
    3230                 3235                 3240

Ala Ala  Ala Gly Gly Ala Ala  Cys Thr Gly Cys Ala  Gly Cys Gly
    3245                 3250                 3255

Cys Cys  Gly Ala Thr Thr Thr  Gly Ala Gly Gly Gly  Thr Gly Gly
    3260                 3265                 3270

Ala Gly  Ala Thr Ala Thr Ala  Gly Ala Thr Ala Ala  Thr Ala Ala
    3275                 3280                 3285

Thr Ala  Ala Thr Ala Thr Thr  Ala Ala Thr Ala Ala  Thr Ala Ala
    3290                 3295                 3300

Thr Ala  Ala Thr Gly Gly Cys  Cys Ala Cys Ala Thr  Gly Gly Ala
    3305                 3310                 3315

Thr Cys  Gly Ala Ala Cys Ala  Cys Thr Cys Ala Thr  Gly Ala Thr
    3320                 3325                 3330

Gly Thr  Gly Cys Cys Ala Ala  Ala Thr Gly Cys Thr  Gly Thr Gly
    3335                 3340                 3345

Cys Thr  Ala Ala Gly Thr Gly  Cys Thr Thr Thr Ala  Cys Gly Ala
    3350                 3355                 3360

Ala Cys  Ala Thr Thr Cys Gly  Thr Cys Ala Thr Ala  Thr Cys Ala
    3365                 3370                 3375

Gly Gly  Ala Thr Gly Ala Cys  Cys Thr Cys Gly Ala  Gly Ala Gly
    3380                 3385                 3390

Cys Thr  Gly Ala Gly Gly Cys  Thr Cys Thr Ala Gly  Cys Ala Cys
    3395                 3400                 3405

Cys Thr  Ala Ala Ala Ala Cys  Cys Ala Cys Gly Thr  Gly Cys Cys
    3410                 3415                 3420

Cys Ala  Ala Ala Cys Cys Cys  Ala Cys Cys Ala Gly  Thr Thr Thr
    3425                 3430                 3435

Ala Ala  Ala Ala Cys Gly Gly  Thr Gly Thr Gly Thr  Gly Thr Thr
    3440                 3445                 3450

Cys Gly  Gly Ala Gly Gly Gly  Gly Thr Gly Ala Ala  Ala Gly Cys
    3455                 3460                 3465

Ala Thr  Thr Ala Ala Gly Ala  Ala Gly Cys Cys Cys  Ala Gly Thr
    3470                 3475                 3480

Gly Cys  Cys Cys Thr Cys Cys  Thr Gly Gly Ala Gly  Thr Gly Ala
    3485                 3490                 3495

Gly Ala  Cys Ala Ala Gly Gly  Gly Cys Thr Cys Gly  Gly Cys Cys
    3500                 3505                 3510

Thr Thr  Ala Ala Gly Gly Ala  Gly Cys Thr Gly Ala  Ala Gly Ala
    3515                 3520                 3525

Gly Thr  Cys Thr Gly Gly Gly  Thr Ala Gly Cys Thr  Thr Gly Thr
    3530                 3535                 3540
```

-continued

```
Thr Thr  Ala Gly Gly Gly Thr  Ala Cys Ala Ala Gly  Ala Ala Gly
    3545                 3550                 3555

Cys Cys  Thr Gly Thr Thr Cys  Thr Gly Thr Cys Cys  Ala Gly Cys
    3560                 3565                 3570

Thr Thr  Cys Ala Gly Thr Gly  Ala Cys Ala Cys Ala  Ala Gly Cys
    3575                 3580                 3585

Thr Gly  Cys Thr Thr Thr Ala  Gly Cys Thr Ala Ala  Ala Gly Thr
    3590                 3595                 3600

Cys Cys  Cys Gly Cys Gly Gly  Gly Thr Thr Cys Cys  Gly Gly Cys
    3605                 3610                 3615

Ala Thr  Gly Gly Cys Thr Ala  Gly Gly Cys Thr Gly  Ala Gly Ala
    3620                 3625                 3630

Gly Cys  Ala Gly Gly Gly Ala  Thr Cys Thr Ala Cys  Cys Thr Gly
    3635                 3640                 3645

Gly Cys  Thr Thr Cys Thr Cys  Ala Gly Thr Thr Cys  Thr Thr Thr
    3650                 3655                 3660

Gly Gly  Thr Thr Gly Gly Ala  Ala Gly Gly Ala Gly  Cys Ala Gly
    3665                 3670                 3675

Gly Ala  Ala Ala Thr Cys Ala  Gly Cys Thr Cys Cys  Thr Ala Thr
    3680                 3685                 3690

Thr Cys  Thr Cys Cys Ala Gly  Thr Gly Gly Ala Gly  Ala Gly Ala
    3695                 3700                 3705

Thr Cys  Thr Gly Gly Cys Cys  Thr Cys Ala Gly Cys  Thr Thr Gly
    3710                 3715                 3720

Gly Gly  Cys Thr Ala Gly Ala  Gly Ala Thr Gly Cys  Cys Ala Ala
    3725                 3730                 3735

Gly Gly  Cys Cys Thr Gly Thr  Gly Cys Cys Ala Gly  Gly Thr Thr
    3740                 3745                 3750

Cys Cys  Cys Thr Gly Thr Gly  Cys Cys Cys Thr Cys  Cys Thr Cys
    3755                 3760                 3765

Gly Ala  Gly Gly Thr Gly Gly  Gly Cys Ala Gly Cys  Cys Ala Thr
    3770                 3775                 3780

Cys Ala  Cys Cys Ala Gly Cys  Cys Ala Cys Ala Gly  Thr Thr Ala
    3785                 3790                 3795

Ala Gly  Cys Cys Ala Ala Gly  Cys Cys Cys Cys Cys  Cys Ala Ala
    3800                 3805                 3810

Cys Ala  Thr Gly Thr Ala Thr  Thr Cys Cys Ala Thr  Cys Gly Thr
    3815                 3820                 3825

Gly Cys  Thr Gly Gly Thr Ala  Gly Ala Ala Gly Ala  Gly Thr Cys
    3830                 3835                 3840

Thr Thr  Thr Gly Cys Thr Gly  Thr Thr Gly Cys Thr  Cys Cys Cys
    3845                 3850                 3855

Gly Ala  Ala Ala Gly Cys Cys  Gly Thr Gly Cys Thr  Cys Thr Cys
    3860                 3865                 3870

Cys Ala  Gly Cys Cys Thr Gly  Gly Cys Thr Gly Cys  Cys Ala Gly
    3875                 3880                 3885

Gly Gly  Ala Gly Gly Gly Thr  Gly Gly Gly Cys Cys  Thr Cys Thr
    3890                 3895                 3900

Thr Gly  Gly Thr Thr Cys Cys  Ala Gly Gly Cys Thr  Cys Thr Thr
    3905                 3910                 3915

Gly Ala  Ala Ala Thr Ala Gly  Thr Gly Cys Ala Gly  Cys Cys Thr
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    3920                3925                3930

Thr Thr  Thr Cys Thr Thr Cys  Cys Thr Ala Thr Cys  Thr Cys Thr
    3935                3940                3945

Gly Thr  Gly Gly Cys Thr Thr  Thr Cys Ala Gly Cys  Thr Cys Thr
    3950                3955                3960

Gly Cys  Thr Thr Cys Cys Thr  Thr Gly Gly Thr Thr  Ala Thr Thr
    3965                3970                3975

Ala Gly  Gly Ala Gly Ala Ala  Thr Ala Gly Ala Thr  Gly Gly Gly
    3980                3985                3990

Thr Gly  Ala Thr Gly Thr Cys  Thr Thr Thr Cys Cys  Thr Thr Ala
    3995                4000                4005

Thr Gly  Thr Thr Gly Cys Thr  Thr Thr Thr Thr Cys  Ala Ala Cys
    4010                4015                4020

Ala Thr  Ala Gly Cys Ala Gly  Ala Ala Thr Thr Ala  Ala Thr Gly
    4025                4030                4035

Thr Ala  Gly Gly Gly Ala Gly  Cys Thr Ala Ala Ala  Thr Cys Cys
    4040                4045                4050

Ala Gly  Thr Gly Gly Thr Gly  Thr Gly Thr Gly Thr  Gly Ala Ala
    4055                4060                4065

Thr Gly  Cys Ala Gly Ala Ala  Gly Gly Gly Ala Ala  Thr Gly Cys
    4070                4075                4080

Ala Cys  Cys Cys Cys Ala Cys  Ala Thr Thr Cys Cys  Cys Ala Thr
    4085                4090                4095

Gly Ala  Thr Gly Gly Ala Ala  Gly Thr Cys Thr Gly  Cys Gly Thr
    4100                4105                4110

Ala Ala  Cys Cys Ala Ala Thr  Ala Ala Ala Thr Thr  Gly Thr Gly
    4115                4120                4125

Cys Cys  Thr Thr Thr Cys Thr  Cys Ala Cys Thr Cys  Ala Ala Ala
    4130                4135                4140

Ala Cys  Cys Cys
    4145


<210> SEQ ID NO 4
<211> LENGTH: 457
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 4

Ala Ala Gly Cys Thr Gly Ala Thr Gly Thr Cys Ala Cys Thr Gly Cys
1               5                   10                  15

Thr Cys Thr Gly Cys Ala Ala Gly Gly Ala Gly Cys Thr Cys Cys Ala
            20                  25                  30

Thr Gly Gly Gly Thr Ala Ala Cys Gly Gly Ala Gly Ala Gly Cys Cys
        35                  40                  45

Cys Thr Gly Ala Gly Ala Gly Ala Gly Gly Gly Gly Thr Gly Gly Gly
    50                  55                  60

Gly Gly Ala Gly Cys Thr Thr Cys Ala Thr Gly Gly Gly Thr Ala Ala
65                  70                  75                  80

Thr Gly Gly Gly Ala Gly Cys Cys Cys Cys Thr Ala Cys Cys Cys Ala
                85                  90                  95

Cys Cys Cys Ala Gly Gly Ala Gly Gly Ala Thr Gly Gly Cys Cys Ala
            100                 105                 110
```

-continued

```
Cys Ala Gly Cys Ala Ala Gly Ala Gly Ala Ala Ala Gly Thr Gly Cys
        115                 120                 125

Thr Cys Ala Thr Thr Ala Gly Ala Gly Thr Gly Ala Cys Cys Cys Thr
    130                 135                 140

Gly Gly Gly Thr Cys Thr Cys Cys Thr Cys Thr Cys Thr Gly Thr Cys
145                 150                 155                 160

Cys Ala Gly Ala Thr Gly Thr Cys Thr Cys Thr Gly Cys Ala Gly Cys
                165                 170                 175

Ala Cys Thr Cys Ala Cys Ala Gly Thr Ala Ala Thr Thr Gly Gly Cys
            180                 185                 190

Cys Cys Ala Gly Gly Thr Gly Gly Ala Gly Thr Cys Thr Gly Gly Ala
        195                 200                 205

Ala Thr Gly Thr Thr Cys Cys Ala Gly Gly Cys Thr Thr Gly Thr Thr
    210                 215                 220

Gly Gly Ala Ala Gly Cys Thr Cys Thr Thr Gly Cys Thr Cys Thr Cys
225                 230                 235                 240

Ala Thr Ala Gly Ala Ala Thr Cys Thr Gly Ala Gly Cys Thr Cys Thr
                245                 250                 255

Ala Ala Cys Thr Gly Ala Gly Cys Thr Gly Gly Gly Ala Ala Ala Gly
            260                 265                 270

Thr Thr Gly Ala Thr Cys Ala Thr Thr Thr Gly Thr Thr Thr Ala Thr
        275                 280                 285

Thr Cys Cys Thr Thr Thr Thr Ala Gly Gly Gly Thr Ala Thr Thr Gly
    290                 295                 300

Gly Gly Gly Gly Gly Gly Cys Ala Cys Gly Gly Ala Thr Gly Thr Ala
305                 310                 315                 320

Thr Gly Cys Ala Thr Gly Cys Thr Gly Gly Thr Ala Thr Gly Thr Ala
                325                 330                 335

Thr Gly Cys Ala Thr Gly Cys Thr Gly Gly Gly Gly Ala Thr Gly Thr
            340                 345                 350

Ala Gly Gly Gly Cys Cys Thr Cys Ala Thr Gly Thr Gly Thr Gly Cys
        355                 360                 365

Thr Ala Ala Ala Thr Ala Cys Ala Thr Gly Thr Gly Cys Cys Thr Ala
    370                 375                 380

Thr Thr Cys Thr Gly Thr Ala Ala Thr Gly Thr Thr Thr Thr Cys Thr
385                 390                 395                 400

Thr Gly Thr Thr Thr Gly Thr Thr Thr Thr Thr Ala Ala Cys Thr Cys
                405                 410                 415

Ala Ala Ala Thr Thr Ala Ala Thr Thr Ala Gly Ala Gly Gly Cys Ala
            420                 425                 430

Gly Thr Thr Thr Cys Thr Cys Thr Gly Thr Thr Thr Ala Cys Cys Ala
        435                 440                 445

Gly Cys Cys Cys Gly Gly Gly Cys Cys
    450                 455


<210> SEQ ID NO 5
<211> LENGTH: 938
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 5

Ala Ala Ala Thr Cys Ala Cys Cys Ala Cys Ala Cys Gly Gly Cys Cys
1               5                   10                  15
```

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```
Ala Ala Thr Ala Cys Thr Cys Cys Cys Cys Cys Cys Cys Ala Ala Cys
            20                  25                  30

Thr Cys Cys Thr Cys Cys Cys Ala Ala Ala Thr Cys Cys Cys Cys Thr
        35                  40                  45

Cys Thr Ala Cys Cys Cys Ala Cys Thr Cys Ala Ala Ala Thr Thr Cys
    50                  55                  60

Thr Thr Ala Thr Cys Thr Thr Gly Thr Ala Thr Thr Cys Thr Thr Thr
65                  70                  75                  80

Ala Thr Cys Ala Thr Thr Ala Thr Thr Ala Thr Ala Cys Ala Thr Ala
                85                  90                  95

Thr Gly Thr Gly Thr Ala Thr Ala Thr Ala Thr Gly Thr Gly Thr Gly
            100                 105                 110

Thr Gly Thr Gly Thr Ala Thr Ala Thr Ala Thr Ala Thr Ala Thr Ala
        115                 120                 125

Thr Ala Cys Thr Ala Thr Ala Thr Ala Cys Thr Gly Cys Thr Ala Ala
    130                 135                 140

Thr Gly Ala Gly Thr Ala Ala Cys Ala Thr Thr Thr Ala Gly Thr Gly
145                 150                 155                 160

Thr Thr Ala Thr Thr Cys Ala Thr Thr Gly Asn Thr Gly Cys Asn Thr
                165                 170                 175

Gly Thr Thr Thr Asn Cys Ala Ala Thr Gly Asn Gly Cys Thr Thr Thr
            180                 185                 190

Cys Cys Ala Gly Gly Asn Gly Gly Cys Thr Gly Gly Gly Gly Gly Gly
        195                 200                 205

Ala Asn Gly Gly Cys Thr Cys Ala Gly Asn Gly Gly Gly Cys Ala Ala
    210                 215                 220

Ala Ala Thr Thr Cys Thr Ala Gly Cys Thr Gly Cys Ala Cys Ala Ala
225                 230                 235                 240

Gly Cys Cys Thr Ala Ala Gly Gly Ala Cys Cys Ala Gly Gly Gly Thr
                245                 250                 255

Thr Cys Ala Gly Ala Thr Cys Cys Cys Cys Ala Ala Thr Ala Thr Ala
            260                 265                 270

Ala Ala Gly Gly Cys Thr Gly Gly Cys Thr Gly Gly Ala Cys Ala Thr
        275                 280                 285

Gly Gly Gly Gly Gly Cys Thr Thr Gly Cys Cys Thr Ala Thr Gly Ala
    290                 295                 300

Thr Ala Cys Thr Ala Gly Cys Ala Thr Gly Cys Thr Thr Gly Cys Thr
305                 310                 315                 320

Gly Gly Ala Ala Gly Cys Ala Ala Ala Gly Ala Cys Ala Gly Gly Gly
                325                 330                 335

Ala Ala Thr Cys Cys Cys Thr Gly Gly Ala Gly Ala Cys Thr Thr Ala
            340                 345                 350

Asn Ala Ala Thr Cys Thr Cys Ala Asn Ala Ala Gly Thr Gly Ala Thr
        355                 360                 365

Cys Thr Gly Gly Gly Cys Thr Gly Gly Ala Cys Ala Gly Ala Cys Thr
    370                 375                 380

Ala Gly Cys Thr Gly Ala Ala Cys Thr Gly Gly Cys Cys Ala Gly Cys
385                 390                 395                 400

Thr Cys Thr Gly Gly Gly Thr Thr Cys Ala Thr Asn Ala Ala Asn Ala
                405                 410                 415
```

-continued

```
Ala Ala Cys Cys Cys Thr Asn Cys Cys Thr Cys Cys Ala Thr Ala Ala
            420                 425                 430

Cys Ala Thr Ala Ala Ala Gly Thr Gly Thr Gly Ala Asn Gly Gly Ala
        435                 440                 445

Asn Ala Ala Ala Gly Gly Cys Ala Cys Cys Thr Ala Ala Thr Gly Thr
    450                 455                 460

Cys Ala Ala Cys Cys Thr Cys Ala Ala Ala Cys Cys Cys Cys Thr Ala
465                 470                 475                 480

Cys Cys Thr Gly Cys Ala Thr Gly Thr Gly Cys Ala Cys Ala Cys Ala
                485                 490                 495

Cys Ala Thr Ala Cys Ala Thr Cys Cys Ala Cys Ala Cys Cys Ala Cys
            500                 505                 510

Ala Cys Ala Cys Ala Cys Ala Cys Gly Cys Ala Cys Ala Cys Ala Cys
        515                 520                 525

Ala Cys Ala Cys Ala Cys Ala Cys Ala Cys Cys Ala Cys Ala Cys Ala
    530                 535                 540

Cys Ala Cys Ala Cys Ala Cys Ala Cys Ala Cys Ala Ala Ala Thr Ala
545                 550                 555                 560

Ala Ala Thr Ala Ala Gly Thr Ala Ala Ala Thr Ala Ala Ala Thr Ala
                565                 570                 575

Ala Ala Ala Thr Ala Thr Thr Thr Ala Gly Cys Thr Cys Thr Cys Cys
            580                 585                 590

Ala Gly Ala Cys Cys Ala Ala Ala Thr Cys Thr Thr Gly Gly Thr Gly
        595                 600                 605

Ala Ala Ala Cys Cys Cys Ala Thr Gly Cys Ala Thr Thr Thr Gly Cys
    610                 615                 620

Ala Thr Thr Thr Gly Thr Gly Thr Gly Thr Gly Thr Cys Cys Thr Ala
625                 630                 635                 640

Cys Ala Ala Ala Cys Ala Cys Thr Gly Ala Ala Gly Gly Thr Thr Ala
                645                 650                 655

Ala Gly Ala Ala Gly Cys Ala Thr Gly Cys Thr Cys Cys Thr Thr Ala
            660                 665                 670

Gly Thr Ala Ala Thr Thr Thr Thr Ala Thr Ala Gly Cys Ala Gly Thr
        675                 680                 685

Thr Thr Gly Cys Gly Thr Thr Thr Cys Cys Ala Gly Ala Thr Thr Gly
    690                 695                 700

Ala Ala Ala Ala Cys Ala Gly Ala Thr Thr Cys Thr Ala Thr Ala Gly
705                 710                 715                 720

Gly Cys Thr Ala Cys Ala Cys Ala Gly Thr Gly Cys Thr Ala Ala Ala
                725                 730                 735

Thr Gly Gly Ala Thr Thr Ala Thr Gly Cys Thr Cys Ala Gly Ala Thr
            740                 745                 750

Ala Cys Ala Gly Ala Thr Thr Gly Ala Ala Ala Ala Gly Gly Ala Thr
        755                 760                 765

Ala Cys Ala Gly Ala Thr Thr Gly Ala Ala Ala Ala Gly Gly Gly Thr
    770                 775                 780

Cys Gly Gly Gly Gly Thr Cys Thr Gly Gly Gly Cys Cys Ala Gly Gly
785                 790                 795                 800

Ala Thr Gly Ala Cys Gly Gly Gly Cys Cys Ala Ala Cys Thr Ala Thr
                805                 810                 815

Cys Thr Thr Thr Gly Cys Cys Cys Gly Gly Gly Cys Thr Thr Gly Thr
```

-continued

```
            820                 825                 830

Cys Cys Thr Thr Cys Ala Gly Gly Gly Ala Ala Gly Gly Gly Thr Thr
        835                 840                 845

Ala Cys Ala Gly Gly Ala Thr Thr Cys Ala Cys Cys Ala Cys Thr Gly
    850                 855                 860

Gly Gly Gly Thr Gly Thr Gly Gly Cys Cys Thr Ala Thr Cys Thr Gly
865                 870                 875                 880

Cys Thr Gly Thr Thr Ala Gly Gly Ala Cys Cys Thr Gly Ala Ala Thr
                885                 890                 895

Thr Gly Cys Cys Thr Gly Gly Ala Gly Thr Gly Thr Thr Thr Cys Thr
            900                 905                 910

Ala Gly Thr Thr Cys Cys Cys Ala Cys Thr Ala Gly Thr Thr Gly Thr
        915                 920                 925

Thr Gly Ala Ala Cys Thr Thr Thr Ala Cys
    930                 935


<210> SEQ ID NO 6
<211> LENGTH: 986
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 6

Gly Cys Ala Asn Thr Cys Thr Gly Ala Gly Gly Ala Cys Thr Cys Thr
1               5                   10                  15

Gly Cys Cys Ala Thr Cys Cys Thr Gly Gly Ala Gly Thr Cys Thr Cys
            20                  25                  30

Thr Gly Cys Ala Gly Ala Gly Gly Thr Thr Gly Thr Thr Thr Gly Ala
        35                  40                  45

Cys Cys Ala Ala Cys Ala Gly Cys Thr Cys Thr Cys Cys Cys Cys Ala
    50                  55                  60

Gly Gly Cys Cys Thr Thr Cys Gly Cys Cys Cys Ala Cys Gly Ala Cys
65                  70                  75                  80

Cys Thr Cys Ala Gly Gly Thr Ala Ala Gly Gly Gly Gly Thr Thr Thr
                85                  90                  95

Gly Gly Ala Thr Thr Thr Gly Gly Ala Ala Ala Gly Ala Thr Gly Cys
            100                 105                 110

Ala Ala Thr Thr Gly Cys Thr Ala Thr Ala Gly Gly Ala Gly Gly Gly
        115                 120                 125

Ala Cys Thr Cys Thr Gly Ala Ala Gly Gly Cys Ala Gly Ala Cys Ala
    130                 135                 140

Gly Ala Cys Gly Cys Ala Cys Cys Gly Cys Cys Thr Cys Cys Thr Cys
145                 150                 155                 160

Ala Cys Gly Thr Thr Gly Gly Cys Thr Ala Gly Thr Cys Thr Ala Ala
                165                 170                 175

Thr Ala Thr Ala Ala Ala Cys Ala Thr Cys Gly Cys Gly Gly Thr Gly
            180                 185                 190

Gly Ala Thr Gly Gly Thr Gly Ala Gly Gly Ala Thr Ala Gly Ala Cys
        195                 200                 205

Thr Cys Cys Ala Thr Gly Cys Cys Cys Thr Thr Thr Thr Gly Thr Gly
    210                 215                 220

Ala Ala Gly Gly Cys Ala Thr Thr Thr Cys Cys Thr Gly Gly Cys Ala
225                 230                 235                 240
```

-continued

```
Thr Cys Ala Gly Cys Thr Cys Cys Thr Gly Ala Cys Thr Thr Cys Ala
                245                 250                 255

Gly Ala Gly Thr Thr Thr Cys Ala Cys Cys Cys Ala Thr Cys Ala Gly
            260                 265                 270

Ala Cys Ala Ala Ala Thr Thr Gly Cys Cys Thr Gly Gly Thr Gly Thr
        275                 280                 285

Thr Gly Gly Ala Gly Gly Ala Gly Gly Ala Gly Gly Thr Gly Ala Gly
    290                 295                 300

Cys Ala Gly Gly Gly Cys Cys Ala Thr Thr Cys Cys Cys Ala Thr Cys
305                 310                 315                 320

Ala Thr Thr Thr Cys Thr Cys Cys Thr Cys Ala Gly Ala Ala Ala Thr
                325                 330                 335

Gly Gly Ala Ala Ala Gly Gly Cys Ala Ala Gly Gly Ala Ala Ala Ala
            340                 345                 350

Cys Ala Thr Gly Ala Gly Gly Thr Thr Cys Thr Thr Cys Ala Gly Ala
        355                 360                 365

Cys Ala Cys Thr Thr Ala Ala Thr Cys Cys Cys Thr Gly Gly Gly Ala
    370                 375                 380

Cys Thr Gly Cys Ala Ala Ala Ala Thr Gly Gly Thr Gly Gly Thr Gly
385                 390                 395                 400

Cys Cys Cys Cys Thr Cys Cys Thr Cys Cys Ala Cys Ala Gly Cys Thr
                405                 410                 415

Gly Cys Thr Cys Ala Cys Gly Gly Cys Gly Gly Gly Gly Cys Ala Gly
            420                 425                 430

Gly Ala Gly Ala Thr Gly Ala Gly Gly Gly Cys Cys Gly Ala Ala Thr
        435                 440                 445

Gly Ala Ala Gly Cys Ala Thr Ala Asn Ala Thr Cys Thr Ala Gly Cys
    450                 455                 460

Thr Ala Thr Thr Thr Thr Thr Thr Thr Thr Thr Thr Ala Gly Asn Gly
465                 470                 475                 480

Cys Cys Thr Thr Cys Ala Asn Thr Ala Ala Ala Thr Thr Thr Ala Ala
                485                 490                 495

Ala Ala Thr Cys Ala Ala Ala Thr Ala Ala Gly Gly Gly Ala Ala Gly
            500                 505                 510

Gly Gly Asn Cys Cys Thr Ala Ala Ala Thr Cys Thr Thr Thr Ala Thr
        515                 520                 525

Asn Thr Thr Asn Thr Gly Gly Cys Thr Thr Thr Asn Thr Ala Ala Ala
    530                 535                 540

Ala Gly Thr Asn Ala Ala Ala Asn Cys Thr Thr Asn Thr Cys Cys Cys
545                 550                 555                 560

Ala Gly Gly Gly Asn Gly Cys Gly Gly Thr Gly Gly Cys Cys Cys Ala
                565                 570                 575

Cys Cys Cys Cys Thr Thr Thr Asn Ala Thr Cys Asn Ala Cys Ala Cys
            580                 585                 590

Thr Thr Gly Gly Gly Ala Gly Gly Cys Ala Ala Ala Gly Gly Cys Ala
        595                 600                 605

Asn Cys Cys Gly Ala Thr Thr Cys Thr Gly Ala Asn Thr Thr Gly Ala
    610                 615                 620

Asn Gly Cys Cys Asn Gly Cys Cys Thr Gly Gly Thr Cys Thr Asn Asn
625                 630                 635                 640

Asn Gly Asn Gly Gly Ala Gly Thr Thr Cys Cys Ala Asn Gly Ala Cys
```

-continued

```
               645                 650                 655

Ala Asn Cys Cys Ala Gly Gly Cys Thr Thr Cys Cys Cys Ala Asn Gly
            660                 665                 670

Thr Thr Thr Thr Thr Thr Thr Thr Thr Cys Ala Cys Ala Ala Ala Ala
        675                 680                 685

Cys Cys Cys Thr Thr Thr Thr Thr Thr Ala Ala Ala Ala Cys Cys Cys
    690                 695                 700

Thr Asn Thr Cys Thr Ala Ala Thr Cys Cys Asn Thr Ala Cys Thr Cys
705                 710                 715                 720

Asn Thr Thr Asn Asn Asn Cys Cys Asn Thr Cys Ala Asn Thr Ala Cys
               725                 730                 735

Cys Ala Thr Asn Asn Cys Ala Asn Asn Thr Cys Cys Cys Thr Cys Thr
            740                 745                 750

Thr Thr Cys Asn Cys Cys Thr Asn Cys Asn Asn Thr Cys Thr Ala Cys
        755                 760                 765

Thr Thr Thr Thr Asn Thr Asn Cys Cys Asn Cys Thr Asn Asn Thr Gly
    770                 775                 780

Asn Asn Cys Asn Ala Thr Thr Ala Thr Thr Thr Thr Cys Cys Thr Cys
785                 790                 795                 800

Thr Thr Cys Asn Cys Thr Thr Asn Thr Gly Thr Thr Ala Thr Ala Thr
               805                 810                 815

Asn Ala Asn Ala Thr Ala Ala Thr Thr Cys Thr Cys Cys Cys Ala Ala
            820                 825                 830

Cys Cys Cys Cys Thr Cys Ala Cys Cys Cys Cys Thr Cys Thr Thr Thr
        835                 840                 845

Ala Thr Thr Cys Thr Asn Ala Asn Asn Asn Asn Asn Ala Thr Thr Thr
    850                 855                 860

Thr Gly Asn Cys Ala Thr Cys Thr Gly Cys Cys Thr Cys Cys Asn Asn
865                 870                 875                 880

Thr Thr Ala Asn Asn Asn Thr Thr Asn Asn Thr Cys Cys Thr Cys Asn
               885                 890                 895

Cys Thr Thr Cys Ala Asn Cys Thr Asn Cys Thr Thr Cys Cys Ala Thr
            900                 905                 910

Thr Asn Gly Gly Thr Thr Gly Thr Asn Ala Cys Thr Cys Asn Ala Asn
        915                 920                 925

Asn Thr Thr Thr Asn Cys Thr Asn Thr Cys Thr Cys Thr Thr Ala Asn
    930                 935                 940

Asn Asn Cys Thr Thr Cys Asn Cys Gly Asn Asn Asn Asn Thr Thr Cys
945                 950                 955                 960

Thr Cys Cys Ala Asn Thr Cys Cys Asn Cys Thr Asn Asn Cys Cys Thr
               965                 970                 975

Asn Cys Asn Cys Cys Ala Asn Cys Cys Cys
            980                 985


<210> SEQ ID NO 7
<211> LENGTH: 1001
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 7

Gly Gly Gly Ala Gly Asn Asn Asn Asn Ala Ala Thr Thr Ala Gly Asn
1               5                   10                  15
```

-continued

```
Asn Ala Ala Gly Ala Asn Ala Asn Asn Asn Thr Thr Thr Thr Asn Thr
            20                  25                  30

Thr Thr Thr Asn Ala Gly Gly Ala Cys Cys Gly Cys Asn Asn Thr Ala
        35                  40                  45

Thr Gly Thr Thr Thr Ala Thr Asn Ala Gly Ala Ala Gly Ala Asn Asn
    50                  55                  60

Gly Gly Asn Gly Ala Asn Asn Gly Ala Asn Asn Thr Asn Thr Ala Ala
65                  70                  75                  80

Gly Gly Ala Asn Cys Ala Cys Cys Ala Asn Ala Gly Asn Cys Gly Asn
                85                  90                  95

Cys Asn Asn Ala Ala Gly Gly Thr Thr Thr Thr Asn Ala Ala Thr Ala
            100                 105                 110

Asn Asn Gly Ala Gly Gly Asn Ala Gly Asn Cys Gly Ala Asn Ala Ala
        115                 120                 125

Ala Ala Ala Asn Ala Asn Thr Thr Thr Asn Cys Ala Thr Asn Thr Asn
    130                 135                 140

Thr Thr Thr Thr Gly Asn Cys Ala Cys Cys Asn Asn Gly Ala Asn Thr
145                 150                 155                 160

Thr Thr Thr Gly Ala Ala Thr Ala Thr Asn Ala Asn Ala Thr Asn Ala
                165                 170                 175

Thr Gly Ala Ala Ala Ala Asn Asn Asn Asn Thr Gly Thr Gly Thr Asn
            180                 185                 190

Thr Gly Asn Asn Thr Gly Thr Gly Thr Gly Thr Asn Thr Gly Thr Asn
        195                 200                 205

Thr Gly Thr Gly Thr Gly Asn Asn Thr Gly Thr Cys Thr Gly Thr Cys
    210                 215                 220

Thr Ala Thr Asn Gly Gly Thr Gly Thr Gly Thr Gly Thr Gly Cys Asn
225                 230                 235                 240

Ala Gly Asn Gly Ala Gly Thr Gly Ala Gly Thr Ala Gly Thr Gly Ala
                245                 250                 255

Gly Gly Ala Gly Ala Gly Ala Asn Ala Ala Gly Ala Ala Ala Gly Asn
            260                 265                 270

Ala Thr Ala Thr Gly Ala Gly Asn Ala Ala Ala Gly Asn Gly Cys Ala
        275                 280                 285

Gly Cys Thr Thr Gly Cys Asn Ala Ala Gly Ala Gly Gly Gly Ala Thr
    290                 295                 300

Cys Thr Cys Thr Cys Asn Thr Ala Cys Gly Gly Thr Gly Thr Gly Gly
305                 310                 315                 320

Gly Thr Cys Asn Cys Ala Ala Ala Gly Thr Thr Thr Gly Ala Cys Thr
                325                 330                 335

Cys Cys Ala Gly Ala Thr Thr Gly Cys Cys Ala Thr Gly Cys Thr Thr
            340                 345                 350

Gly Gly Gly Gly Cys Ala Ala Ala Thr Thr Cys Cys Thr Thr Thr Thr
        355                 360                 365

Asn Cys Cys Ala Asn Ala Ala Ala Cys Cys Ala Thr Cys Thr Thr Gly
    370                 375                 380

Cys Gly Thr Gly Ala Cys Thr Thr Asn Thr Cys Thr Ala Asn Thr Gly
385                 390                 395                 400

Cys Thr Cys Cys Thr Gly Gly Cys Thr Thr Thr Ala Gly Gly Gly Asn
                405                 410                 415

Gly Gly Cys Thr Thr Thr Thr Asn Thr Gly Thr Asn Thr Gly Thr Thr
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            420                 425                 430

Thr Thr Asn Ala Thr Thr Thr Thr Thr Gly Thr Thr Thr Thr Cys Ala
        435                 440                 445

Thr Gly Ala Gly Ala Thr Ala Gly Gly Ala Cys Cys Cys Cys Cys Ala
    450                 455                 460

Ala Ala Thr Ala Gly Cys Cys Thr Cys Cys Thr Thr Gly Ala Gly Thr
465                 470                 475                 480

Cys Ala Thr Ala Cys Cys Thr Ala Ala Ala Cys Cys Thr Thr Cys Cys
                485                 490                 495

Ala Cys Cys Ala Cys Ala Cys Cys Cys Ala Gly Cys Thr Thr Ala Gly
            500                 505                 510

Cys Thr Thr Thr Thr Cys Ala Thr Thr Thr Thr Cys Thr Ala Ala Ala
        515                 520                 525

Cys Ala Thr Gly Thr Cys Thr Gly Cys Gly Thr Ala Gly Gly Ala Ala
    530                 535                 540

Thr Cys Gly Thr Cys Thr Thr Cys Cys Thr Ala Ala Thr Thr Ala Thr
545                 550                 555                 560

Thr Ala Cys Cys Ala Gly Thr Cys Gly Ala Thr Gly Thr Thr Cys Ala
                565                 570                 575

Ala Thr Thr Ala Gly Cys Gly Gly Thr Thr Gly Thr Ala Ala Cys Ala
            580                 585                 590

Ala Gly Gly Cys Cys Cys Cys Ala Gly Ala Gly Thr Gly Thr Gly Ala
        595                 600                 605

Ala Thr Cys Thr Ala Thr Thr Gly Cys Thr Ala Ala Gly Ala Thr Thr
    610                 615                 620

Cys Thr Thr Thr Cys Cys Gly Gly Ala Ala Gly Thr Ala Gly Ala Thr
625                 630                 635                 640

Gly Ala Cys Ala Cys Ala Thr Cys Ala Gly Ala Thr Thr Ala Ala Thr
                645                 650                 655

Ala Ala Gly Thr Gly Thr Thr Gly Thr Cys Ala Ala Ala Cys Thr Cys
            660                 665                 670

Ala Thr Cys Ala Gly Thr Gly Ala Ala Thr Gly Ala Ala Cys Cys Ala
        675                 680                 685

Thr Thr Thr Cys Cys Cys Ala Ala Cys Ala Gly Thr Thr Cys Ala Thr
    690                 695                 700

Cys Thr Gly Thr Thr Thr Cys Cys Thr Cys Cys Ala Cys Cys Ala Ala
705                 710                 715                 720

Ala Thr Cys Thr Gly Thr Thr Gly Gly Thr Gly Gly Ala Gly Cys Ala
                725                 730                 735

Gly Cys Thr Gly Gly Gly Thr Thr Ala Cys Ala Cys Ala Thr Gly Gly
            740                 745                 750

Gly Cys Gly Ala Gly Cys Thr Gly Gly Gly Cys Thr Cys Ala Gly Cys
        755                 760                 765

Cys Gly Cys Gly Gly Thr Gly Cys Cys Ala Gly Cys Cys Ala Thr Thr
    770                 775                 780

Thr Thr Thr Cys Cys Ala Gly Cys Ala Thr Gly Cys Thr Ala Thr Gly
785                 790                 795                 800

Gly Ala Ala Thr Ala Thr Ala Gly Gly Gly Gly Thr Gly Thr Thr Ala
                805                 810                 815

Thr Cys Ala Gly Gly Cys Cys Ala Gly Gly Gly Thr Gly Gly Gly Ala
            820                 825                 830
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Ala Ala Ala Gly Cys Cys Thr Gly Gly Gly Ala Ala Thr Ala Gly Cys
        835                 840                 845

Gly Ala Gly Cys Cys Ala Gly Ala Thr Ala Gly Cys Cys Thr Cys Ala
    850                 855                 860

Cys Cys Cys Gly Gly Gly Ala Cys Ala Thr Thr Gly Ala Cys Cys Ala
865                 870                 875                 880

Thr Cys Cys Cys Ala Gly Cys Cys Ala Thr Gly Thr Ala Gly Ala Thr
                885                 890                 895

Ala Ala Ala Thr Cys Ala Gly Ala Gly Thr Thr Gly Ala Cys Ala Thr
            900                 905                 910

Cys Ala Cys Cys Ala Ala Ala Gly Cys Cys Ala Gly Cys Cys Ala Cys
        915                 920                 925

Thr Gly Ala Cys Thr Gly Cys Ala Thr Gly Thr Cys Thr Thr Ala Thr
    930                 935                 940

Gly Cys Thr Cys Thr Gly Ala Ala Gly Gly Thr Gly Ala Ala Gly Thr
945                 950                 955                 960

Cys Ala Gly Ala Gly Thr Cys Cys Cys Thr Gly Gly Gly Cys Ala Thr
                965                 970                 975

Thr Cys Cys Thr Cys Ala Gly Ala Ala Ala Ala Gly Cys Thr Cys Cys
            980                 985                 990

Cys Ala Ala Ala Gly Gly Ala Asn  Gly
        995                 1000


<210> SEQ ID NO 8
<211> LENGTH: 6498
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 8

Gly Thr Ala Ala Cys Gly Gly Ala Gly Ala Gly Cys Cys Cys Thr Gly
1               5                   10                  15

Ala Gly Ala Gly Ala Gly Gly Gly Gly Thr Gly Gly Gly Gly Gly Ala
            20                  25                  30

Gly Cys Thr Thr Cys Ala Thr Gly Gly Gly Thr Ala Ala Thr Gly Gly
        35                  40                  45

Gly Ala Gly Cys Cys Cys Cys Thr Ala Cys Cys Cys Ala Cys Cys Cys
    50                  55                  60

Ala Gly Gly Ala Gly Gly Ala Thr Gly Gly Cys Cys Ala Cys Ala Gly
65                  70                  75                  80

Cys Ala Ala Gly Ala Gly Ala Ala Ala Gly Thr Gly Cys Thr Cys Ala
                85                  90                  95

Thr Thr Ala Gly Ala Gly Thr Gly Ala Cys Cys Cys Thr Gly Gly Gly
            100                 105                 110

Thr Cys Thr Cys Cys Thr Cys Thr Cys Thr Gly Thr Cys Cys Ala Gly
        115                 120                 125

Ala Thr Gly Thr Cys Thr Cys Thr Gly Cys Ala Gly Cys Ala Cys Thr
    130                 135                 140

Cys Ala Cys Ala Gly Thr Ala Ala Thr Thr Gly Gly Cys Cys Cys Ala
145                 150                 155                 160

Gly Gly Thr Gly Gly Ala Gly Thr Cys Thr Gly Gly Ala Ala Thr Gly
                165                 170                 175

Thr Thr Cys Cys Ala Gly Gly Cys Thr Thr Gly Thr Thr Gly Gly Ala
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            180                 185                 190

Ala Gly Cys Thr Cys Thr Thr Gly Cys Thr Cys Thr Cys Ala Thr Ala
        195                 200                 205

Gly Ala Ala Thr Cys Thr Gly Ala Gly Cys Thr Cys Thr Ala Ala Cys
    210                 215                 220

Thr Gly Ala Gly Cys Thr Gly Gly Gly Ala Ala Ala Gly Thr Thr Gly
225                 230                 235                 240

Ala Thr Cys Ala Thr Thr Thr Gly Thr Thr Thr Ala Thr Thr Cys Cys
                245                 250                 255

Thr Thr Thr Thr Ala Gly Gly Gly Thr Ala Thr Thr Gly Gly Gly Gly
            260                 265                 270

Gly Gly Gly Cys Ala Cys Gly Gly Ala Thr Gly Thr Ala Thr Gly Cys
        275                 280                 285

Ala Thr Gly Cys Thr Gly Gly Thr Ala Thr Gly Thr Ala Thr Gly Cys
    290                 295                 300

Ala Thr Gly Cys Thr Gly Gly Gly Gly Ala Thr Gly Thr Ala Gly Gly
305                 310                 315                 320

Gly Cys Cys Thr Cys Ala Thr Gly Thr Gly Thr Gly Cys Thr Ala Ala
                325                 330                 335

Ala Thr Ala Cys Ala Thr Gly Thr Gly Cys Cys Thr Ala Thr Thr Cys
            340                 345                 350

Thr Gly Thr Ala Ala Thr Gly Thr Thr Thr Thr Cys Thr Thr Gly Thr
        355                 360                 365

Thr Thr Gly Thr Thr Thr Thr Thr Ala Ala Cys Thr Cys Ala Ala Ala
    370                 375                 380

Thr Thr Ala Ala Thr Thr Ala Gly Ala Gly Gly Cys Ala Gly Thr Thr
385                 390                 395                 400

Thr Cys Thr Cys Thr Gly Thr Thr Ala Ala Ala Ala Ala Ala Ala Ala
                405                 410                 415

Ala Ala Ala Gly Gly Thr Gly Gly Ala Ala Gly Ala Cys Ala Cys Thr
            420                 425                 430

Gly Cys Cys Ala Thr Cys Thr Cys Ala Thr Thr Thr Gly Thr Gly Thr
        435                 440                 445

Thr Gly Gly Gly Ala Cys Thr Thr Gly Ala Gly Ala Thr Ala Thr Ala
    450                 455                 460

Thr Ala Thr Ala Thr Ala Thr Ala Thr Ala Thr Ala Thr Ala Thr Ala
465                 470                 475                 480

Thr Ala Thr Ala Thr Ala Thr Ala Thr Ala Thr Ala Thr Ala Thr Ala
                485                 490                 495

Thr Ala Thr Ala Ala Thr Thr Thr Ala Thr Thr Thr Ala Thr Thr Thr
            500                 505                 510

Ala Thr Thr Thr Ala Thr Thr Thr Gly Thr Gly Thr Ala Thr Gly Thr
        515                 520                 525

Gly Thr Gly Thr Ala Thr Ala Ala Gly Ala Ala Ala Gly Cys Gly Gly
    530                 535                 540

Gly Gly Gly Ala Cys Ala Cys Thr Cys Ala Thr Gly Thr Gly Cys Cys
545                 550                 555                 560

Ala Thr Gly Gly Thr Gly Thr Gly Thr Ala Thr Gly Gly Gly Gly Ala
                565                 570                 575

Cys Ala Cys Ala Cys Gly Thr Gly Thr Cys Cys Thr Gly Thr Gly Gly
            580                 585                 590
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Gly Gly Gly Ala Ala Cys Ala Thr Thr Gly Thr Gly Thr Cys Ala Gly
        595                 600                 605

Gly Gly Gly Ala Ala Cys Ala Ala Ala Cys Ala Thr Gly Thr Gly Cys
    610                 615                 620

Thr Gly Ala Gly Gly Gly Thr Gly Gly Gly Gly Gly Gly Ala Thr Ala
625                 630                 635                 640

Thr Ala Thr Ala Thr Gly Thr Gly Cys Cys Ala Cys Thr Gly Thr Gly
                645                 650                 655

Gly Thr Gly Ala Thr Thr Thr Gly Gly Thr Thr Gly Gly Gly Gly Gly
            660                 665                 670

Ala Gly Ala Cys Ala Thr Gly Thr Ala Thr Gly Thr Gly Cys Thr Ala
        675                 680                 685

Thr Gly Ala Thr Ala Cys Cys Thr Gly Thr Gly Thr Gly Thr Ala Gly
    690                 695                 700

Gly Ala Cys Ala Gly Ala Gly Gly Ala Cys Ala Cys Ala Cys Thr Cys
705                 710                 715                 720

Ala Cys Ala Cys Ala Gly Gly Ala Gly Cys Cys Thr Thr Cys Thr Thr
                725                 730                 735

Ala Cys Cys Thr Gly Cys Thr Gly Ala Gly Cys Thr Gly Thr Cys Thr
            740                 745                 750

Cys Ala Ala Gly Cys Ala Gly Thr Cys Cys Ala Ala Gly Cys Cys Cys
        755                 760                 765

Thr Cys Cys Ala Gly Gly Cys Thr Gly Thr Ala Gly Cys Cys Ala Cys
    770                 775                 780

Thr Cys Thr Thr Cys Cys Thr Cys Cys Thr Thr Gly Cys Thr Ala Cys
785                 790                 795                 800

Ala Gly Thr Cys Cys Cys Ala Cys Ala Thr Cys Cys Ala Gly Cys Cys
                805                 810                 815

Ala Ala Cys Ala Cys Ala Thr Ala Ala Ala Gly Gly Cys Thr Cys Thr
            820                 825                 830

Gly Gly Cys Ala Gly Gly Ala Ala Ala Thr Ala Ala Ala Thr Thr Ala
        835                 840                 845

Ala Ala Thr Thr Thr Gly Cys Thr Thr Thr Gly Thr Gly Thr Gly Thr
    850                 855                 860

Gly Gly Gly Thr Gly Cys Thr Gly Ala Cys Gly Gly Cys Thr Cys Ala
865                 870                 875                 880

Ala Gly Thr Cys Thr Thr Cys Cys Gly Gly Thr Gly Ala Thr Gly Gly
                885                 890                 895

Thr Ala Ala Thr Gly Thr Thr Thr Ala Ala Ala Gly Cys Ala Ala Gly
            900                 905                 910

Cys Cys Ala Ala Cys Ala Thr Cys Ala Gly Thr Thr Cys Thr Cys Cys
        915                 920                 925

Ala Gly Thr Gly Cys Cys Gly Ala Ala Gly Thr Thr Ala Thr Thr Gly
    930                 935                 940

Ala Ala Thr Gly Ala Cys Thr Gly Ala Cys Cys Ala Ala Thr Gly Gly
945                 950                 955                 960

Gly Thr Ala Ala Cys Ala Cys Thr Thr Ala Gly Gly Ala Thr Thr Thr
                965                 970                 975

Thr Thr Ala Ala Ala Ala Ala Thr Thr Ala Thr Thr Thr Thr Gly Ala
            980                 985                 990
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Thr Thr Gly Thr Ala Cys Ala Thr  Thr Thr Thr Gly Ala  Ala Thr Thr
        995                1000                1005

Ala Cys  Ala Thr Thr Ala Ala  Thr Cys Thr Thr Ala  Ala Ala Ala
    1010                1015                1020

Thr Ala  Ala Ala Cys Thr Ala  Cys Ala Ala Ala Cys  Ala Thr Ala
    1025                1030                1035

Ala Ala  Cys Ala Cys Ala Cys  Thr Gly Thr Gly Gly  Thr Thr Gly
    1040                1045                1050

Gly Ala  Gly Cys Thr Gly Gly  Gly Cys Ala Thr Ala  Gly Thr Gly
    1055                1060                1065

Gly Cys  Ala Cys Ala Thr Gly  Cys Cys Thr Thr Thr  Ala Ala Thr
    1070                1075                1080

Thr Cys  Cys Ala Gly Ala Ala  Cys Thr Thr Gly Gly  Gly Ala Gly
    1085                1090                1095

Gly Cys  Ala Gly Ala Gly Gly  Cys Thr Gly Gly Cys  Ala Thr Ala
    1100                1105                1110

Thr Cys  Thr Cys Thr Ala Thr  Gly Ala Cys Thr Thr  Thr Gly Ala
    1115                1120                1125

Gly Gly  Cys Cys Ala Gly Cys  Cys Thr Gly Gly Thr  Cys Thr Ala
    1130                1135                1140

Thr Ala  Thr Ala Ala Thr Gly  Ala Gly Thr Thr Cys  Cys Ala Gly
    1145                1150                1155

Gly Ala  Cys Ala Gly Ala Gly  Ala Gly Ala Thr Cys  Cys Thr Gly
    1160                1165                1170

Thr Cys  Thr Cys Ala Cys Ala  Ala Ala Cys Ala Gly  Ala Gly Ala
    1175                1180                1185

Ala Ala  Ala Cys Cys Cys Cys  Ala Thr Ala Ala Cys  Thr Ala Thr
    1190                1195                1200

Ala Cys  Thr Thr Thr Thr Ala  Thr Thr Gly Thr Ala  Cys Thr Gly
    1205                1210                1215

Gly Thr  Thr Gly Gly Thr Cys  Thr Ala Cys Ala Gly  Thr Gly Thr
    1220                1225                1230

Ala Ala  Ala Gly Ala Ala Thr  Thr Gly Gly Cys Ala  Ala Ala Gly
    1235                1240                1245

Ala Ala  Thr Ala Thr Gly Ala  Ala Ala Gly Ala Thr  Thr Ala Cys
    1250                1255                1260

Ala Cys  Thr Gly Gly Gly Ala  Ala Gly Ala Ala Ala  Cys Thr Gly
    1265                1270                1275

Ala Ala  Ala Gly Cys Cys Ala  Thr Cys Cys Ala Gly  Ala Gly Thr
    1280                1285                1290

Ala Ala  Thr Gly Ala Ala Gly  Cys Ala Ala Ala Cys  Cys Cys Cys
    1295                1300                1305

Thr Cys  Ala Cys Ala Ala Ala  Thr Gly Thr Gly Gly  Gly Ala Ala
    1310                1315                1320

Ala Cys  Ala Thr Thr Thr Cys  Ala Cys Ala Thr Gly  Gly Gly Thr
    1325                1330                1335

Gly Ala  Gly Gly Gly Cys Thr  Thr Gly Cys Ala Gly  Cys Cys Ala
    1340                1345                1350

Gly Cys  Cys Thr Gly Thr Gly  Cys Thr Ala Ala Thr  Thr Thr Ala
    1355                1360                1365

Thr Gly  Thr Thr Thr Thr Gly  Gly Thr Ala Cys Gly  Thr Gly Ala
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    1370                1375                1380

Gly Cys  Ala Cys Thr Thr Ala  Gly Ala Gly Cys Ala  Gly Thr Thr
    1385                1390                1395

Thr Cys  Cys Ala Gly Thr Thr  Cys Thr Cys Thr Gly  Gly Thr Gly
    1400                1405                1410

Cys Thr  Cys Thr Ala Cys Cys  Ala Ala Thr Cys Thr  Thr Ala Gly
    1415                1420                1425

Cys Thr  Thr Gly Gly Thr Thr  Ala Ala Thr Ala Thr  Thr Cys Ala
    1430                1435                1440

Gly Gly  Gly Ala Thr Gly Ala  Gly Thr Cys Thr Thr  Cys Cys Ala
    1445                1450                1455

Thr Cys  Ala Cys Cys Gly Gly  Thr Ala Ala Thr Cys  Thr Ala Ala
    1460                1465                1470

Thr Thr  Thr Gly Cys Cys Ala  Thr Thr Cys Thr Ala  Thr Thr Thr
    1475                1480                1485

Ala Ala  Ala Gly Gly Cys Thr  Cys Thr Thr Ala Ala  Ala Gly Gly
    1490                1495                1500

Cys Ala  Cys Ala Gly Gly Cys  Ala Gly Thr Gly Cys  Ala Thr Thr
    1505                1510                1515

Gly Gly  Gly Thr Ala Ala Ala  Thr Gly Thr Gly Gly  Cys Ala Ala
    1520                1525                1530

Ala Thr  Ala Ala Thr Thr Thr  Cys Thr Thr Thr Gly  Ala Cys Ala
    1535                1540                1545

Ala Ala  Thr Cys Gly Ala Cys  Cys Ala Ala Thr Thr  Gly Thr Cys
    1550                1555                1560

Ala Gly  Ala Thr Thr Gly Gly  Cys Cys Thr Gly Cys  Thr Ala Gly
    1565                1570                1575

Thr Cys  Ala Thr Thr Thr Gly  Thr Thr Thr Cys Ala  Ala Thr Gly
    1580                1585                1590

Ala Gly  Ala Ala Cys Thr Gly  Thr Thr Thr Thr Thr  Thr Cys Thr
    1595                1600                1605

Cys Ala  Ala Ala Gly Gly Ala  Thr Gly Cys Thr Cys  Thr Thr Gly
    1610                1615                1620

Thr Ala  Cys Ala Cys Cys Gly  Gly Cys Thr Ala Gly  Ala Ala Gly
    1625                1630                1635

Cys Ala  Gly Gly Gly Cys Thr  Gly Thr Cys Ala Thr  Thr Thr Thr
    1640                1645                1650

Thr Ala  Thr Ala Gly Gly Thr  Cys Thr Cys Thr Gly  Thr Gly Gly
    1655                1660                1665

Thr Ala  Thr Thr Thr Thr Gly  Thr Thr Gly Thr Thr  Gly Thr Thr
    1670                1675                1680

Gly Thr  Thr Cys Thr Gly Thr  Thr Gly Thr Thr Gly  Cys Ala Ala
    1685                1690                1695

Ala Thr  Cys Ala Thr Thr Thr  Ala Thr Cys Ala Cys  Thr Gly Ala
    1700                1705                1710

Gly Gly  Gly Ala Ala Ala Ala  Thr Ala Cys Ala Cys  Ala Cys Ala
    1715                1720                1725

Ala Ala  Gly Gly Gly Cys Cys  Cys Thr Thr Thr Cys  Thr Thr Thr
    1730                1735                1740

Ala Ala  Ala Ala Gly Thr Ala  Thr Ala Cys Ala Thr  Gly Thr Ala
    1745                1750                1755
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Thr Cys  Ala Thr Thr Thr Thr  Gly Thr Gly Ala Cys  Ala Gly Cys
    1760                 1765                 1770

Thr Cys  Ala Thr Ala Ala Gly  Ala Ala Gly Cys Thr  Gly Thr Thr
    1775                 1780                 1785

Thr Thr  Thr Thr Thr Cys Thr  Gly Cys Cys Thr Gly  Gly Ala Cys
    1790                 1795                 1800

Ala Cys  Ala Gly Gly Thr Cys  Cys Thr Gly Ala Cys  Cys Thr Gly
    1805                 1810                 1815

Thr Gly  Cys Thr Gly Thr Gly  Thr Cys Cys Thr Thr  Gly Cys Thr
    1820                 1825                 1830

Ala Ala  Gly Cys Thr Thr Thr  Gly Thr Cys Ala Gly  Ala Cys Cys
    1835                 1840                 1845

Cys Thr  Thr Cys Cys Ala Cys  Ala Gly Cys Thr Cys  Cys Cys Cys
    1850                 1855                 1860

Cys Cys  Ala Ala Cys Ala Ala  Cys Gly Ala Gly Thr  Thr Cys Cys
    1865                 1870                 1875

Cys Cys  Ala Gly Thr Ala Cys  Cys Thr Gly Cys Cys  Thr Cys Ala
    1880                 1885                 1890

Cys Cys  Thr Cys Ala Thr Cys  Ala Cys Thr Ala Thr  Gly Gly Thr
    1895                 1900                 1905

Gly Ala  Cys Ala Gly Cys Ala  Gly Cys Cys Thr Cys  Thr Gly Ala
    1910                 1915                 1920

Thr Gly  Cys Gly Cys Thr Gly  Ala Cys Thr Cys Thr  Cys Thr Gly
    1925                 1930                 1935

Gly Cys  Ala Cys Ala Thr Thr  Ala Thr Gly Gly Cys  Ala Gly Thr
    1940                 1945                 1950

Gly Thr  Thr Ala Ala Ala Ala  Gly Cys Thr Thr Cys  Cys Ala Thr
    1955                 1960                 1965

Cys Thr  Cys Thr Cys Thr Cys  Thr Thr Thr Gly Cys  Thr Gly Ala
    1970                 1975                 1980

Ala Thr  Ala Ala Thr Gly Ala  Ala Cys Cys Thr Cys  Ala Gly Gly
    1985                 1990                 1995

Thr Thr  Gly Thr Thr Cys Ala  Ala Gly Ala Gly Ala  Cys Cys Gly
    2000                 2005                 2010

Gly Ala  Ala Thr Gly Thr Thr  Cys Thr Thr Cys Ala  Cys Cys Thr
    2015                 2020                 2025

Gly Cys  Cys Thr Gly Cys Ala  Cys Ala Cys Ala Thr  Cys Thr Cys
    2030                 2035                 2040

Thr Thr  Cys Ala Cys Thr Thr  Thr Cys Thr Thr Thr  Thr Ala Thr
    2045                 2050                 2055

Ala Gly  Ala Thr Cys Ala Gly  Gly Thr Ala Gly Gly  Gly Ala Cys
    2060                 2065                 2070

Thr Gly  Gly Gly Cys Gly Thr  Gly Thr Ala Gly Ala  Thr Gly Gly
    2075                 2080                 2085

Ala Ala  Cys Ala Ala Ala Cys  Thr Gly Thr Thr Thr  Thr Cys Cys
    2090                 2095                 2100

Gly Thr  Thr Cys Cys Cys Cys  Ala Gly Cys Cys Ala  Thr Cys Thr
    2105                 2110                 2115

Cys Thr  Gly Cys Ala Gly Gly  Thr Gly Cys Ala Cys  Thr Cys Cys
    2120                 2125                 2130
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Ala Cys  Ala Thr Ala Ala Ala  Thr Cys Ala Ala Gly  Thr Gly Thr
    2135                2140                2145

Thr Ala  Ala Ala Ala Gly Thr  Gly Cys Thr Thr Thr  Gly Ala Thr
    2150                2155                2160

Thr Ala  Ala Ala Cys Ala Gly  Gly Ala Cys Ala Gly  Gly Cys Gly
    2165                2170                2175

Cys Gly  Thr Thr Cys Thr Thr  Gly Ala Gly Thr Thr  Cys Ala Thr
    2180                2185                2190

Cys Thr  Gly Thr Thr Cys Ala  Cys Ala Thr Ala Cys  Thr Gly Thr
    2195                2200                2205

Cys Thr  Gly Gly Cys Ala Ala  Gly Cys Gly Cys Thr  Gly Ala Cys
    2210                2215                2220

Thr Gly  Ala Gly Gly Gly Thr  Cys Thr Cys Cys Thr  Cys Thr Gly
    2225                2230                2235

Thr Ala  Cys Cys Cys Thr Gly  Thr Thr Cys Thr Gly  Ala Gly Ala
    2240                2245                2250

Ala Cys  Thr Ala Ala Cys Ala  Ala Ala Ala Gly Ala  Cys Gly Ala
    2255                2260                2265

Ala Thr  Cys Ala Ala Cys Ala  Thr Ala Cys Ala Gly  Ala Ala Ala
    2270                2275                2280

Ala Cys  Thr Gly Thr Thr Ala  Thr Thr Thr Ala Gly  Thr Gly Ala
    2285                2290                2295

Cys Thr  Gly Ala Thr Thr Ala  Ala Ala Cys Thr Ala  Ala Cys Gly
    2300                2305                2310

Ala Ala  Gly Gly Cys Ala Thr  Gly Gly Gly Cys Thr  Gly Gly Ala
    2315                2320                2325

Gly Ala  Ala Ala Thr Ala Ala  Cys Thr Cys Ala Gly  Cys Ala Gly
    2330                2335                2340

Thr Thr  Ala Ala Gly Ala Ala  Cys Ala Thr Thr Thr  Gly Cys Thr
    2345                2350                2355

Gly Ala  Thr Cys Thr Thr Gly  Cys Ala Gly Ala Gly  Gly Ala Cys
    2360                2365                2370

Cys Thr  Gly Gly Gly Thr Thr  Gly Gly Gly Thr Thr  Cys Cys Thr
    2375                2380                2385

Ala Gly  Cys Ala Cys Ala Cys  Ala Cys Ala Gly Gly  Gly Ala Cys
    2390                2395                2400

Ala Gly  Thr Thr Cys Cys Ala  Gly Thr Cys Cys Cys  Gly Gly Thr
    2405                2410                2415

Gly Thr  Gly Thr Cys Cys Thr  Thr Thr Thr Cys Thr  Cys Ala Cys
    2420                2425                2430

Thr Thr  Cys Thr Gly Thr Gly  Gly Ala Cys Ala Cys  Ala Ala Gly
    2435                2440                2445

Thr Thr  Thr Thr Ala Cys Ala  Cys Ala Thr Ala Gly  Thr Gly Cys
    2450                2455                2460

Ala Cys  Ala Cys Ala Cys Ala  Thr Ala Cys Ala Cys  Thr Cys Ala
    2465                2470                2475

Cys Ala  Thr Ala Thr Ala Thr  Ala Ala Ala Ala Cys  Ala Gly Ala
    2480                2485                2490

Ala Cys  Ala Thr Thr Thr Ala  Ala Ala Ala Gly Thr  Ala Thr Gly
    2495                2500                2505

Thr Thr  Thr Ala Ala Ala Thr  Ala Ala Cys Gly Gly  Ala Ala Thr
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    2510                2515                2520

Cys Ala  Thr Thr Thr Ala Thr  Ala Thr Ala Gly Gly  Thr Thr Thr
    2525                2530                2535

Thr Cys  Ala Thr Thr Thr Ala  Cys Ala Thr Ala Gly  Gly Thr Ala
    2540                2545                2550

Ala Ala  Thr Ala Gly Gly Cys  Ala Ala Ala Ala Ala  Thr Cys Thr
    2555                2560                2565

Gly Cys  Ala Thr Thr Thr Thr  Ala Thr Thr Gly Thr  Thr Thr Cys
    2570                2575                2580

Thr Ala  Ala Gly Thr Thr Thr  Thr Ala Ala Thr Thr  Thr Ala Thr
    2585                2590                2595

Thr Thr  Thr Thr Cys Thr Cys  Thr Gly Thr Gly Thr  Gly Thr Ala
    2600                2605                2610

Cys Ala  Thr Ala Cys Gly Cys  Ala Thr Gly Cys Cys  Thr Cys Cys
    2615                2620                2625

Thr Thr  Ala Thr Cys Thr Gly  Thr Ala Thr Gly Thr  Gly Cys Gly
    2630                2635                2640

Thr Gly  Cys Ala Cys Thr Gly  Thr Gly Thr Gly Cys  Ala Thr Gly
    2645                2650                2655

Cys Ala  Thr Gly Ala Ala Cys  Cys Cys Ala Cys Ala  Gly Ala Gly
    2660                2665                2670

Ala Cys  Cys Ala Gly Ala Ala  Gly Ala Gly Thr Ala  Cys Cys Ala
    2675                2680                2685

Cys Ala  Gly Ala Thr Thr Cys  Thr Cys Thr Gly Gly  Ala Gly Cys
    2690                2695                2700

Thr Gly  Gly Ala Gly Thr Gly  Ala Thr Thr Gly Ala  Thr Ala Gly
    2705                2710                2715

Gly Cys  Thr Gly Thr Thr Gly  Gly Gly Ala Gly Cys  Cys Ala Cys
    2720                2725                2730

Thr Cys  Cys Ala Cys Ala Thr  Gly Gly Gly Gly Ala  Thr Thr Cys
    2735                2740                2745

Ala Gly  Ala Gly Thr Thr Gly  Ala Ala Cys Thr Thr  Cys Gly Thr
    2750                2755                2760

Thr Cys  Thr Cys Thr Gly Cys  Ala Ala Gly Ala Ala  Cys Ala Gly
    2765                2770                2775

Cys Cys  Ala Gly Cys Thr Cys  Thr Thr Ala Ala Cys  Thr Gly Ala
    2780                2785                2790

Thr Gly  Gly Cys Thr Thr Thr  Thr Ala Cys Cys Thr  Cys Cys Ala
    2795                2800                2805

Gly Cys  Cys Ala Cys Cys Thr  Thr Thr Thr Cys Cys  Thr Cys Ala
    2810                2815                2820

Thr Thr  Thr Thr Thr Ala Ala  Ala Ala Thr Thr Thr  Cys Cys Thr
    2825                2830                2835

Thr Cys  Cys Thr Thr Cys Cys  Thr Thr Thr Thr Thr  Gly Ala Gly
    2840                2845                2850

Ala Cys  Ala Gly Gly Gly Thr  Cys Thr Cys Ala Ala  Thr Ala Cys
    2855                2860                2865

Thr Thr  Ala Gly Cys Thr Cys  Ala Thr Cys Cys Cys  Ala Ala Cys
    2870                2875                2880

Thr Thr  Gly Ala Cys Cys Cys  Cys Ala Cys Thr Cys  Thr Thr Cys
    2885                2890                2895
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Thr Cys  Thr Thr Gly Cys Cys  Thr Thr Ala Gly Thr  Cys Ala Cys
    2900                 2905                 2910

Cys Ala  Cys Ala Ala Thr Gly  Thr Thr Thr Ala Gly  Thr Thr Thr
    2915                 2920                 2925

Ala Thr  Ala Ala Gly Cys Ala  Thr Gly Cys Gly Thr  Cys Ala Cys
    2930                 2935                 2940

Thr Ala  Thr Gly Cys Cys Cys  Gly Gly Cys Thr Thr  Thr Ala Ala
    2945                 2950                 2955

Ala Thr  Ala Ala Ala Cys Thr  Cys Ala Cys Cys Cys  Ala Thr Ala
    2960                 2965                 2970

Ala Thr  Cys Cys Cys Ala Gly  Cys Ala Cys Thr Gly  Ala Ala Gly
    2975                 2980                 2985

Thr Ala  Gly Ala Cys Ala Ala  Ala Ala Gly Gly Gly  Ala Gly Gly
    2990                 2995                 3000

Ala Thr  Cys Gly Ala Thr Gly  Gly Gly Gly Cys Thr  Gly Ala Cys
    3005                 3010                 3015

Thr Gly  Gly Cys Cys Ala Cys  Ala Ala Gly Cys Cys  Gly Thr Gly
    3020                 3025                 3030

Cys Thr  Thr Cys Ala Ala Gly  Thr Thr Cys Ala Ala  Thr Gly Ala
    3035                 3040                 3045

Ala Gly  Ala Cys Cys Cys Thr  Gly Thr Cys Thr Cys  Ala Ala Gly
    3050                 3055                 3060

Gly Gly  Ala Ala Thr Ala Ala  Gly Gly Cys Ala Cys  Ala Gly Ala
    3065                 3070                 3075

Gly Gly  Ala Thr Ala Gly Ala  Gly Cys Cys Ala Thr  Ala Cys Gly
    3080                 3085                 3090

Cys Cys  Thr Gly Ala Cys Cys  Thr Cys Cys Thr Cys  Cys Thr Cys
    3095                 3100                 3105

Thr Gly  Gly Cys Cys Thr Cys  Thr Ala Cys Cys Cys  Ala Gly Gly
    3110                 3115                 3120

Cys Ala  Cys Ala Thr Gly Thr  Gly Cys Ala Thr Ala  Cys Ala Cys
    3125                 3130                 3135

Ala Cys  Ala Cys Cys Ala Cys  Ala Cys Ala Cys Ala  Cys Ala Cys
    3140                 3145                 3150

Ala Cys  Ala Cys Ala Cys Ala  Cys Ala Cys Ala Cys  Ala Cys Ala
    3155                 3160                 3165

Cys Ala  Cys Ala Cys Ala Cys  Ala Gly Ala Gly Ala  Gly Ala Gly
    3170                 3175                 3180

Ala Gly  Ala Gly Ala Gly Ala  Gly Ala Gly Ala Gly  Ala Gly Ala
    3185                 3190                 3195

Gly Ala  Gly Ala Gly Ala Gly  Ala Gly Ala Gly Ala  Gly Ala Gly
    3200                 3205                 3210

Ala Gly  Ala Gly Ala Gly Ala  Gly Ala Ala Ala Cys  Thr Thr Thr
    3215                 3220                 3225

Thr Thr  Cys Cys Thr Cys Thr  Thr Thr Thr Thr Thr  Thr Thr Thr
    3230                 3235                 3240

Ala Ala  Ala Ala Ala Thr Ala  Thr Thr Ala Thr Thr  Thr Ala Thr
    3245                 3250                 3255

Thr Thr  Cys Ala Thr Gly Thr  Ala Thr Ala Thr Gly  Ala Gly Thr
    3260                 3265                 3270
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Ala Cys  Ala Cys Thr Gly Thr  Thr Gly Cys Thr Gly  Thr Cys Thr
    3275                3280                3285

Thr Cys  Ala Gly Ala Cys Ala  Cys Cys Cys Cys Ala  Ala Ala Ala
    3290                3295                3300

Gly Ala  Ala Gly Gly Cys Ala  Thr Cys Ala Gly Ala  Thr Cys Cys
    3305                3310                3315

Cys Ala  Thr Thr Gly Ala Cys  Ala Ala Ala Thr Gly  Gly Thr Thr
    3320                3325                3330

Gly Thr  Gly Ala Gly Cys Cys  Ala Cys Cys Ala Thr  Gly Thr Gly
    3335                3340                3345

Gly Thr  Thr Gly Cys Thr Gly  Gly Gly Ala Ala Thr  Thr Gly Ala
    3350                3355                3360

Ala Cys  Thr Cys Ala Gly Gly  Ala Cys Cys Thr Cys  Thr Gly Gly
    3365                3370                3375

Ala Ala  Ala Ala Gly Cys Ala  Gly Thr Cys Ala Gly  Thr Gly Cys
    3380                3385                3390

Thr Cys  Thr Thr Ala Ala Cys  Cys Ala Thr Cys Thr  Cys Thr Thr
    3395                3400                3405

Cys Ala  Gly Cys Cys Cys Cys  Ala Cys Ala Ala Ala  Gly Ala Ala
    3410                3415                3420

Ala Cys  Thr Thr Thr Thr Ala  Ala Thr Gly Ala Gly  Cys Ala Ala
    3425                3430                3435

Ala Thr  Ala Ala Thr Thr Gly  Cys Thr Thr Cys Cys  Ala Ala Gly
    3440                3445                3450

Thr Ala  Ala Ala Thr Ala Cys  Thr Ala Cys Thr Ala  Ala Thr Ala
    3455                3460                3465

Thr Ala  Thr Thr Thr Cys Thr  Ala Ala Cys Cys Ala  Thr Ala Cys
    3470                3475                3480

Thr Ala  Thr Ala Cys Ala Ala  Gly Gly Ala Ala Thr  Thr Ala Thr
    3485                3490                3495

Thr Ala  Ala Ala Gly Ala Ala  Cys Gly Gly Ala Thr  Ala Ala Thr
    3500                3505                3510

Ala Gly  Gly Ala Gly Ala Ala  Thr Ala Ala Ala Ala  Ala Ala Thr
    3515                3520                3525

Thr Ala  Thr Ala Ala Gly Thr  Cys Ala Cys Thr Thr  Thr Ala Thr
    3530                3535                3540

Ala Ala  Thr Gly Cys Thr Ala  Thr Cys Thr Ala Ala  Thr Cys Cys
    3545                3550                3555

Ala Thr  Cys Thr Ala Gly Ala  Ala Cys Ala Ala Ala  Ala Ala Cys
    3560                3565                3570

Ala Cys  Thr Gly Thr Ala Ala  Thr Ala Ala Thr Gly  Cys Ala Ala
    3575                3580                3585

Ala Ala  Gly Ala Gly Cys Gly  Cys Ala Gly Thr Gly  Cys Cys Thr
    3590                3595                3600

Ala Gly  Ala Thr Thr Ala Ala  Ala Thr Ala Ala Ala  Thr Ala Ala
    3605                3610                3615

Ala Ala  Thr Gly Cys Ala Gly  Ala Cys Cys Ala Ala  Thr Ala Ala
    3620                3625                3630

Gly Thr  Ala Ala Ala Cys Thr  Thr Thr Ala Thr Ala  Gly Cys Ala
    3635                3640                3645

Gly Cys  Ala Cys Ala Thr Gly  Gly Ala Ala Ala Thr  Gly Ala Cys
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    3650                3655                3660

Gly Ala  Ala Ala Thr Thr Cys  Cys Thr Ala Ala Cys  Ala Ala Ala
    3665                3670                3675

Ala Ala  Gly Cys Thr Cys Ala  Ala Gly Ala Thr Gly  Gly Gly Cys
    3680                3685                3690

Ala Gly  Thr Thr Thr Ala Thr  Thr Thr Ala Ala Ala  Gly Thr Gly
    3695                3700                3705

Ala Ala  Ala Thr Ala Cys Ala  Gly Gly Ala Gly Ala  Ala Ala Thr
    3710                3715                3720

Ala Ala  Ala Gly Cys Ala Cys  Ala Gly Ala Ala Ala  Gly Ala Thr
    3725                3730                3735

Ala Cys  Thr Cys Ala Ala Ala  Gly Gly Cys Ala Thr  Ala Gly Ala
    3740                3745                3750

Ala Gly  Thr Thr Ala Ala Cys  Ala Thr Ala Gly Gly  Gly Gly Gly
    3755                3760                3765

Gly Cys  Thr Gly Gly Cys Gly  Ala Gly Ala Thr Gly  Gly Cys Thr
    3770                3775                3780

Cys Thr  Ala Cys Ala Gly Gly  Thr Ala Ala Gly Ala  Gly Cys Ala
    3785                3790                3795

Cys Cys  Cys Gly Ala Cys Thr  Gly Cys Thr Cys Thr  Thr Cys Cys
    3800                3805                3810

Ala Ala  Ala Gly Gly Thr Cys  Cys Thr Gly Ala Gly  Thr Thr Cys
    3815                3820                3825

Ala Ala  Ala Thr Cys Cys Cys  Ala Gly Cys Ala Ala  Cys Cys Ala
    3830                3835                3840

Cys Ala  Thr Gly Gly Thr Gly  Gly Cys Thr Cys Ala  Cys Ala Ala
    3845                3850                3855

Cys Cys  Ala Thr Cys Cys Gly  Thr Ala Ala Thr Gly  Ala Gly Ala
    3860                3865                3870

Thr Thr  Thr Gly Ala Cys Thr  Cys Cys Cys Thr Cys  Thr Thr Cys
    3875                3880                3885

Thr Gly  Gly Thr Gly Thr Gly  Thr Cys Thr Gly Ala  Ala Gly Ala
    3890                3895                3900

Cys Ala  Gly Cys Thr Ala Cys  Ala Gly Thr Gly Thr  Ala Cys Thr
    3905                3910                3915

Thr Ala  Ala Cys Ala Thr Ala  Thr Ala Ala Thr Ala  Ala Ala Thr
    3920                3925                3930

Ala Ala  Ala Thr Ala Ala Ala  Ala Cys Thr Thr Thr  Ala Ala Ala
    3935                3940                3945

Ala Ala  Ala Ala Ala Ala Ala  Thr Thr Ala Ala Ala  Gly Ala Ala
    3950                3955                3960

Gly Thr  Thr Ala Ala Cys Ala  Thr Ala Gly Ala Ala  Gly Cys Cys
    3965                3970                3975

Cys Ala  Cys Thr Cys Ala Gly  Gly Ala Cys Cys Cys  Cys Ala Cys
    3980                3985                3990

Thr Cys  Ala Gly Thr Cys Cys  Thr Ala Gly Ala Gly  Thr Ala Thr
    3995                4000                4005

Gly Ala  Cys Ala Thr Thr Ala  Thr Thr Ala Thr Gly  Gly Ala Cys
    4010                4015                4020

Ala Thr  Thr Ala Ala Ala Ala  Ala Gly Ala Gly Ala  Ala Ala Ala
    4025                4030                4035
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Thr Thr  Cys Ala Gly Cys Ala  Gly Thr Ala Gly Thr  Gly Thr Gly
    4040                4045                4050

Cys Ala  Thr Gly Cys Ala Cys  Thr Gly Cys Ala Thr  Ala Thr Ala
    4055                4060                4065

Thr Ala  Cys Ala Cys Ala Ala  Ala Thr Cys Cys Thr  Thr Gly Ala
    4070                4075                4080

Gly Thr  Thr Thr Cys Ala Thr  Ala Cys Cys Ala Ala  Ala Thr Gly
    4085                4090                4095

Cys Cys  Thr Thr Thr Ala Gly  Ala Cys Cys Ala Cys  Thr Thr Gly
    4100                4105                4110

Thr Gly  Gly Cys Thr Cys Thr  Gly Cys Ala Ala Ala  Cys Cys Thr
    4115                4120                4125

Gly Thr  Ala Ala Thr Cys Cys  Thr Ala Gly Cys Ala  Cys Thr Thr
    4130                4135                4140

Gly Thr  Gly Ala Ala Ala Ala  Gly Gly Thr Cys Ala  Gly Cys Thr
    4145                4150                4155

Cys Ala  Gly Gly Ala Ala Cys  Thr Thr Thr Gly Gly  Gly Ala Ala
    4160                4165                4170

Gly Gly  Thr Cys Ala Thr Gly  Ala Ala Ala Cys Thr  Cys Thr Thr
    4175                4180                4185

Gly Cys  Cys Cys Cys Thr Cys  Cys Ala Gly Ala Ala  Gly Gly Gly
    4190                4195                4200

Ala Gly  Ala Gly Gly Cys Thr  Ala Ala Thr Thr Ala  Ala Cys Ala
    4205                4210                4215

Thr Thr  Thr Cys Thr Cys Ala  Gly Ala Cys Cys Ala  Cys Ala Gly
    4220                4225                4230

Gly Gly  Cys Gly Gly Gly Ala  Ala Cys Cys Gly Ala  Cys Cys Thr
    4235                4240                4245

Gly Cys  Gly Gly Gly Thr Gly  Gly Gly Gly Ala Cys  Ala Gly Ala
    4250                4255                4260

Cys Thr  Gly Thr Thr Gly Cys  Cys Cys Ala Thr Thr  Thr Cys Cys
    4265                4270                4275

Ala Gly  Ala Cys Thr Ala Gly  Gly Gly Ala Ala Gly  Thr Cys Cys
    4280                4285                4290

Thr Thr  Gly Thr Cys Ala Cys  Cys Thr Cys Ala Thr  Thr Cys Cys
    4295                4300                4305

Cys Thr  Ala Ala Ala Gly Ala  Cys Cys Ala Ala Thr  Cys Ala Ala
    4310                4315                4320

Thr Thr  Thr Ala Ala Ala Gly  Gly Gly Thr Gly Cys  Ala Cys Thr
    4325                4330                4335

Gly Thr  Thr Cys Cys Gly Cys  Cys Ala Ala Thr Cys  Ala Thr Ala
    4340                4345                4350

Thr Thr  Gly Thr Gly Cys Cys  Thr Ala Gly Thr Thr  Gly Cys Thr
    4355                4360                4365

Gly Ala  Thr Gly Cys Thr Cys  Thr Ala Thr Thr Cys  Thr Gly Cys
    4370                4375                4380

Cys Cys  Thr Thr Ala Gly Ala  Ala Ala Cys Cys Gly  Thr Ala Thr
    4385                4390                4395

Ala Ala  Ala Ala Ala Cys Thr  Ala Gly Cys Gly Ala  Ala Gly Gly
    4400                4405                4410
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Gly Gly  Thr Ala Cys Cys Ala  Gly Gly Gly Gly Thr  Ala Ala Cys
    4415                 4420                 4425

Cys Cys  Cys Cys Thr Cys Thr  Cys Cys Thr Thr Cys  Ala Gly Gly
    4430                 4435                 4440

Thr Cys  Thr Gly Gly Gly Ala  Cys Ala Ala Thr Cys  Cys Cys Ala
    4445                 4450                 4455

Cys Thr  Ala Cys Ala Cys Thr  Gly Gly Ala Ala Cys  Ala Ala Thr
    4460                 4465                 4470

Ala Ala  Thr Thr Thr Cys Cys  Thr Cys Thr Gly Gly  Cys Thr Thr
    4475                 4480                 4485

Thr Thr  Thr Gly Cys Ala Thr  Thr Gly Ala Thr Cys  Ala Cys Ala
    4490                 4495                 4500

Gly Cys  Thr Cys Cys Ala Cys  Thr Thr Cys Gly Thr  Gly Gly Thr
    4505                 4510                 4515

Ala Ala  Gly Thr Thr Ala Ala  Gly Ala Cys Thr Cys  Cys Cys Thr
    4520                 4525                 4530

Gly Gly  Ala Gly Thr Cys Thr  Thr Ala Cys Ala Thr  Thr Gly Gly
    4535                 4540                 4545

Cys Ala  Ala Ala Thr Gly Cys  Ala Gly Gly Cys Ala  Ala Ala Ala
    4550                 4555                 4560

Gly Ala  Ala Thr Cys Cys Gly  Ala Ala Ala Cys Thr  Cys Ala Ala
    4565                 4570                 4575

Gly Gly  Thr Cys Ala Thr Cys  Thr Ala Ala Ala Ala  Cys Thr Ala
    4580                 4585                 4590

Cys Ala  Thr Ala Gly Cys Ala  Ala Gly Cys Ala Thr  Gly Cys Thr
    4595                 4600                 4605

Gly Cys  Thr Ala Gly Cys Cys  Thr Gly Gly Gly Cys  Thr Cys Cys
    4610                 4615                 4620

Ala Thr  Gly Ala Gly Ala Cys  Cys Cys Thr Gly Gly  Gly Gly Gly
    4625                 4630                 4635

Ala Gly  Gly Gly Gly Cys Ala  Gly Ala Gly Gly Gly  Ala Gly Ala
    4640                 4645                 4650

Cys Cys  Gly Thr Thr Cys Ala  Gly Ala Ala Gly Ala  Cys Ala Gly
    4655                 4660                 4665

Thr Cys  Ala Ala Gly Ala Thr  Gly Thr Thr Gly Cys  Ala Gly Cys
    4670                 4675                 4680

Ala Gly  Cys Ala Cys Ala Gly  Gly Cys Ala Gly Cys  Cys Thr Gly
    4685                 4690                 4695

Gly Cys  Cys Ala Cys Cys Ala  Gly Thr Gly Cys Thr  Gly Thr Cys
    4700                 4705                 4710

Ala Cys  Cys Ala Gly Ala Cys  Ala Thr Gly Thr Thr  Ala Ala Thr
    4715                 4720                 4725

Gly Thr  Thr Gly Gly Ala Ala  Thr Ala Ala Ala Gly  Cys Cys Thr
    4730                 4735                 4740

Cys Ala  Ala Thr Cys Ala Thr  Gly Ala Cys Thr Cys  Thr Cys Cys
    4745                 4750                 4755

Cys Ala  Gly Thr Thr Thr Thr  Ala Thr Ala Ala Thr  Thr Gly Gly
    4760                 4765                 4770

Ala Ala  Ala Thr Ala Ala Gly  Ala Ala Ala Gly Gly  Ala Ala Ala
    4775                 4780                 4785

Gly Ala  Cys Thr Ala Thr Ala  Gly Gly Ala Ala Cys  Ala Ala Cys
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    4790                4795                4800

Thr Gly  Thr Gly Thr Thr Cys  Ala Gly Ala Ala Cys  Ala Cys Thr
    4805                4810                4815

Ala Thr  Thr Thr Ala Thr Ala  Ala Thr Ala Gly Cys  Ala Ala Ala
    4820                4825                4830

Gly Ala  Thr Cys Thr Cys Ala  Gly Ala Gly Thr Ala  Ala Cys Cys
    4835                4840                4845

Cys Ala  Ala Ala Cys Thr Thr  Cys Thr Ala Gly Ala  Cys Ala Thr
    4850                4855                4860

Thr Gly  Ala Thr Thr Thr Gly  Gly Gly Ala Ala Gly  Ala Thr Cys
    4865                4870                4875

Thr Cys  Thr Thr Gly Gly Cys  Ala Gly Cys Thr Thr  Ala Thr Thr
    4880                4885                4890

Thr Thr  Gly Ala Ala Ala Ala  Cys Thr Thr Thr Ala  Cys Ala Ala
    4895                4900                4905

Thr Gly  Thr Thr Ala Ala Ala  Thr Ala Thr Gly Thr  Ala Ala Ala
    4910                4915                4920

Ala Ala  Cys Ala Ala Gly Gly  Ala Cys Ala Gly Thr  Thr Thr Thr
    4925                4930                4935

Gly Thr  Thr Thr Thr Thr Thr  Gly Thr Thr Thr Thr  Gly Thr Thr
    4940                4945                4950

Thr Thr  Gly Thr Thr Thr Thr  Gly Thr Thr Thr Thr  Ala Gly Gly
    4955                4960                4965

Gly Ala  Thr Ala Thr Ala Thr  Ala Thr Thr Cys Ala  Thr Ala Thr
    4970                4975                4980

Ala Thr  Gly Thr Ala Thr Ala  Thr Gly Ala Ala Thr  Gly Ala Ala
    4985                4990                4995

Ala Ala  Cys Cys Cys Ala Ala  Ala Cys Thr Thr Ala  Ala Ala Ala
    5000                5005                5010

Thr Thr  Cys Cys Cys Cys Ala  Cys Thr Ala Thr Gly  Cys Thr Thr
    5015                5020                5025

Thr Ala  Ala Ala Gly Gly Cys  Thr Thr Thr Cys Thr  Gly Ala Cys
    5030                5035                5040

Ala Ala  Thr Ala Ala Cys Ala  Gly Ala Ala Ala Gly  Ala Gly Ala
    5045                5050                5055

Ala Ala  Thr Ala Gly Ala Gly  Ala Ala Thr Cys Cys  Ala Thr Ala
    5060                5065                5070

Ala Ala  Ala Ala Cys Thr Ala  Gly Thr Thr Cys Thr  Gly Ala Ala
    5075                5080                5085

Ala Cys  Thr Ala Thr Cys Ala  Ala Thr Ala Gly Gly  Cys Thr Thr
    5090                5095                5100

Gly Ala  Cys Ala Cys Thr Cys  Thr Thr Thr Ala Gly  Cys Thr Gly
    5105                5110                5115

Cys Cys  Ala Gly Gly Ala Gly  Ala Gly Cys Thr Gly  Ala Ala Thr
    5120                5125                5130

Cys Thr  Gly Ala Ala Cys Ala  Cys Ala Gly Gly Gly  Ala Ala Cys
    5135                5140                5145

Cys Cys  Cys Ala Cys Cys Cys  Ala Gly Cys Ala Cys  Cys Cys Cys
    5150                5155                5160

Ala Ala  Ala Thr Thr Thr Gly  Gly Ala Thr Thr Ala  Thr Thr Gly
    5165                5170                5175
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Thr Thr  Thr Thr Ala Thr Thr  Thr Thr Ala Thr Cys  Thr Thr Thr
    5180                 5185                 5190

Cys Cys  Cys Cys Thr Ala Cys  Cys Cys Cys Cys Ala  Ala Gly Ala
    5195                 5200                 5205

Cys Ala  Gly Gly Gly Thr Thr  Thr Cys Thr Cys Thr  Gly Cys Gly
    5210                 5215                 5220

Thr Gly  Gly Thr Cys Cys Thr  Gly Gly Cys Thr Gly  Thr Cys Cys
    5225                 5230                 5235

Thr Gly  Gly Ala Ala Cys Thr  Cys Gly Gly Ala Gly  Ala Thr Cys
    5240                 5245                 5250

Cys Thr  Cys Thr Gly Cys Cys  Thr Cys Thr Cys Thr  Gly Cys Cys
    5255                 5260                 5265

Thr Cys  Thr Cys Thr Gly Cys  Cys Thr Cys Thr Cys  Thr Cys Thr
    5270                 5275                 5280

Cys Thr  Cys Thr Cys Thr Gly  Cys Cys Thr Cys Thr  Cys Thr Cys
    5285                 5290                 5295

Thr Gly  Cys Cys Thr Cys Thr  Cys Thr Cys Thr Cys  Thr Cys Thr
    5300                 5305                 5310

Cys Thr  Cys Thr Cys Thr Cys  Thr Gly Cys Cys Thr  Cys Thr Cys
    5315                 5320                 5325

Thr Cys  Thr Cys Thr Cys Thr  Cys Thr Cys Thr Gly  Cys Cys Cys
    5330                 5335                 5340

Cys Thr  Cys Gly Cys Thr Gly  Cys Cys Thr Cys Thr  Cys Thr Cys
    5345                 5350                 5355

Thr Gly  Cys Cys Thr Cys Thr  Cys Thr Cys Thr Gly  Cys Cys Cys
    5360                 5365                 5370

Cys Thr  Cys Thr Cys Thr Gly  Cys Cys Cys Cys Thr  Cys Thr Cys
    5375                 5380                 5385

Thr Gly  Cys Cys Cys Cys Thr  Cys Thr Cys Thr Cys  Thr Thr Cys
    5390                 5395                 5400

Cys Cys  Cys Thr Cys Thr Cys  Thr Gly Cys Cys Thr  Cys Thr Cys
    5405                 5410                 5415

Thr Cys  Thr Cys Thr Gly Cys  Cys Cys Cys Thr Cys  Thr Cys Thr
    5420                 5425                 5430

Gly Cys  Cys Thr Cys Thr Cys  Thr Gly Cys Cys Thr  Cys Thr Gly
    5435                 5440                 5445

Cys Cys  Thr Cys Cys Thr Gly  Ala Gly Thr Gly Cys  Thr Gly Gly
    5450                 5455                 5460

Gly Ala  Thr Thr Thr Ala Ala  Ala Gly Gly Cys Ala  Thr Cys Ala
    5465                 5470                 5475

Gly Cys  Cys Ala Thr Cys Ala  Cys Thr Thr Cys Cys  Ala Gly Cys
    5480                 5485                 5490

Thr Thr  Cys Cys Thr Thr Thr  Ala Thr Cys Ala Thr  Thr Thr Thr
    5495                 5500                 5505

Ala Ala  Ala Ala Ala Gly Ala  Ala Thr Thr Thr Cys  Cys Thr Ala
    5510                 5515                 5520

Thr Gly  Thr Gly Ala Cys Thr  Ala Cys Thr Gly Thr  Ala Thr Thr
    5525                 5530                 5535

Thr Ala  Ala Ala Thr Cys Ala  Cys Cys Ala Cys Ala  Cys Gly Gly
    5540                 5545                 5550
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Cys Cys  Ala Ala Thr Ala Cys  Thr Cys Cys Cys Cys  Cys Cys Cys
    5555                 5560                 5565

Ala Ala  Cys Thr Cys Cys Thr  Cys Cys Cys Ala Ala  Ala Thr Cys
    5570                 5575                 5580

Cys Cys  Cys Thr Cys Thr Ala  Cys Cys Cys Ala Cys  Thr Cys Ala
    5585                 5590                 5595

Ala Ala  Thr Thr Cys Thr Thr  Ala Thr Cys Thr Thr  Gly Thr Ala
    5600                 5605                 5610

Thr Thr  Cys Thr Thr Thr Ala  Thr Cys Ala Thr Thr  Ala Thr Thr
    5615                 5620                 5625

Ala Thr  Ala Cys Ala Thr Ala  Thr Gly Thr Gly Thr  Ala Thr Ala
    5630                 5635                 5640

Thr Ala  Thr Gly Thr Gly Thr  Gly Thr Gly Thr Gly  Thr Ala Thr
    5645                 5650                 5655

Ala Thr  Ala Thr Ala Thr Ala  Thr Ala Thr Ala Cys  Thr Ala Thr
    5660                 5665                 5670

Ala Thr  Ala Cys Thr Gly Cys  Thr Ala Ala Thr Gly  Ala Gly Thr
    5675                 5680                 5685

Ala Ala  Cys Ala Thr Thr Thr  Ala Gly Thr Gly Thr  Thr Ala Thr
    5690                 5695                 5700

Thr Cys  Ala Thr Thr Gly Thr  Thr Gly Cys Ala Thr  Gly Thr Thr
    5705                 5710                 5715

Thr Thr  Cys Ala Ala Thr Gly  Thr Gly Cys Thr Thr  Thr Cys Cys
    5720                 5725                 5730

Ala Gly  Gly Ala Gly Gly Cys  Thr Gly Gly Gly Gly  Gly Gly Ala
    5735                 5740                 5745

Thr Gly  Gly Cys Thr Cys Ala  Gly Thr Gly Gly Gly  Cys Ala Ala
    5750                 5755                 5760

Ala Ala  Thr Thr Cys Thr Ala  Gly Cys Thr Gly Cys  Ala Cys Ala
    5765                 5770                 5775

Ala Gly  Cys Cys Thr Ala Ala  Gly Gly Ala Cys Cys  Ala Gly Gly
    5780                 5785                 5790

Gly Thr  Thr Cys Ala Gly Ala  Thr Cys Cys Cys Cys  Ala Ala Thr
    5795                 5800                 5805

Ala Thr  Ala Ala Ala Gly Gly  Cys Thr Gly Gly Cys  Thr Gly Gly
    5810                 5815                 5820

Ala Cys  Ala Thr Gly Gly Thr  Gly Gly Cys Thr Thr  Gly Cys Cys
    5825                 5830                 5835

Thr Ala  Thr Gly Ala Thr Ala  Cys Thr Ala Gly Cys  Ala Thr Gly
    5840                 5845                 5850

Cys Thr  Thr Gly Cys Thr Gly  Gly Ala Ala Gly Cys  Ala Ala Ala
    5855                 5860                 5865

Gly Ala  Cys Ala Gly Gly Gly  Ala Ala Thr Cys Cys  Cys Thr Gly
    5870                 5875                 5880

Gly Ala  Gly Ala Cys Thr Thr  Ala Gly Ala Ala Thr  Cys Thr Cys
    5885                 5890                 5895

Ala Gly  Ala Ala Gly Thr Gly  Ala Thr Cys Thr Gly  Gly Gly Cys
    5900                 5905                 5910

Thr Gly  Gly Ala Cys Ala Gly  Ala Cys Thr Ala Gly  Cys Thr Gly
    5915                 5920                 5925

Ala Ala  Cys Thr Gly Gly Cys  Cys Ala Gly Cys Thr  Cys Thr Gly
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    5930                5935                5940

Gly Gly  Thr Thr Cys Ala Thr  Cys Ala Ala Gly Ala  Ala Ala Cys
    5945                5950                5955

Cys Cys  Thr Ala Cys Cys Thr  Cys Cys Ala Thr Ala  Ala Cys Ala
    5960                5965                5970

Thr Ala  Ala Ala Gly Thr Gly  Thr Gly Ala Thr Gly  Gly Ala Gly
    5975                5980                5985

Ala Ala  Ala Gly Gly Cys Ala  Cys Cys Thr Ala Ala  Thr Gly Thr
    5990                5995                6000

Cys Ala  Ala Cys Cys Thr Cys  Ala Ala Ala Cys Cys  Cys Cys Thr
    6005                6010                6015

Ala Cys  Cys Thr Gly Cys Ala  Thr Gly Thr Gly Cys  Ala Cys Ala
    6020                6025                6030

Cys Ala  Cys Ala Thr Ala Cys  Ala Thr Cys Cys Ala  Cys Ala Cys
    6035                6040                6045

Cys Ala  Cys Ala Cys Ala Cys  Ala Cys Ala Cys Ala  Cys Ala Cys
    6050                6055                6060

Ala Cys  Ala Cys Ala Cys Ala  Cys Ala Cys Ala Cys  Ala Cys Ala
    6065                6070                6075

Cys Cys  Ala Cys Ala Cys Ala  Cys Ala Cys Ala Cys  Ala Cys Ala
    6080                6085                6090

Cys Ala  Cys Ala Ala Ala Thr  Ala Ala Ala Thr Ala  Ala Gly Thr
    6095                6100                6105

Ala Ala  Ala Thr Ala Ala Ala  Thr Ala Ala Ala Ala  Thr Ala Thr
    6110                6115                6120

Thr Thr  Ala Gly Cys Thr Cys  Thr Cys Cys Ala Gly  Ala Cys Cys
    6125                6130                6135

Ala Ala  Ala Thr Cys Thr Thr  Gly Gly Thr Gly Ala  Ala Ala Cys
    6140                6145                6150

Cys Cys  Ala Thr Gly Cys Ala  Thr Thr Thr Gly Cys  Ala Thr Thr
    6155                6160                6165

Thr Gly  Thr Gly Thr Gly Thr  Gly Thr Cys Cys Thr  Ala Cys Ala
    6170                6175                6180

Ala Ala  Cys Ala Cys Thr Gly  Ala Ala Gly Gly Thr  Thr Ala Ala
    6185                6190                6195

Gly Ala  Ala Gly Cys Ala Thr  Gly Cys Thr Cys Cys  Thr Thr Ala
    6200                6205                6210

Gly Thr  Ala Ala Thr Thr Thr  Thr Ala Thr Ala Gly  Cys Ala Gly
    6215                6220                6225

Thr Thr  Thr Gly Cys Gly Thr  Thr Thr Cys Cys Ala  Gly Ala Thr
    6230                6235                6240

Thr Gly  Ala Ala Ala Ala Cys  Ala Gly Ala Thr Thr  Cys Thr Ala
    6245                6250                6255

Thr Ala  Gly Gly Cys Thr Ala  Cys Ala Cys Ala Gly  Thr Gly Cys
    6260                6265                6270

Thr Ala  Ala Ala Thr Gly Gly  Ala Thr Thr Ala Thr  Gly Cys Thr
    6275                6280                6285

Cys Ala  Gly Ala Thr Ala Cys  Ala Gly Ala Thr Thr  Gly Ala Ala
    6290                6295                6300

Ala Ala  Gly Gly Ala Thr Ala  Cys Ala Gly Ala Thr  Thr Gly Ala
    6305                6310                6315
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Ala Ala  Ala Gly Gly Gly Thr  Cys Gly Gly Gly Gly  Thr Cys Thr
    6320                 6325                 6330

Gly Gly  Gly Cys Cys Ala Gly  Gly Ala Thr Gly Ala  Cys Gly Gly
    6335                 6340                 6345

Gly Cys  Cys Ala Ala Cys Thr  Ala Thr Cys Thr Thr  Thr Gly Cys
    6350                 6355                 6360

Cys Cys  Gly Gly Gly Cys Thr  Thr Gly Thr Cys Cys  Thr Thr Cys
    6365                 6370                 6375

Ala Gly  Gly Gly Ala Ala Gly  Gly Gly Thr Thr Ala  Cys Ala Gly
    6380                 6385                 6390

Gly Ala  Thr Thr Cys Ala Cys  Cys Ala Cys Thr Gly  Gly Gly Gly
    6395                 6400                 6405

Thr Gly  Thr Gly Gly Cys Cys  Thr Ala Thr Cys Thr  Gly Cys Thr
    6410                 6415                 6420

Gly Thr  Thr Ala Gly Gly Ala  Cys Cys Thr Gly Ala  Ala Thr Thr
    6425                 6430                 6435

Gly Cys  Cys Thr Gly Gly Ala  Gly Thr Gly Thr Thr  Thr Cys Thr
    6440                 6445                 6450

Ala Gly  Thr Thr Cys Cys Cys  Ala Cys Thr Ala Gly  Thr Thr Gly
    6455                 6460                 6465

Thr Thr  Gly Ala Ala Cys Thr  Thr Thr Ala Cys Cys  Thr Thr Gly
    6470                 6475                 6480

Ala Ala  Cys Cys Thr Cys Thr  Gly Cys Thr Cys Cys  Cys Ala Gly
    6485                 6490                 6495


<210> SEQ ID NO 9
<211> LENGTH: 361
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Ala Ala Thr Thr Thr Thr Cys Thr Ala Cys Ala Gly Gly Cys Thr Ala
1               5                  10                  15

Thr Ala Gly Ala Gly Thr Gly Cys Ala Gly Thr Thr Thr Gly Gly Cys
            20                  25                  30

Thr Ala Ala Ala Gly Cys Ala Ala Ala Ala Cys Cys Thr Ala Gly Gly
        35                  40                  45

Thr Ala Cys Ala Gly Thr Cys Ala Gly Gly Gly Ala Cys Thr Ala Cys
    50                  55                  60

Ala Cys Ala Ala Thr Thr Cys Cys Ala Gly Thr Thr Cys Gly Cys Thr
65                  70                  75                  80

Gly Thr Gly Gly Gly Thr Thr Gly Gly Gly Ala Ala Gly Gly Gly Ala
                85                  90                  95

Thr Gly Gly Gly Thr Gly Gly Gly Cys Cys Ala Gly Thr Gly Cys Thr
            100                 105                 110

Gly Gly Cys Ala Ala Gly Cys Cys Thr Thr Gly Ala Thr Cys Thr Thr
        115                 120                 125

Thr Gly Cys Cys Cys Gly Gly Gly Cys Thr Thr Gly Thr Cys Cys Thr
    130                 135                 140

Thr Cys Thr Gly Gly Gly Gly Ala Gly Ala Ala Thr Thr Ala Cys Cys
145                 150                 155                 160

Thr Gly Cys Thr Thr Cys Thr Gly Cys Thr Gly Gly Ala Cys Thr Gly
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                165                 170                 175

Ala Gly Gly Gly Thr Gly Cys Cys Cys Thr Cys Ala Thr Cys Thr Cys
            180                 185                 190

Thr Gly Gly Cys Thr Ala Gly Ala Gly Cys Cys Cys Gly Thr Gly Cys
        195                 200                 205

Thr Gly Cys Cys Ala Thr Gly Gly Ala Ala Gly Ala Cys Thr Cys Thr
    210                 215                 220

Thr Thr Cys Cys Gly Gly Thr Gly Cys Cys Cys Ala Cys Thr Ala Ala
225                 230                 235                 240

Ala Thr Cys Cys Thr Thr Gly Ala Thr Gly Thr Thr Cys Ala Cys Cys
                245                 250                 255

Thr Thr Gly Thr Cys Cys Cys Cys Thr Gly Cys Cys Cys Cys Cys Ala
            260                 265                 270

Gly Ala Gly Ala Ala Gly Thr Cys Ala Thr Cys Cys Gly Gly Ala Cys
        275                 280                 285

Cys Cys Thr Cys Cys Cys Ala Thr Cys Cys Cys Thr Gly Gly Ala Gly
    290                 295                 300

Thr Cys Thr Cys Thr Gly Cys Ala Gly Ala Gly Gly Thr Thr Ala Thr
305                 310                 315                 320

Thr Thr Gly Ala Cys Cys Ala Gly Cys Ala Gly Cys Thr Cys Thr Cys
                325                 330                 335

Cys Cys Cys Gly Gly Gly Cys Cys Thr Cys Cys Gly Thr Cys Cys Ala
            340                 345                 350

Cys Gly Thr Cys Cys Thr Cys Ala Gly
        355                 360


<210> SEQ ID NO 10
<211> LENGTH: 279
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Gly Thr Ala Ala Thr Gly Gly Cys Thr Gly Gly Cys Cys Cys Ala Cys
1               5                   10                  15

Gly Gly Gly Gly Gly Cys Gly Gly Gly Cys Ala Gly Gly Thr Gly Gly
            20                  25                  30

Gly Gly Gly Cys Gly Gly Cys Cys Ala Cys Cys Ala Gly Gly Thr Gly
        35                  40                  45

Ala Gly Ala Gly Ala Ala Ala Cys Ala Gly Cys Thr Cys Ala Thr Gly
    50                  55                  60

Ala Gly Ala Gly Cys Gly Ala Cys Cys Thr Cys Thr Gly Cys Cys Thr
65                  70                  75                  80

Cys Thr Gly Cys Cys Thr Gly Gly Cys Thr Gly Ala Ala Cys Ala Ala
                85                  90                  95

Ala Thr Gly Cys Cys Thr Cys Thr Gly Cys Cys Gly Cys Ala Cys Thr
            100                 105                 110

Cys Ala Cys Ala Ala Thr Ala Ala Thr Thr Gly Ala Gly Thr Gly Gly
        115                 120                 125

Thr Gly Ala Gly Cys Ala Cys Ala Gly Cys Thr Thr Gly Gly Ala Ala
    130                 135                 140

Ala Thr Cys Thr Cys Thr Gly Thr Gly Gly Thr Thr Gly Thr Thr Thr
145                 150                 155                 160
```

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```
Gly Gly Ala Gly Gly Thr Cys Thr Thr Gly Thr Thr Ala Thr Cys Ala
                165                 170                 175

Thr Gly Gly Ala Ala Thr Thr Thr Gly Ala Ala Cys Ala Gly Thr Ala
            180                 185                 190

Gly Cys Thr Thr Gly Thr Gly Thr Gly Thr Gly Cys Thr Gly Cys Ala
        195                 200                 205

Gly Cys Thr Thr Thr Thr Thr Ala Cys Ala Ala Cys Thr Ala Ala Ala
    210                 215                 220

Gly Thr Thr Ala Ala Thr Thr Gly Gly Ala Gly Gly Cys Cys Ala Gly
225                 230                 235                 240

Thr Thr Gly Cys Thr Cys Thr Gly Gly Gly Ala Ala Gly Cys Gly Gly
                245                 250                 255

Ala Thr Gly Gly Gly Gly Thr Gly Gly Gly Ala Gly Gly Ala Cys Ala
            260                 265                 270

Thr Gly Gly Cys Cys Ala Gly
        275
```

<210> SEQ ID NO 11
<211> LENGTH: 784
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(784)
<223> OTHER INFORMATION: SHIP cDNA

<400> SEQUENCE: 11

```
ggcaatttct gagaggcaac aggcggcagg tctcagccta gagagggccc tgaactactt     60

tgctggagtg tccgtcctgg gagtggctgc tgacccagtc caggagaccc atgcctgcca    120

tggtccctgg gtggaaccat ggcaacatca cccgctccaa ggcagaggag ctactttcca    180

gagccggcaa ggacgggagc ttccttgtgc gtgccagcga gtccatcccc cgggcctacg    240

cactctgcgt gctgttccgg aattgtgttt acacttacag gattctgccc aatgaggacg    300

ataaattcac tgttcaggca tccgaaggtg tccccatgag gttcttcacg aagctggacc    360

agctcatcga cttttacaag aaggaaaaca tggggctggt gacccacctg cagtaccccg    420

tgcccctgga ggaggaggat gctattgatg aggctgagga ggacactgta gaaagtgtca    480

tgtcaccacc tgagctgcct cccagaaaca ttcctatgtc tgccgggccc agcgaggcca    540

aggaccttcc tcttgcaaca gagaaccccc gagcccctga ggtcacccgg ctgagtctct    600

ccgagacact gtttcagcgt ctacagagca tggataccag tgggcttccc gaggagcacc    660

tgaaagccat ccaggattat ctgagcactc agctcctcct ggattccgac tttttgaaga    720

cgggctccag caacctccct cacctgaaga agctgatgtc actgctctgc aaggagctcc    780

atgg                                                                 784
```

<210> SEQ ID NO 12
<211> LENGTH: 225
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(225)
<223> OTHER INFORMATION: SHIP amino acid sequence

<400> SEQUENCE: 12

-continued

```
Met Pro Ala Met Val Pro Gly Trp Asn His Gly Asn Ile Thr Arg Ser
1               5                   10                  15

Lys Ala Glu Glu Leu Leu Ser Arg Ala Gly Lys Asp Gly Ser Phe Leu
            20                  25                  30

Val Arg Ala Ser Glu Ser Ile Pro Arg Ala Tyr Ala Leu Cys Val Leu
        35                  40                  45

Phe Arg Asn Cys Val Tyr Thr Tyr Arg Ile Leu Pro Asn Glu Asp Asp
    50                  55                  60

Lys Phe Thr Val Gln Ala Ser Glu Gly Val Pro Met Arg Phe Phe Thr
65                  70                  75                  80

Lys Leu Asp Gln Leu Ile Asp Phe Tyr Lys Lys Glu Asn Met Gly Leu
                85                  90                  95

Val Thr His Leu Gln Tyr Pro Val Pro Leu Glu Glu Glu Asp Ala Ile
            100                 105                 110

Asp Glu Ala Glu Glu Asp Thr Val Glu Ser Val Met Ser Pro Pro Glu
        115                 120                 125

Leu Pro Pro Arg Asn Ile Pro Met Ser Ala Gly Pro Ser Glu Ala Lys
    130                 135                 140

Asp Leu Pro Leu Ala Thr Glu Asn Pro Arg Ala Pro Glu Val Thr Arg
145                 150                 155                 160

Leu Ser Leu Ser Glu Thr Leu Phe Gln Arg Leu Gln Ser Met Asp Thr
                165                 170                 175

Ser Gly Leu Pro Glu Glu His Leu Lys Ala Ile Gln Asp Tyr Leu Ser
            180                 185                 190

Thr Gln Leu Leu Leu Asp Ser Asp Phe Leu Lys Thr Gly Ser Ser Asn
        195                 200                 205

Leu Pro His Leu Lys Lys Leu Met Ser Leu Leu Cys Lys Glu Leu His
    210                 215                 220

Gly
225
```

<210> SEQ ID NO 13
<211> LENGTH: 2946
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(2946)
<223> OTHER INFORMATION: s-SHIP cDNA (partial)

<400> SEQUENCE: 13

```
gttcccacta gttgttgaac tttaccttga acctctgctc ccagggaagt catcaggact     60

ctgccatccc tggagtctct gcagaggttg tttgaccaac agctctcccc aggccttcgc    120

ccacgacctc aggtgcccgg agaggccagt cccatcacca tggttgccaa actcagccaa    180

ttgacaagtc tgctgtcttc cattgaagat aaggtcaagt ccttgctgca cgagggctca    240

gaatctacca acaggcgttc ccttatccct ccggtcacct ttgaggtgaa gtcagagtcc    300

ctgggcattc ctcagaaaat gcatctcaaa gtggacgttg agtctgggaa actgatcgtt    360

aagaagtcca aggatggttc tgaggacaag ttctacagcc acaaaaaaat cctgcagctc    420

attaagtccc agaagtttct aaacaagttg gtgattttgg tggagacgga gaaggagaaa    480

atcctgagga aggaatatgt ttttgctgac tctaagaaaa gagaaggctt ctgtcaactc    540

ctgcagcaga tgaagaacaa gcattcggag cagccagagc ctgacatgat caccatcttc    600
```

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attggcactt ggaacatggg taatgcaccc cctcccaaga agatcacgtc ctggtttctc 660

tccaaggggc agggaaagac acgggacgac tctgctgact acatccccca tgacatctat 720

gtgattggca cccaggagga tccccttgga gagaaggagt ggctggagct actcaggcac 780

tccctgcaag aagtcaccag catgacattt aaaacagttg ccatccacac cctctggaac 840

attcgcatag tggtgcttgc caagccagag catgagaatc ggatcagcca tatctgcact 900

gacaacgtga agacaggcat cgccaacacc ctgggaaaca agggagcagt gggagtgtcc 960

ttcatgttca atggaacctc cttggggttc gtcaacagcc acttgacttc tggaagcgaa 1020

aaaaagctca ggagaaatca aaactatatg aacatcctgc ggttcctggc cctgggagac 1080

aagaagctaa gcccatttaa catcacccac cgcttcaccc acctcttctg gcttggggat 1140

ctcaactacc gcgtggagct gcccacttgg gaggcagagg ccatcatcca gaagatcaag 1200

caacagcagt attcagacct tctggcccac gaccaactgc tcctggagag gaaggaccag 1260

aaggtcttcc tgcactttga ggaggaagag atcaccttcg cccccaccta tcgatttgaa 1320

agactgaccc gggacaagta tgcatacacg aagcagaaag caacagggat gaagtacaac 1380

ttgccgtcct ggtgcgaccg agtcctctgg aagtcttacc cgctggtgca tgtggtctgt 1440

cagtcctatg gcagtaccag tgacatcatg acgagtgacc acagccctgt ctttgccacg 1500

tttgaagcgg gagtcacatc tcaattcgtc tccaagaatg gtcctggcac tgtagatagc 1560

caagggcaga tcgagtttct tgcatgctac gccacactga agaccaagtc ccagactaag 1620

ttctacttgg agttccactc aagctgctta gagagttttg tcaagagtca ggaaggagag 1680

aatgaagagg gaagtgaagg agagctggtg gtacggtttg gagagactct tcccaagcta 1740

aagcccatta tctctgaccc cgagtactta ctggaccagc atatcctgat cagcattaaa 1800

tcctctgaca gtgacgagtc ctatggtgaa ggctgcattg cccttcgctt ggagaccaca 1860

gaggctcagc atcctatcta cacgcctctc acccaccatg gggagatgac tggccacttc 1920

aggggagaga ttaagctgca gacctcccag ggcaagatga gggagaagct ctatgacttt 1980

gtgaagacag agcgggatga atccagtgga atgaaatgct tgaagaacct caccagccat 2040

gaccctatga ggcaatggga gccttctggc agggtccctg catgtggtgt ctccagcctc 2100

aatgagatga tcaatccaaa ctacattggt atggggcctt ttggacagcc cctgcatggg 2160

aaatcaaccc tgtccccaga tcagcaactc acagcttgga gttatgacca gctacccaaa 2220

gactcctccc tggggcctgg gaggggggag ggtcctccaa cccctccctc ccaaccacct 2280

ctgtcgccaa agaagttttc atcttccaca gccaaccgag gtccctgccc cagggtgcaa 2340

gaggcaagac ctggggatct gggaaaggtg gaagctctgc tccaggagga cctgctgctg 2400

acgaagcccg agatgtttga gaacccactg tatggatccg tgagttcctt ccctaagctg 2460

gtgcccagga aagagcagga gtctcccaag atgctgcgga aggagccccc gccctgtcca 2520

gacccaggaa tctcatcacc cagcatcgtg ctccccaaag cccaagaggt ggagagtgtc 2580

aaggggacaa gcaaacaggc ccctgtgcct gtccttggcc ccacaccccg gatccgctcc 2640

tttacctgtt cttcttctgc tgagggcaga atgaccagtg gggacaagag ccaagggaag 2700

cccaaggcct cagccagttc ccaagcccca gtgccagtca agaggcctgt caagccttcc 2760

aggtcagaaa tgagccagca gacaacaccc atcccagctc cacggccacc cctgccagtc 2820

aagagtcctg ctgtcctgca gctgcaacat tccaaaggca gagactaccg tgacaacaca 2880

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gaactccccc accatggcaa gcaccgccaa gaggaggggc tgcttggcag gactgccatg 2940

cagtga 2946

<210> SEQ ID NO 14
<211> LENGTH: 928
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(928)
<223> OTHER INFORMATION: s-SHIP amino acid sequence (partial)

<400> SEQUENCE: 14

Met Val Ala Lys Leu Ser Gln Leu Thr Ser Leu Leu Ser Ser Ile Glu
1 5 10 15

Asp Lys Val Lys Ser Leu Leu His Glu Gly Ser Glu Ser Thr Asn Arg
20 25 30

Arg Ser Leu Ile Pro Pro Val Thr Phe Glu Val Lys Ser Glu Ser Leu
35 40 45

Gly Ile Pro Gln Lys Met His Leu Lys Val Asp Val Glu Ser Gly Lys
50 55 60

Leu Ile Val Lys Lys Ser Lys Asp Gly Ser Glu Asp Lys Phe Tyr Ser
65 70 75 80

His Lys Lys Ile Leu Gln Leu Ile Lys Ser Gln Lys Phe Leu Asn Lys
85 90 95

Leu Val Ile Leu Val Glu Thr Glu Lys Glu Lys Ile Leu Arg Lys Glu
100 105 110

Tyr Val Phe Ala Asp Ser Lys Lys Arg Glu Gly Phe Cys Gln Leu Leu
115 120 125

Gln Gln Met Lys Asn Lys His Ser Glu Gln Pro Glu Pro Asp Met Ile
130 135 140

Thr Ile Phe Ile Gly Thr Trp Asn Met Gly Asn Ala Pro Pro Pro Lys
145 150 155 160

Lys Ile Thr Ser Trp Phe Leu Ser Lys Gly Gln Gly Lys Thr Arg Asp
165 170 175

Asp Ser Ala Asp Tyr Ile Pro His Asp Ile Tyr Val Ile Gly Thr Gln
180 185 190

Glu Asp Pro Leu Gly Glu Lys Glu Trp Leu Glu Leu Leu Arg His Ser
195 200 205

Leu Gln Glu Val Thr Ser Met Thr Phe Lys Thr Val Ala Ile His Thr
210 215 220

Leu Trp Asn Ile Arg Ile Val Val Leu Ala Lys Pro Glu His Glu Asn
225 230 235 240

Arg Ile Ser His Ile Cys Thr Asp Asn Val Lys Thr Gly Ile Ala Asn
245 250 255

Thr Leu Gly Asn Lys Gly Ala Val Gly Val Ser Phe Met Phe Asn Gly
260 265 270

Thr Ser Leu Gly Phe Val Asn Ser His Leu Thr Ser Gly Ser Glu Lys
275 280 285

Lys Leu Arg Arg Asn Gln Asn Tyr Met Asn Ile Leu Arg Phe Leu Ala
290 295 300

Leu Gly Asp Lys Lys Leu Ser Pro Phe Asn Ile Thr His Arg Phe Thr
305 310 315 320

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His Leu Phe Trp Leu Gly Asp Leu Asn Tyr Arg Val Glu Leu Pro Thr
               325                 330                 335

Trp Glu Ala Glu Ala Ile Ile Gln Lys Ile Lys Gln Gln Gln Tyr Ser
           340                 345                 350

Asp Leu Leu Ala His Asp Gln Leu Leu Leu Glu Arg Lys Asp Gln Lys
       355                 360                 365

Val Phe Leu His Phe Glu Glu Glu Glu Ile Thr Phe Ala Pro Thr Tyr
   370                 375                 380

Arg Phe Glu Arg Leu Thr Arg Asp Lys Tyr Ala Tyr Thr Lys Gln Lys
385                 390                 395                 400

Ala Thr Gly Met Lys Tyr Asn Leu Pro Ser Trp Cys Asp Arg Val Leu
               405                 410                 415

Trp Lys Ser Tyr Pro Leu Val His Val Val Cys Gln Ser Tyr Gly Ser
           420                 425                 430

Thr Ser Asp Ile Met Thr Ser Asp His Ser Pro Val Phe Ala Thr Phe
       435                 440                 445

Glu Ala Gly Val Thr Ser Gln Phe Val Ser Lys Asn Gly Pro Gly Thr
   450                 455                 460

Val Asp Ser Gln Gly Gln Ile Glu Phe Leu Ala Cys Tyr Ala Thr Leu
465                 470                 475                 480

Lys Thr Lys Ser Gln Thr Lys Phe Tyr Leu Glu Phe His Ser Ser Cys
               485                 490                 495

Leu Glu Ser Phe Val Lys Ser Gln Glu Gly Glu Asn Glu Glu Gly Ser
           500                 505                 510

Glu Gly Glu Leu Val Val Arg Phe Gly Glu Thr Leu Pro Lys Leu Lys
       515                 520                 525

Pro Ile Ile Ser Asp Pro Glu Tyr Leu Leu Asp Gln His Ile Leu Ile
   530                 535                 540

Ser Ile Lys Ser Ser Asp Ser Asp Glu Ser Tyr Gly Glu Gly Cys Ile
545                 550                 555                 560

Ala Leu Arg Leu Glu Thr Thr Glu Ala Gln His Pro Ile Tyr Thr Pro
               565                 570                 575

Leu Thr His His Gly Glu Met Thr Gly His Phe Arg Gly Glu Ile Lys
           580                 585                 590

Leu Gln Thr Ser Gln Gly Lys Met Arg Glu Lys Leu Tyr Asp Phe Val
       595                 600                 605

Lys Thr Glu Arg Asp Glu Ser Ser Gly Met Lys Cys Leu Lys Asn Leu
   610                 615                 620

Thr Ser His Asp Pro Met Arg Gln Trp Glu Pro Ser Gly Arg Val Pro
625                 630                 635                 640

Ala Cys Gly Val Ser Ser Leu Asn Glu Met Ile Asn Pro Asn Tyr Ile
               645                 650                 655

Gly Met Gly Pro Phe Gly Gln Pro Leu His Gly Lys Ser Thr Leu Ser
           660                 665                 670

Pro Asp Gln Gln Leu Thr Ala Trp Ser Tyr Asp Gln Leu Pro Lys Asp
       675                 680                 685

Ser Ser Leu Gly Pro Gly Arg Gly Glu Gly Pro Pro Thr Pro Pro Ser
   690                 695                 700

Gln Pro Pro Leu Ser Pro Lys Lys Phe Ser Ser Ser Thr Ala Asn Arg
705                 710                 715                 720
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```
Gly Pro Cys Pro Arg Val Gln Glu Ala Arg Pro Gly Asp Leu Gly Lys
               725                 730                 735

Val Glu Ala Leu Leu Gln Glu Asp Leu Leu Leu Thr Lys Pro Glu Met
            740                 745                 750

Phe Glu Asn Pro Leu Tyr Gly Ser Val Ser Ser Phe Pro Lys Leu Val
        755                 760                 765

Pro Arg Lys Glu Gln Glu Ser Pro Lys Met Leu Arg Lys Glu Pro Pro
    770                 775                 780

Pro Cys Pro Asp Pro Gly Ile Ser Ser Pro Ser Ile Val Leu Pro Lys
785                 790                 795                 800

Ala Gln Glu Val Glu Ser Val Lys Gly Thr Ser Lys Gln Ala Pro Val
               805                 810                 815

Pro Val Leu Gly Pro Thr Pro Arg Ile Arg Ser Phe Thr Cys Ser Ser
            820                 825                 830

Ser Ala Glu Gly Arg Met Thr Ser Gly Asp Lys Ser Gln Gly Lys Pro
        835                 840                 845

Lys Ala Ser Ala Ser Ser Gln Ala Pro Val Pro Val Lys Arg Pro Val
    850                 855                 860

Lys Pro Ser Arg Ser Glu Met Ser Gln Gln Thr Thr Pro Ile Pro Ala
865                 870                 875                 880

Pro Arg Pro Pro Leu Pro Val Lys Ser Pro Ala Val Leu Gln Leu Gln
               885                 890                 895

His Ser Lys Gly Arg Asp Tyr Arg Asp Asn Thr Glu Leu Pro His His
            900                 905                 910

Gly Lys His Arg Gln Glu Glu Gly Leu Leu Gly Arg Thr Ala Met Gln
        915                 920                 925


<210> SEQ ID NO 15
<211> LENGTH: 178
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(178)
<223> OTHER INFORMATION: first exon of s-SHIP and adjacent intronic
      sequence

<400> SEQUENCE: 15

attgcctgga gtgtttctag ttcccactag ttgttgaact ttaccttgaa cctctgctcc     60

cagggaagtc atcaggactc tgccatccct ggagtctctg cagaggttgt ttgaccaaca    120

gctctcccca ggccttcgcc cacgacctca ggtaaggggt ttggatttgg aaagatgc      178


<210> SEQ ID NO 16
<211> LENGTH: 188
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(188)
<223> OTHER INFORMATION: first exon of SIP-110 and flanking intronic
      sequences

<400> SEQUENCE: 16

catggaagac tctttccggt gcccactaat ccttgatgtt caccttgtcc cctgccccca     60

gagaagtcat ccggaccctc ccatccctgg agtctctgca gaggttattt gaccagcagc    120

tctccccggg cctccgtcca cgtcctcagg taaagggtct tggggttgaa aaggtgagat    180
```

-continued

taataccc 188

<210> SEQ ID NO 17
<211> LENGTH: 130
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(130)
<223> OTHER INFORMATION: first exon of SIP-110

<400> SEQUENCE: 17

cgcccactaa tccttgatgt tcaccttgtc ccctgccccc agagaagtca tccggaccct 60

cccatccctg gagtctctgc agaggttatt tgaccagcag ctctccccgg gcctccgtcc 120

acgtcctcag 130

<210> SEQ ID NO 18
<211> LENGTH: 132
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(132)
<223> OTHER INFORMATION: first exon of s-SHIP

<400> SEQUENCE: 18

gttcccacta gttgttgaac tttaccttga acctctgctc ccagggaagt catcaggact 60

ctgccatccc tggagtctct gcagaggttg tttgaccaac agctctcccc aggccttcgc 120

ccacgacctc ag 132

We claim:

1. A method for identifying the presence of stem cells in a cell sample, comprising detecting the presence of cells expressing s-SHIP RNA within the cell sample.

2. The method of claim 1, wherein the presence of stem cells in the sample is indicated by the presence of s-SHIP enzymatic activity.

3. The method of claim 1, wherein said detecting comprises adding anti-SHIP monoclonal antibody P2C6 or P1C1 to the sample under conditions, and for a time, suitable for antibody binding; and detecting the presence of the antibodies bound to the cells in the sample, wherein the presence of stem cells in the sample is indicated by cells that express the s-SHIP isoform.

4. The method of claim 3, wherein the antibodies are labeled with a flourochrome.

5. The method of claim 4, wherein the detection of antibodies is by fluorescence activated cell sorting.

6. The method of claim 1, wherein the stem cells are embryonic stem cells.

7. The method of claim 1, wherein the stem cells are tissue-specific stem cells.

8. The method of claim 7, wherein then stem cells are hematopoietic stem cells.

9. The method of claim 3, wherein the stem cells are hematopoietic stem cells and the monoclonal antibody is P2C6.

10. A method for inhibiting proliferation of stem cells, comprising contacting the cells with s-SHIP thereby increasing competition with mSosI for Grb2 in the stem cells.

11. The method of claim 10, wherein the stem cells are selected from the group consisting of hematopoietic progenitors of mature blood cells, hematopoietic progenitors of lymph cells, and embryonic stem cells.

12. A method of inhibiting differentiation of stem cells, comprising contacting the stem cells with s-SHIP enzyme whereby the accumulation of the s-SHIP enzyme prevents the accumulation of $PI^{3},^{4,5},P_3$, or other signaling pathways and intermediates influenced by s-SHIP activity.

13. The method of claim 12, wherein the stem cells are selected from the group consisting of hematopoietic progenitors of mature blood cells and hematopoietic progenitors of lymphoid cells.

14. A recombinant nucleic acid promoter fragment isolated from an internal region of the SHIP gene where s-SHIP transcription is controlled, wherein the promoter fragment comprises a nucleotide fragment internal to the SHIP gene.

15. The recombinant nucleotide promoter fragment of claim 14, wherein the amino acid sequence is selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10.

16. The recombinant nucleotide promoter fragment of claim 14, wherein the fragment is found in stem cells selected from the group consisting of: murine embryonic

stem cells, murine hematopoietic stem cells, human embryonic stem cells, and human hematopoietic stem cells.

17. A method for inducing proliferation of stem cells, comprising introducing anti-SHIP shRNA into the cell by electroporation.

18. The method of claim 17, wherein the stem cells are selected from the group consisting of hematopoietic progenitors of mature blood cells, hematopoietic progenitors of lymph cells, and embryonic stem cells.

19. A method for identifying stem cells in a cell sample, comprising detecting s-SHIP by immunofluorescence.

20. The method of claim 19, wherein the cell sample is a complex mixture of cells.

21. The method of claim 20, wherein the cell sample is in vivo.

22. The method of claim 20, wherein the presence of stem cells is indicated by the presence of the s-SHIP isoform.

23. A method for inducing proliferation in stem cells, comprising introducing an inhibitor of s-SHIP activity.

24. The method of claim 23, wherein the inhibitor of s-SHIP is a dominant negative mutant.

25. The method of claim 23, wherein the inhibitor of s-SHIP is shRNA.

26. The method of claim 23, wherein the stem cells are selected from the group consisting of hematopoietic progenitors of mature blood cells, hematopoietic progenitors of lymph cells, and embryonic stem cells.

27. The method of claim 23, wherein the stem cells are induced to differentiate.

28. A method for identifying stem cell-specific signaling components, comprising contacting the signaling component with s-SHIP.

* * * * *

专利名称(译)	含有肌醇5'-磷酸酶同种型的新型SH2与Grb2衔接蛋白结合		
公开(公告)号	US20070224124A1	公开(公告)日	2007-09-27
申请号	US11/726028	申请日	2007-03-19
[标]申请(专利权)人(译)	南佛罗里达大学		
申请(专利权)人(译)	南佛罗里达大学		
当前申请(专利权)人(译)	南佛罗里达大学		
[标]发明人	KERR WILLIAM G NINOS JOHN M		
发明人	KERR, WILLIAM G. NINOS, JOHN M.		
IPC分类号	C12N15/87 A61K49/00 C12N5/00 G01N33/53 C07H21/04		
CPC分类号	G01N33/56966 C12N9/16		
优先权	60/319583 2002-09-30 US		
外部链接	Espacenet USPTO		

摘要(译)

含有肌醇5'-磷酸（SHIP）的SH2在通过Shc和受体的细胞质尾部募集到膜后调节免疫细胞的活化。描述了在原始干细胞群（s-SHIP）中表达的约104kd的新型SHIP同种型。发现s-SHIP在全能胚胎干细胞中表达，排除在分化的造血细胞中表达的145-kd SHIP同种型。 s-SHIP也在原始造血干细胞中表达，但在谱系定型的造血细胞中不表达。在胚胎干细胞中，s-SHIP与衔接蛋白Grb2结合而没有酪氨酸磷酸化，并且组成性地存在于细胞膜上。据推测，s-SHIP调节原始干细胞群的激活阈值。