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(54) **METHOD OF IDENTIFYING A COMPOUND FOR INHIBITING OR STIMULATING HUMAN G PROTEIN-COUPLED RECEPTORS**

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(57) **ABSTRACT**

The invention disclosed in this patent document relates to transmembrane receptors, more particularly to endogenous, human orphan G protein-coupled receptors.

32 Claims, 5 Drawing Sheets

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* cited by examiner

	1	2	3	4	5	6	7	8
A		Amygdala	Caudate Nucleus	Cerebellum	Cerebral Cortex	Frontal Cortex	Hippocampus	Medulla Oblongata
B	Occipital Cortex	Putamen	Substantia Nigra	Temporal Cortex	Thalamus	Accumbens	Spinal Cord	
C	Heart	Aorta	Skeletal Muscle	Colon	Bladder	Uterus	Prostate	Stomach
D	Testis	Ovary	Pancreas	Pituitary	Adrenal Gland	Thyroid	Salivary Gland	Mammary Gland
E	Kidney	Liver	Small Intestine	Spleen	Thymus	Peripheral Leukocyte	Lymph Node	Bone Marrow
F	Appendix	Lung	Trachea	Placenta				
G	Fetal Brain	Fetal Heart	Fetal Kidney	Fetal Liver	Fetal Spleen	Fetal Thymus	Fetal Lung	
H								

FIG. 1A

	1	2	3	4	5	6	7	8	9	10	11	12
A		Cerebellum Left	Substantia Nigra	Heart	Esophagus	Colon Transverse	Kidney	Lung	Liver	Leukemia HL-60	Fetal Brain	
B	Cerebral Cortex	Cerebellum Right	Accumbens	Aorta	Stomach	Colon Descending	Skeletal Muscle	Placenta	Pancreas	HeLa S3	Fetal Heart	
C	Frontal Cortex	Corpus Callosum	Thalamus	Atrium Left	Duodenum	Rectum	Spleen	Bladder	Adrenal Gland	Leukemia K562	Fetal Kidney	
D	Parietal Lobe	Amygdala	Pituitary Gland	Atrium Right	Jejunum		Thymus	Uterus	Thyroid	Leukemia MOLT-4	Fetal Liver	
E	Occipital Cortex	Claudete Nucleus	Spiral Cord	Ventricle Left	Ileum		Peripheral Leukocyte	Prostate	Salivary Gland	Burkitt's Lymphoma Raji	Fetal Spleen	
F	Temporal Cortex	Hippocampus		Ventricle Right	Ileocecum		Lymph Node	Testis	Mammary Gland	Burkitt's Lymphoma Daudi	Fetal Thymus	
G	Paracentral Gyrus of Cerebral Cortex	Medulla Oblongata		Inter Ventricular Septum	Appendix		Bone Marrow	Ovary		Colorectal Adenocarcinoma SW480	Fetal Lung	
H	Pons	Putamen		Apex of the Heart	Colon Ascending		Trachea			Lung Carcinoma A549		

FIG. 1B

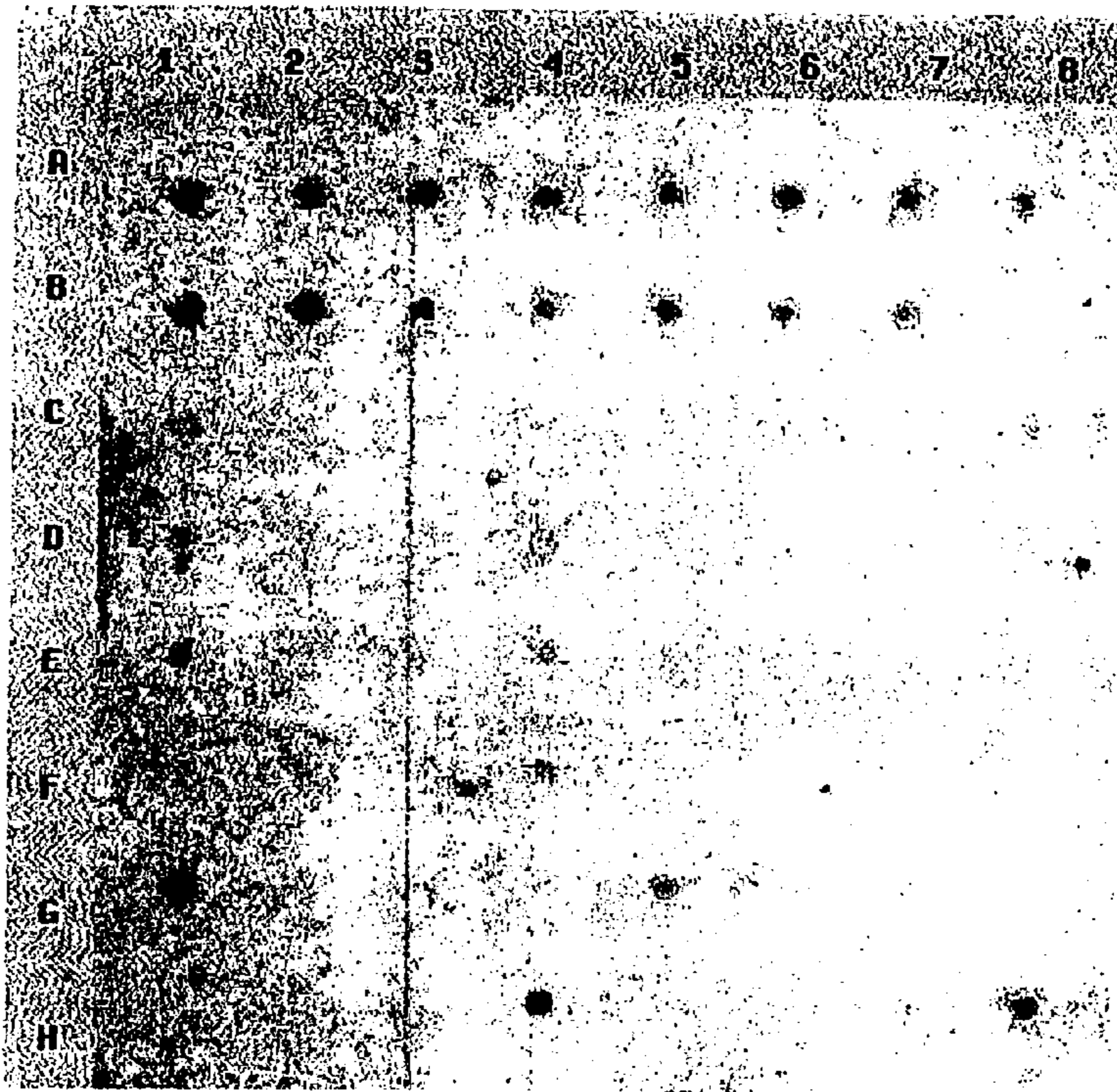


FIG. 2A

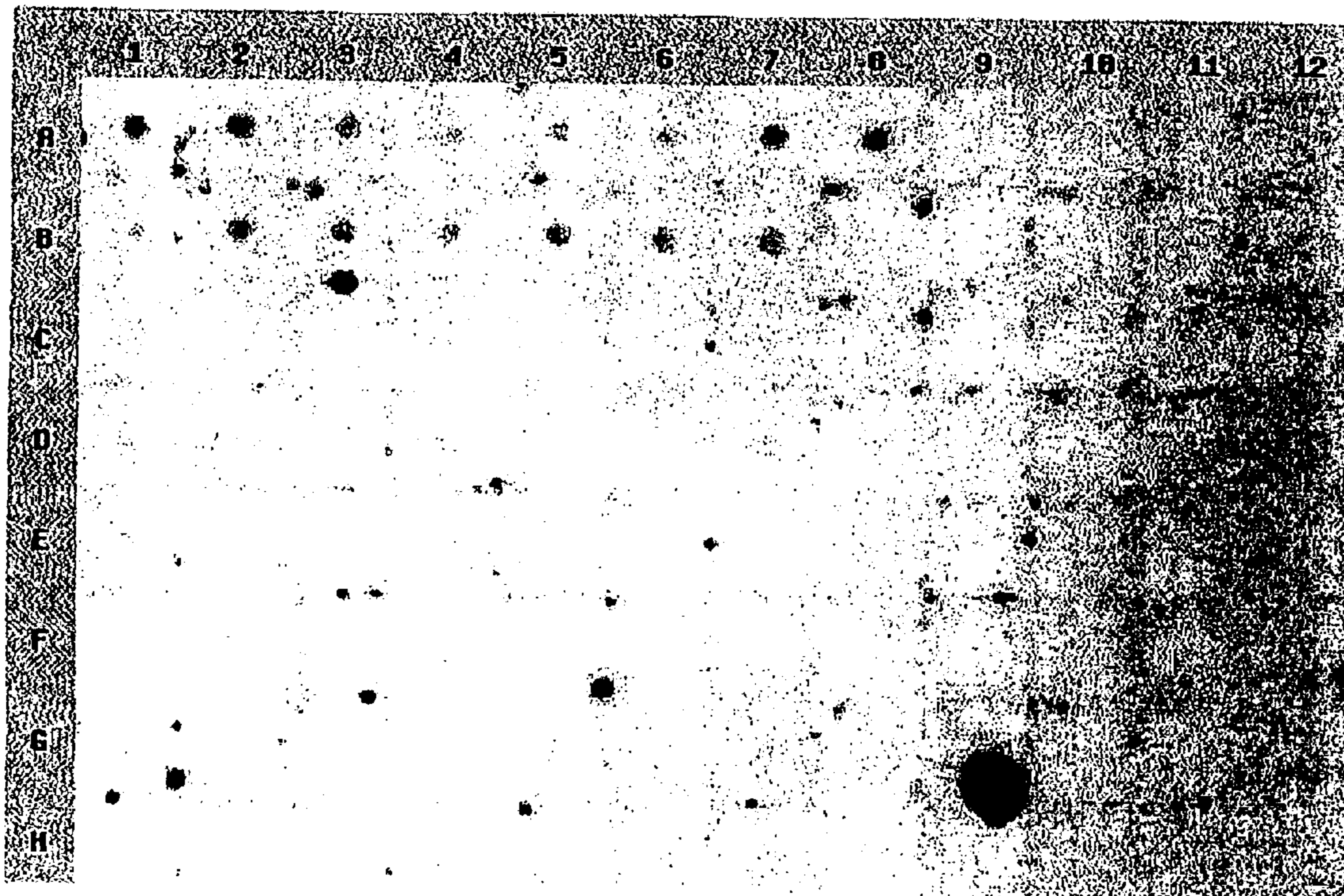


FIG. 2B

FIG. 3

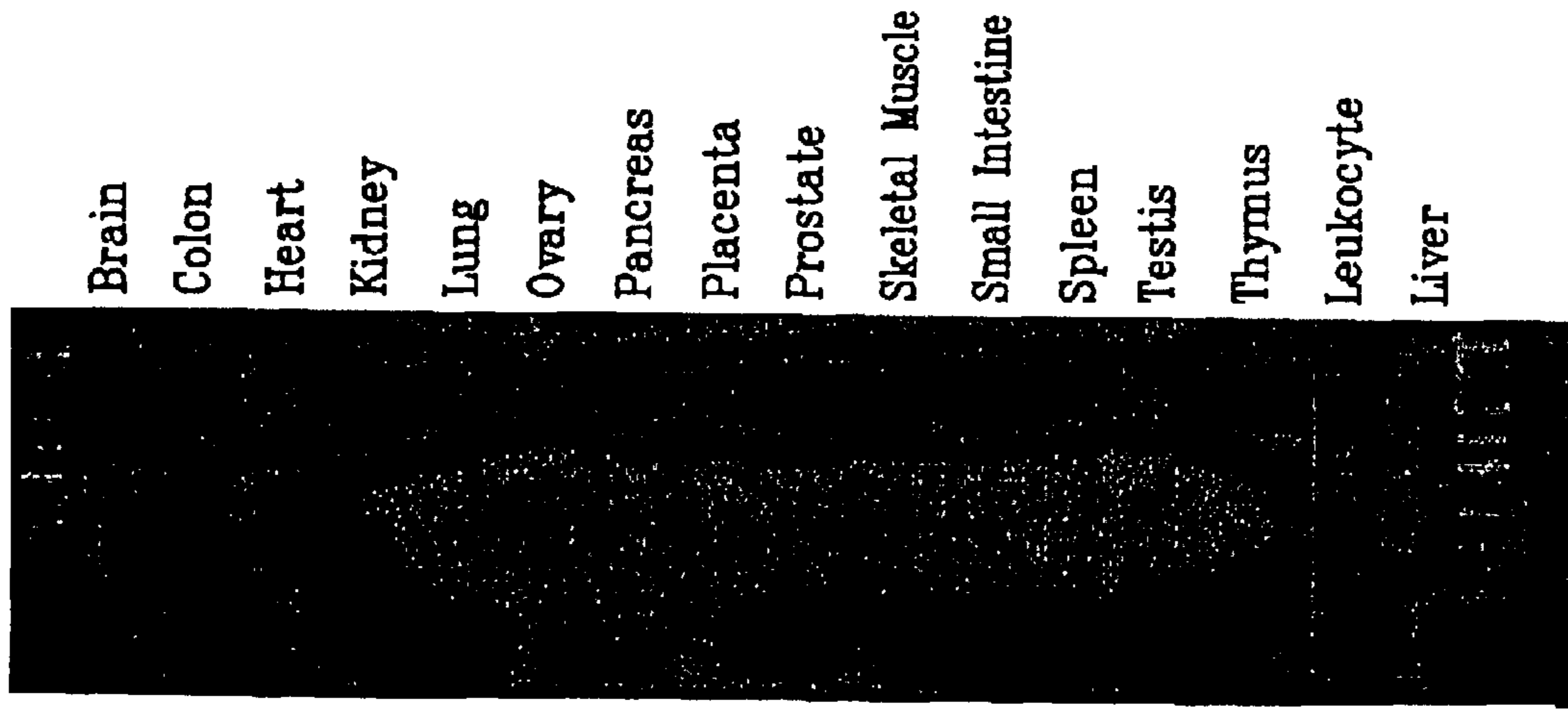


FIG. 4

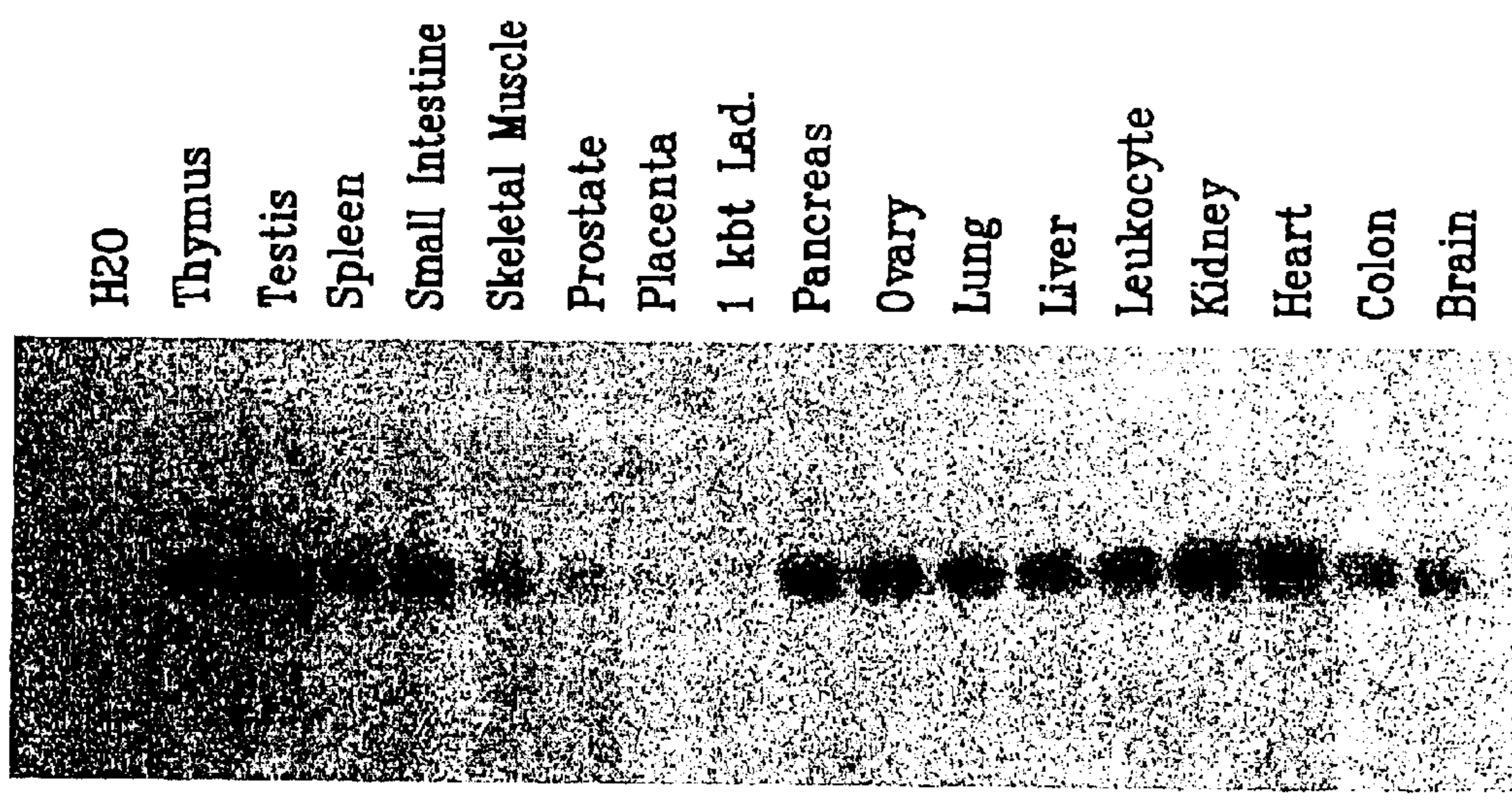
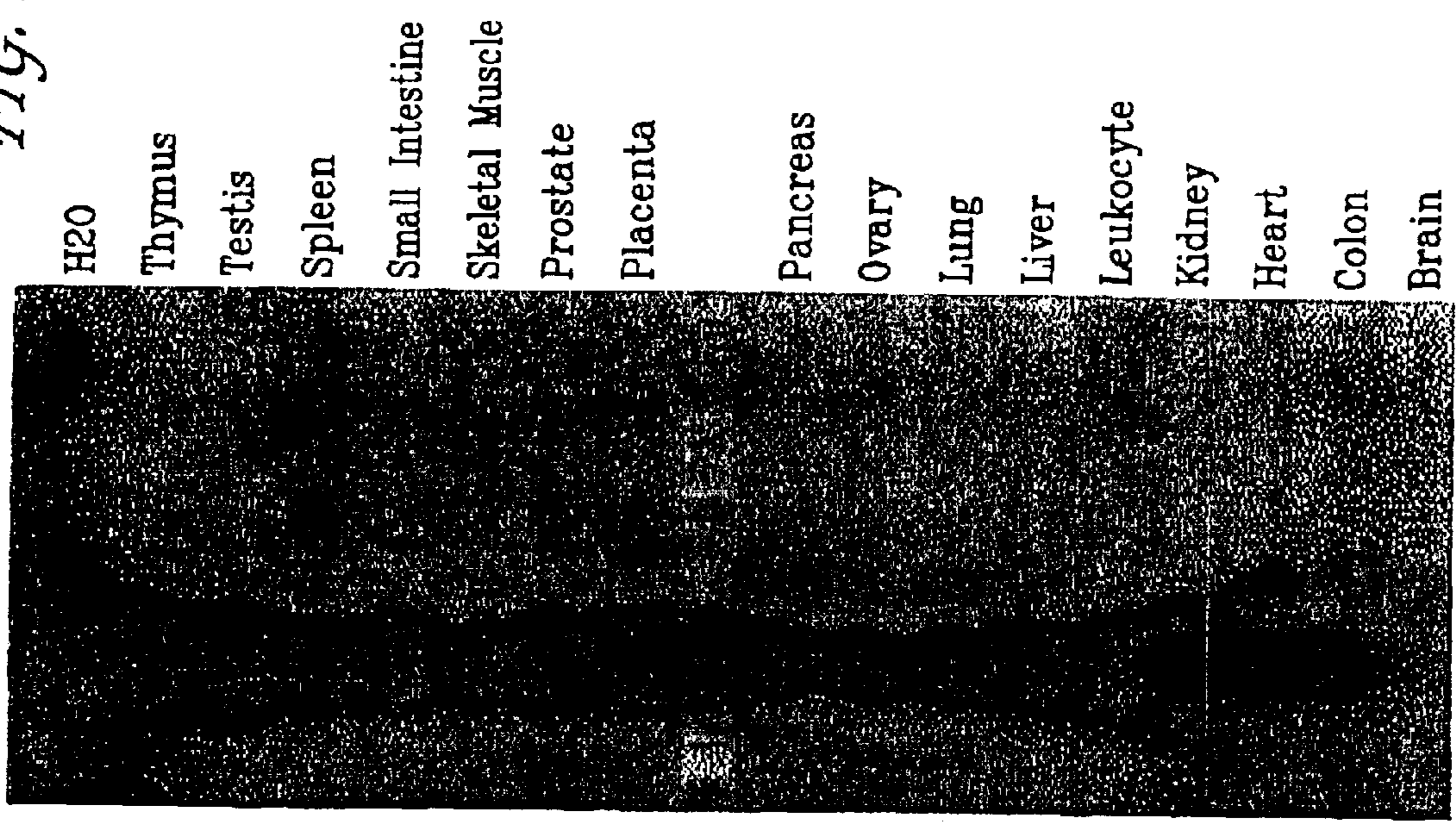


FIG. 5



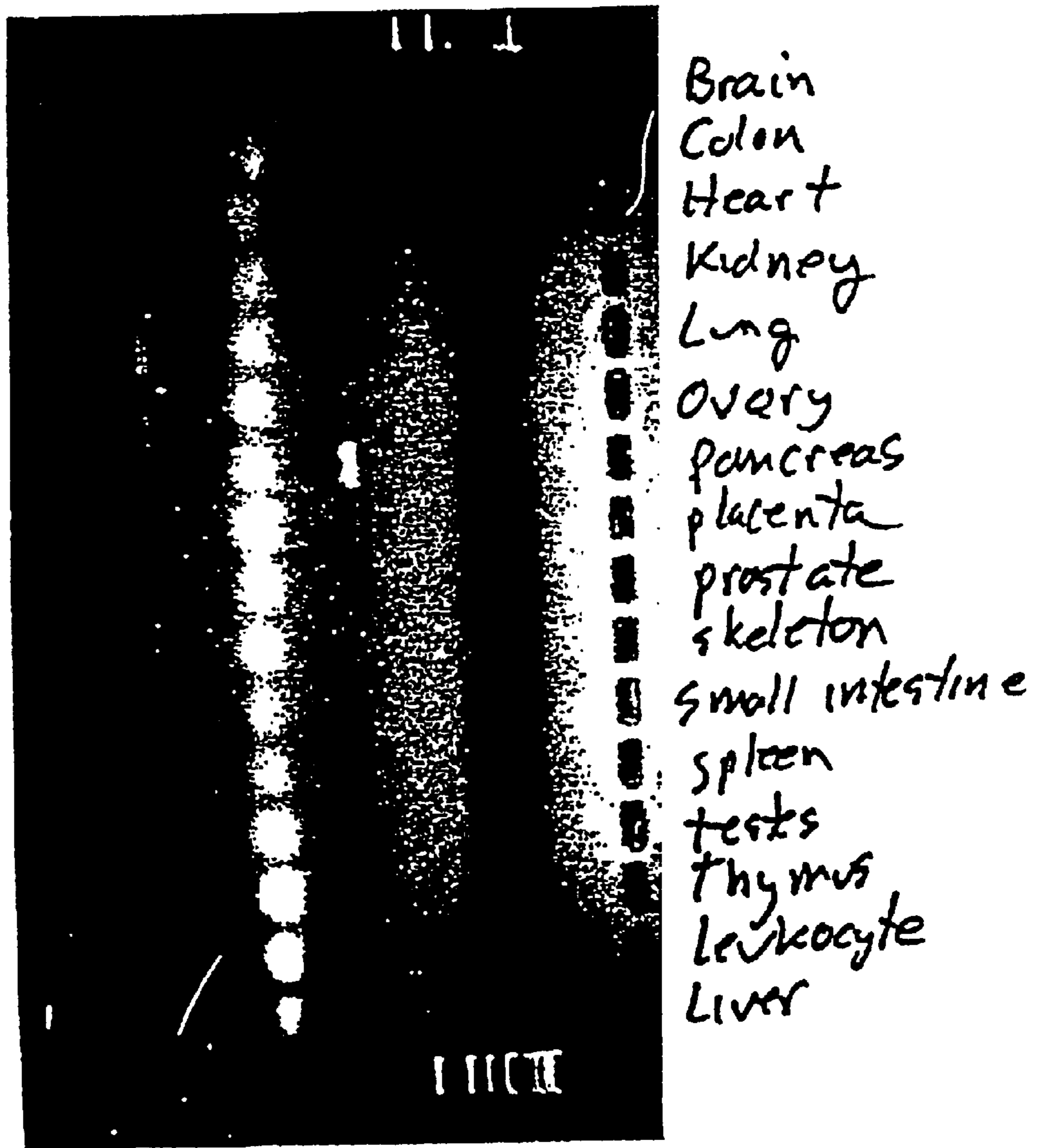


Figure 6

**METHOD OF IDENTIFYING A COMPOUND
FOR INHIBITING OR STIMULATING
HUMAN G PROTEIN-COUPLED RECEPTORS**

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This application is a continuation of *Application* Ser. No. 10/272,983, filed Oct. 17, 2002, which is a continuation of *Application* Ser. No. 09/417,044, filed Oct. 12, 1999, now abandoned, and claims priority benefit of Provisional Application [Ser.] No. 60/121,852 filed Feb. 26, 1999, [Ser.] *Provisional Application* No. 60/109,213, filed Nov. 20, 1998, [Ser.] *Provisional Application* No. 60/120,416, filed Feb. 16, 1999, [Ser.] *Provisional Application* No. 60/123,946, filed Mar. 12, 1999, [Ser.] *Provisional Application* No. 60/123,949, filed Mar. 12, 1999, [Ser.] *Provisional Application* No. 60/136,436, filed May 28, 1999, [Ser.] *Provisional Application* No. 60/136,439, [field] filed May 28, 1999, [Ser.] *Provisional Application* No. 60/136,567, [file] filed May 28, 1999, [Ser.] *Provisional Application* No. 60/137,127, filed May 28, 1999, [Ser.] *Provisional Application* No. 60/137,131, filed May 28, 1999, [Ser.] *Provisional Application* No. 60/141,448, filed Jun. 29, 1999, [Ser.] *Provisional Application* No. 60/136,437, filed May 28, 1999, [Ser.] *Provisional Application* No. 60/156,653, filed Sep. 29, 1999, [Ser.] *Provisional Application* No. [60/156,333] 60/156,633, filed Sep. [28] 29, 1999, [Ser.] *Provisional Application* No. 60/156,555, filed Sep. 29, 1999, [Ser.] *Provisional Application* No. 60/156,634, filed Sep. 29, 1999, [Ser.] *Provisional Application* No. 60/157,280, filed Oct. 1, 1999, [Ser.] *Provisional Application* No. 60/157,294, filed Oct. 1, 1999, [Ser.] *Provisional Application* No. 60/157,281, filed Oct. 1, 1999, [Ser.] *Provisional Application* No. 60/157,293, filed Oct. 1, 1999, and [Ser.] *Provisional Application* No. 60/157,282, filed Oct. 1, 1999, the entirety of each of which is incorporated herein by reference. This patent application is related to U.S. [Ser.] *Application* No. 09/170,496, filed Oct. 13, 1999, and U.S. [Ser.] *Application* No. 09/416,760, filed Oct. 12, 1999, both being incorporated herein by reference in their entirety. This patent application is also related to U.S. [Ser.] *Application* No. 09/364,425, filed Jul. 30, 1999, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention disclosed in this patent document relates to transmembrane receptors, and more particularly to endogenous, orphan, human G protein-coupled receptors (“GPCRs”).

BACKGROUND OF THE INVENTION

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR or GPCRs) class. It is estimated that there are some 100,000 genes within the human genome, and of these, approximately 2% or 2,000 genes, are estimated to code for GPCRs. Receptors, including GPCRs, for which the endogenous ligand has been identified are referred to as “known” receptors, while receptors for which the endogenous ligand has not been identified are referred to as “orphan” receptors. GPCRs represent an important area for the development of pharmaceutical products: from approximately 20 of the 100 known GPCRs, 60% of all prescription pharmaceuticals have been developed.

This distinction is not merely semantic, particularly in the case of GPCRs. Thus, the orphan GPCRs are to the pharmaceutical industry what gold was to California in the late 19th century—an opportunity to drive growth, expansion, enhancement and development.

GPCRs share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane (each span is identified by number, i.e., transmembrane-1 (TM-1), transmembrane-2 (TM-2), etc.). The transmembrane helices are joined by strands of amino acids between transmembrane-2 and transmembrane-3, transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or “extracellular” side, of the cell membrane (these are referred to as “extracellular” regions 1, 2 and 3 (EC-1, EC-2 and EC-3), respectively). The transmembrane helices are also joined by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and transmembrane-5 and transmembrane-6 on the interior, or “intracellular” side, of the cell membrane (these are referred to as “intracellular” regions 1, 2 and 3 (IC-1, IC-2 and IC-3), respectively). The “carboxy” (“C”) terminus of the receptor lies in the intracellular space within the cell, and the “amino” (“N”) terminus of the receptor lies in the extracellular space outside of the cell.

Generally, when an endogenous ligand binds with the receptor (often referred to as “activation” of the receptor), there is a change in the conformation of the intracellular region that allows for coupling between the intracellular region and an intracellular “G-protein.” It has been reported that GPCRs are “promiscuous” with respect to G proteins, i.e., that a GPCR can interact with more than one G protein. See, Kenakin, T, 43 *Life Sciences* 1095 (1988). Although other G proteins exist, currently, Gq, Gs, Gi, and Go are G proteins that have been identified. Endogenous ligand-activated GPCR coupling with the G-protein begins a signaling cascade process (referred to as “signal transduction”). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition. It is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G protein.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an “inactive” state and an “active” state. A receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response. A receptor may be stabilized in an active state by an endogenous ligand or a compound such as a drug.

SUMMARY OF THE INVENTION

Disclosed herein are human endogenous orphan G protein-coupled receptors.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A and 1B provide reference “grids” for certain dot-blot analyses provided herein (see also, FIGS. 2A and 2B, respectively).

FIGS. 2A and 2B provide reproductions of the results of certain dot-blot analyses resulting from hCHN3 and hCHN8, respectively (see also, FIGS. 1A and 1B, respectively).

FIG. 3 provides a reproduction of the results of RT-PCR analysis of hRUP3.

FIG. 4 provides a reproduction of the results of RT-PCR analysis of hRUP4.

FIG. 5 provides a reproduction of the results of RT-PCR analysis of hRUP6.

FIG. 6 is a reproduction of a photograph of the results of the tissue distribution of RUP3 using multiple tissue (human) cDNA. Based upon these tissues, the data support the position that RUP3 is expressed only in the pancreas.

DETAILED DESCRIPTION

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control:

AMINO ACID ABBREVIATIONS used herein are set out in Table 1:

TABLE 1

ALANINE	ALA	A
ARGININE	ARG	R
ASPARAGINE	ASN	N
ASPARTIC ACID	ASP	D
CYSTEINE	CYS	C
GLUTAMIC ACID	GLU	E
GLUTAMINE	GLN	Q
GLYCINE	GLY	G
HISTIDINE	HIS	H
ISOLEUCINE	ILE	I
LEUCINE	LEU	L
LYSINE	LYS	K
METHIONINE	MET	M
PHENYLALANINE	PHE	F
PROLINE	PRO	P
SERINE	SER	S
THREONINE	THR	T
TRYPTOPHAN	TRY	W
TYROSINE	TYR	Y
VALINE	VAL	V

COMPOSITION means a material comprising at least one component.

ENDOGENOUS shall mean a material that a mammal naturally produces. ENDOGENOUS in reference to, for example and not limitation, the term "receptor," shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus. By contrast, the term NON-ENDOGENOUS in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus.

HOST CELL shall mean a cell capable of having a Plasmid and/or Vector incorporated therein. In the case of a prokaryotic Host Cell, a Plasmid is typically replicated as an autonomous molecule as the Host Cell replicates (generally, the Plasmid is thereafter isolated for introduction into a eukaryotic Host Cell); in the case of a eukaryotic Host Cell, a Plasmid is integrated into the cellular DNA of the Host Cell such that when the eukaryotic Host Cell replicates, the Plasmid replicates. Preferably, for the purposes of the invention disclosed herein, the Host Cell is eukaryotic, more preferably, mammalian, and most preferably selected from the group consisting of 293, 293T and COS-7 cells.

LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

MUTANT or MUTATION in reference to an endogenous receptor's nucleic acid and/or amino acid sequence shall mean a specified change or changes to such endogenous sequences such that a mutated form of an endogenous, non-constitutively activated receptor evidences constitutive activation of the receptor. In terms of equivalents to specific sequences, a subsequent mutated form of a human receptor is considered to be equivalent to a first mutation of the human receptor if (a) the level of constitutive activation of the subsequent mutated form of the receptor is substantially the same as that evidenced by the first mutation of the receptor; and (b) the percent sequence (amino acid and/or nucleic acid) homology between the subsequent mutated form of the receptor and the first mutation of the receptor is at least about 80%, more preferably at least about 90% and most preferably at least 95%. Ideally, and owing to the fact that the most preferred mutation disclosed herein for achieving constitutive activation includes a single amino acid and/or codon change between the endogenous and the non-endogenous forms of the GPCR, the percent sequence homology should be at least 98%.

NON-ORPHAN RECEPTOR shall mean an endogenous naturally occurring molecule specific for an endogenous naturally occurring ligand wherein the binding of a ligand to a receptor activates an intracellular signaling pathway.

ORPHAN RECEPTOR shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has not been identified or is not known.

PLASMID shall mean the combination of a Vector and cDNA. Generally, a Plasmid is introduced into a Host Cell for the purposes of replication and/or expression of the cDNA as a protein.

VECTOR in reference to cDNA shall mean a circular DNA capable of incorporating at least one cDNA and capable of incorporation into a Host Cell.

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

Identification of Human GPCRs

The efforts of the Human Genome project have led to the identification of a plethora of information regarding nucleic acid sequences located within the human genome; it has been the case in this endeavor that genetic sequence information has been made available without an understanding or recognition as to whether or not any particular genomic sequence does or may contain open-reading frame information that translate human proteins. Several methods of identifying nucleic acid sequences within the human genome are within the purview of those having ordinary skill in the art. For example, and not limitation, a variety of GPCRs, disclosed herein, were discovered by reviewing the GenBank™ database, while other GPCRs were discovered by utilizing a nucleic acid sequence of a GPCR, previously sequenced, to conduct a BLAST™ search of the EST database. Table A, below, lists the disclosed endogenous orphan GPCRs along with a GPCR's respective homologous GPCR:

TABLE A

Disclosed Human Orphan GPCRs	Accession Number Identified	Open Reading Frame (Base Pairs)	Percent Homology To Designated GPCR	Reference To Homologous GPCR (Accession No.)
hARE-3	AL033379	1,260 bp	52.3% LPA-R	U92642
hARE-4	AC006087	1,119 bp	36% P2Y5	AF000546
hARE-5	AC006255	1,104 bp	32% Oryzias latipes	D43633
hGPR27	AA775870	1,128 bp		
hARE-1	AI090920	999 bp	43% KIAA0001	D13626
hARE-2	AA359504	1,122 bp	53% GPR27	
hPPR1	H67224	1,053 bp	39% EB11	L31581
hG2A	AA754702	1,113 bp	31% GPR4	L36148
hRUP3	AI035423	1,005 bp	30% Drosophila melanogaster	2133653
hRUP4	AI307658	1,296 bp	32% pNPGPR 28% and 29% Zebra fish Ya and Yb, respectively	NP_004876 AAC41276 and AAB94616
hRUP5	AC005849	1,413 bp	25% DEZ 23% FMLPR	Q99788 P21462
hRUP6	AC005871	1,245 bp	48% GPR66	NP_006047
hRUP7	AC007922	1,173 bp	43% H3R	AF140538
hCHN3	EST 36581	1,113 bp	53% GPR27	
hCHN4	AA804531	1,077 bp	32% thrombin	4503637
hCHN6	EST 2134670	1,503 bp	36% edg-1	NP_001391
hCHN8	EST 764455	1,029 bp	47% KIAA0001	D13626
hCHN9	EST 1541536	1,077 bp	41% LTB4R	NM_000752
hCHN10	EST 1365839	1,055 bp	35% P2Y	NM_002563

Receptor homology is useful in terms of gaining an appreciation of a role of the disclosed receptors within the human body. Additionally, such homology can provide insight as to possible endogenous ligand(s) that may be natural activators for the disclosed orphan GPCRs.

B. Receptor Screening

Techniques have become more readily available over the past few years for endogenous-ligand identification (this, primarily, for the purpose of providing a means of conducting receptor-binding assays that require a receptor's endogenous ligand) because the traditional study of receptors has always proceeded from the a priori assumption (historically based) that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been heretofore recognized is that it is the active state of the receptor that is most useful for discovering agonists, partial agonists, and inverse agonists of the receptor. For those diseases which result from an overly active receptor or an under-active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor or enhance the activity of the receptor, respectively, not necessarily a drug which is an antagonist to the endogenous ligand. This is because a compound that reduces or enhances the activity of the active receptor state need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state.

As is known in the art, GPCRs can be "active" in their endogenous state even without the binding of the receptor's

endogenous ligand thereto. Such naturally-active receptors can be screened for the direct identification (i.e., without the need for the receptor's endogenous ligand) of, in particular, inverse agonists. Alternatively, the receptor can be "activated" via, e.g., mutation of the receptor to establish a non-endogenous version of the receptor that is active in the absence of the receptor's endogenous ligand.

Screening candidate compounds against an endogenous or non-endogenous, constitutively activated version of the human orphan GPCRs disclosed herein can provide for the direct identification of candidate compounds which act at this cell surface receptor, without requiring use of the receptor's endogenous ligand. By determining areas within the body where the endogenous version of human GPCRs disclosed herein is expressed and/or over-expressed, it is possible to determine related disease/disorder states which are associated with the expression and/or over-expression of the receptor; such an approach is disclosed in this patent document.

With respect to creation of a mutation that may evidence constitutive activation of human orphan GPCRs disclosed herein is based upon the distance from the proline residue at which is presumed to be located within TM6 of the GPCR typically nears the TM6/IC3 interface (such proline residue appears to be quite conserved). By mutating the amino acid residue located 16 amino acid residues from this residue (presumably located in the IC3 region of the receptor) to, most preferably, a lysine residue, such activation may be obtained. Other amino acid residues may be useful in the mutation at this position to achieve this objective.

C. Disease/Disorder Identification and/or Selection

Preferably, the DNA sequence of the human orphan GPCR can be used to make a probe for (a) dot-blot analysis against tissue-mRNA, and/or (b) RT-PCR identification of the expression of the receptor in tissue samples. The presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be preferably utilized to identify a correlation with a treatment regimen, including but not limited to, a disease associated with that disease. Receptors can equally well be localized to regions of organs by this technique. Based on the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.

As the data below indicate, RUP3 is expressed within the human pancreas, suggesting that RUP3 may play a role in insulin regulation and/or glucagon regulation. Accordingly, candidate compounds identified using a constitutively activated form of RUP3 may be useful for understanding the role of RUP3 in diabetes and/or as therapeutics for diabetes.

D. Screening of Candidate Compounds

1. Generic GPCR Screening Assay Techniques

When a G protein receptor becomes constitutively active (i.e., active in the absence of endogenous ligand binding thereto), it binds to a G protein (e.g., Gq, Gs, Gi, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of GTP, [³⁵S]GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors. It is reported that [³⁵S]GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and avail-

able to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay system is for initial screening of candidate compounds because the system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

2. Specific GPCR Screening Assay Techniques

Once candidate compounds are identified using the "generic" G protein-coupled receptor assay (i.e., an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is preferred. For example, a compound identified by the "generic" assay may not bind to the receptor, but may instead merely "uncouple" the G protein from the intracellular domain.

a. Gs and Gi.

Gs stimulates the enzyme adenylyl cyclase. Gi (and Go), on the other hand, inhibit this enzyme. Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, constitutively activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple the Gi (or Go) protein are associated with decreased cellular levels of cAMP. See, generally, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J. G. et al eds. Sinauer Associates, Inc. (1992). Thus, assays that detect cAMP can be utilized to determine if a candidate compound is, e.g., an inverse agonist to the receptor (i.e., such a compound would decrease the levels of cAMP). A variety of approaches known in the art for measuring cAMP can be utilized; a most preferred approach relies upon the use of anti-cAMP antibodies in an ELISA-based format. Another type of assay that can be utilized is a whole cell second messenger reporter system assay. Promoters on genes drive the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or transcription factor (CREB) which then binds to the promoter at specific sites called cAMP response elements and drives the expression of the gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter gene, e.g., β -galactosidase or luciferase. Thus, a constitutively activated Gs-linked receptor causes the accumulation of cAMP that then activates the gene and expression of the reporter protein. The reporter protein such as β -galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995).

Go and Gq.

Gq and Go are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid PIP₂, releasing two intracellular messengers: diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP₃). Increased accumulation of IP₃ is associated with activation of Gq- and Go-associated receptors. See, generally, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J. G. et al eds. Sinauer Associates, Inc. (1992). Assays that detect IP₃ accumulation can be utilized to determine if a candidate compound is, e.g., an inverse agonist to a Gq- or Go-associated receptor (i.e., such a compound would decrease the levels of IP₃). Gq-dependent receptors can also be examined using an API reporter assay in that Gq-dependent phospholipase C causes activation of genes containing API elements; thus, activated Gq-associated receptors will evidence an increase in the expression of such genes, whereby inverse agonists thereto will evidence a decrease in such expression, and agonists will evidence an increase in such expression. Commercially available assays for such detection are available.

3. GPCR Fusion Protein

The use of an endogenous, constitutively activated orphan GPCR, or a non-endogenous, constitutively activated orphan

GPCR, for screening of candidate compounds for the direct identification of inverse agonists, agonists and partial agonists provides a unique challenge in that, by definition, the receptor is active even in the absence of an endogenous ligand bound thereto. Thus, it is often useful that an approach be utilized that can enhance the signal obtained by the activated receptor. A preferred approach is the use of a GPCR Fusion Protein.

Generally, once it is determined that a GPCR is or has been constitutively activated, using the assay techniques set forth above (as well as others), it is possible to determine the predominant G protein that couples with the endogenous GPCR. Coupling of the G protein to the GPCR provides a signaling pathway that can be assessed. Because it is most preferred that screening take place by use of a mammalian expression system, such a system will be expected to have endogenous G protein therein. Thus, by definition, in such a system, the constitutively activated orphan GPCR will continuously signal. In this regard, it is preferred that this signal be enhanced such that in the presence of, e.g., an inverse agonist to the receptor, it is more likely that it will be able to more readily differentiate, particularly in the context of screening, between the receptor when it is contacted with the inverse agonist.

The GPCR Fusion Protein is intended to enhance the efficacy of G protein coupling with the GPCR. The GPCR Fusion Protein is preferred for screening with a non-endogenous, constitutively activated GPCR because such an approach increases the signal that is most preferably utilized in such screening techniques, although the GPCR Fusion Protein can also be (and preferably is) used with an endogenous, constitutively activated GPCR. This is important in facilitating a significant "signal to noise" ratio; such a significant ratio is import preferred for the screening of candidate compounds as disclosed herein.

The construction of a construct useful for expression of a GPCR Fusion Protein is within the purview of those having ordinary skill in the art. Commercially available expression vectors and systems offer a variety of approaches that can fit the particular needs of an investigator. The criteria of importance for such a GPCR Fusion Protein construct is that the GPCR sequence and the G protein sequence both be in-frame (preferably, the sequence for the GPCR is upstream of the G protein sequence) and that the "stop" codon of the GPCR must be deleted or replaced such that upon expression of the GPCR, the G protein can also be expressed. The GPCR can be linked directly to the G protein, or there can be spacer residues between the two (preferably, no more than about 12, although this number can be readily ascertained by one of ordinary skill in the art). We have a preference (based upon convenience) of use of a spacer in that some restriction sites that are not used will, effectively, upon expression, become a spacer. Most preferably, the G protein that couples to the GPCR will have been identified prior to the creation of the GPCR Fusion Protein construct. Because there are only a few G proteins that have been identified, it is preferred that a construct comprising the sequence of the G protein (i.e., a universal G protein construct) be available for insertion of an endogenous GPCR sequence therein; this provides for efficiency in the context of large-scale screening of a variety of different endogenous GPCRs having different sequences.

E. Other Utility

Although a preferred use of the human orphan GPCRs disclosed herein may be for the direct identification of candidate compounds as inverse agonists, agonists or partial agonists (preferably for use as pharmaceutical agents), these versions of human GPCRs can also be utilized in research settings. For example, in vitro and in vivo systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and diseased, as well as understanding the role

of constitutive activation as it applies to understanding the signaling cascade. The value in human orphan GPCRs is that its utility as a research tool is enhanced in that by determining the location(s) of such receptors within the body, the GPCRs can be used to understand the role of these receptors in the human body before the endogenous ligand therefor is identified. Other uses of the disclosed receptors will become apparent to those in the art based upon, inter alia, a review of this patent document.

Although a preferred use of the non-endogenous versions of the human RUP3 disclosed herein may be for the direct identification of candidate compounds as inverse agonists, agonists or partial agonists (preferably for use as pharmaceutical agents), this version of human RUP3 can also be utilized in research settings. For example, in vitro and in vivo systems incorporating RUP3 can be utilized to further elucidate the roles RUP3 plays in the human condition, particularly with respect to the human pancreas, both nonnal and diseased (and in particular, diseases involving regulation of insulin or glucagon, e.g., diabetes), as well as understanding the role of constitutive activation as it applies to understanding the signaling cascade. A value in non-endogenous human RUP3 is that its utility as a research tool is enhanced in that, because of its unique features, non-endogenous RUP3 can be used to understand the role of RUP3 in the human body before the endogenous ligand therefor is identified. Other uses of the disclosed receptors will become apparent to those in the art based upon, inter alia, a review of the patent document.

EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor modifications to these sequences while achieving the same or substantially similar results reported below. Unless otherwise indicated below, all nucleic acid sequences for the disclosed endogenous orphan human GPCRs have been sequenced and verified. For purposes of equivalent receptors, those of ordinary skill in the art will readily appreciate that conservative substitutions can be made to the disclosed sequences to obtain a functionally equivalent receptor.

Example 1

Endogenous Human GPCRs

1. Identification of Human GPCRs

Several of the disclosed endogenous human GPCRs were identified based upon a review of the GenBank database information. While searching the database, the following cDNA clones were identified as evidenced below.

Disclosed Human Orphan GPCRs	Accession Number	Complete DNA Sequence (Base Pairs)	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ ID. NO.	Amino Acid SEQ ID. NO.
hARE-3	AL033379	111,389 bp	1,260 bp	1	16
hARE-4	AC006087	226,925 bp	1,119 bp	3	4
hARE-5	AC006255	127,605 bp	1,104 bp	5	6
hRUP3	AL035423	140,094 bp	1,005 bp	7	8
hRUP5	AC005849	169,144 bp	1,413 bp	9	10
hRUP6	AC005871	218,807 bp	1,245 bp	11	12
hRUP7	AC007922	158,858 bp	1,173 bp	13	14

Other disclosed endogenous human GPCRs were identified by conducting a BLAST search of EST database (dbest)

using the following EST clones as query sequences. The following EST clones identified were then used as a probe to screen a human genomic library.

Disclosed Human Orphan GPCRs	Query (Sequence)	EST Clone/ Accession No. Identified	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ ID. NO.	Amino Acid SEQ ID. NO.
hGPCR27	Mouse GPCR27	AA775870	1,125 bp	15	16
hARE-1	TDAG	1689643 AI090920	999 bp	17	18
hARE-2	GPCR27	68530 AA359504	1,122 bp	19	20
hPPR1	Bovine PPR1	238667 H67224	1,053 bp	21	22
hG2A	Mouse 1179426	See Example 2(a) below	1,113 bp	23	24
hCHN3	N.A.	EST 36581 (full length)	1,113 bp	25	26
hCHN4	TDAG	1184934 AA804531	1,077 bp	27	28
hCHN6	N.A.	EST 2134670 (full length)	1,503 bp	29	30
hCHN8	KIAA0001	EST 76445	1,029 bp	31	32
hCHN9	1365839	EST 1541536	1,077 bp	33	34
hCHN10	Mouse EST 1365839	Human 1365839	1,005 bp	35	36
hRUP4	N.A.	AI307658	1,296 bp	37	39

N.A. = "not applicable"

2. Full Length Cloning

a. hG2A (Seq. Id. Nos. 23 & 24)

Mouse EST clone 1179426 was used to obtain a human genomic clone containing all but three amino acid hG2A coding sequences. The 5' end of this coding sequence was obtained by using 5'RACE™, and the template for PCR was Clontech's Human Spleen Marathon-ready™ cDNA. The disclosed human G2A was amplified by PCR using the G2A cDNA specific primers for the first and second round PCR as shown in SEQ. ID. NO.: 39 and SEQ. ID. NO.: 40 as follows:

5'-CTGTGTACAGCAGTTCGCAGAGTG-3'(SEQ. ID. NO.: 39; 1st round PCR)

5'-GAGTGCCAGGCAGAGCAGGTAGAC-3'(SEQ. ID. NO.: 40; second round PCR).

PCR was performed using Advantage™ GC Polymerase Kit (Clontech; manufacturing instructions will be followed), at 94° C. for 30 sec followed by 5 cycles of 94° C. for 5 sec and 72° C. for 4 min; and 30 cycles of 94° for 5 sec and 70° for 4 min. An approximate 1.3 Kb PCR fragment was purified from agarose gel, digested with Hind III and Xba I and cloned into the expression vector pRC/CMV2 (Invitrogen). The cloned-insert was sequenced using the T7 Sequenase™ kit (USB Amersham; manufacturer instructions will be followed) and the sequence was compared with the presented sequence. Expression of the human G2A will be detected by probing an RNA dot blot (Clontech; manufacturer instructions will be followed) with the P³²-labeled fragment.

b. hCHN9 (Seq. Id. Nos. 33 & 34)

Sequencing of the EST clone 1541536 indicated that hCHN9 is a partial cDNA clone having only an initiation codon; ie., the termination codon was missing. When hCHN9 was used to "blast" against the data base (nr), the 3' sequence of hCHN9 was 100% homologous to the 5' untranslated region of the leukotriene B4 receptor cDNA, which contained a termination codon in the frame with hCHN9 coding sequence. To determine whether the 5' untranslated region of LTB4R cDNA was the 3' sequence of

hCHN9, PCR was performed using primers based upon the 5' sequence flanking the initiation codon found in hCHN9 and the 3' sequence around the termination codon found in the LTB4R 5' untranslated region. The 5' primer sequence utilized was as follows:

5'-CCCGAATTCCTGCTFGCTCCCAGCTTGGCCC-3'
SEQ. ID. NO.: 41; sense) and

5'-TGTGGATCCTGCTGTCAAAGGTCCCATTCCGG-3'
(SEQ. ID. NO.: 42; antisense).

PCR was performed using thymus cDNA as a template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94° C. for 1 min, 65° C. for 1 min and 72° C. for 1 min and 10 sec. A 1.1 kb fragment consistent with the predicted size was obtained from PCR. This PCR fragment was subcloned into pCMV (see below) and sequenced (see, SEQ. ID. NO.: 33).

c. hRUP4 (Seq. Id. Nos. 37 & 38)

The full length hRUP4 was cloned by RT-PCR with human brain cDNA (Clontech) as templates:

5'-TCACAATGCTAGGTGTGGTC-3' (SEQ. ID. NO.: 43; sense) and

5'-TGCATAGACAATGGGATTACAG-3' (SEQ. ID. NO.: 44; antisense).

PCR was performed using TaqPlus™ Precision™ polymerase (Stratagene; manufacturing instructions will be followed) by the following cycles: 94° C. for 2 min; 94° C. 30 sec; 55° C. for 30 sec, 72° C. for 45 sec, and 72° C. for 10 min. Cycles 2 through 4 were repeated 30 times.

The PCR products were separated on a 1% agarose gel and a 500 bp PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and sequenced using the T7 DNA Sequenase™ kit (Amsham) and the SP6/T7 primers (Stratagene). Sequence analysis revealed that the PCR fragment was indeed an alternatively spliced form of AI307658 having a continuous open reading frame with similarity to other GPCRs. The completed sequence of this PCR fragment was as follows:

5' -TCACAATGCTAGGTGTGGTCTGGCTGGTG (SEQ. ID. NO.: 45)

GCAGTCATAGTAGGATCACCATGTGGCACGTG

CAACAACCTTGAGATCAAATCTGACTTCCTATA

TGAAAAGGAACACATCTGCTGCTTAGAAGAGT

GGACCAGCCCTGTGCACCAGAAGATCTACACC

ACCTTCATCCTTGTTCATCCTCTTCTCCTGCC

TCTTATGGTGATGCTTATTCTGTACGTAAAAT

TGGTTATGAACTTTGGATAAAGAAAAGAGTTG

GGGATGGTTCAGTGCTTCGAACTATTCATGGA

AAAGAAATGTCCAAAATAGCCAGGAAGAAGAA

ACGAGCTGTCATTATGATGGTGACAGTGGTGG

CTCTCTTTGCTGTGTGCTGGGCACCATCCAT

GTTGTCCATATGATGATTGAATACAGTAATTT

TGAAAAGGAATATGATGATGTCACAATCAAGA

TGATTTTTGATATCGTGCAAAATTATTGGATTT

-continued

TCCAACCTCCATCTGTAATCCCATTGTCTATGC

A-3'

Based on the above sequence, two sense oligonucleotide primer sets:

(SEQ. ID. NO.: 46; oligo 1)
5'-CTGCTTAGAAGAGTGGACCAG-3'

(SEQ. ID. NO.: 47; oligo 7)
5'-CTGTGCACGAGAAGATCTACAC-3'

and two antisense oligonucleotide primer sets:

(SEQ. ID. NO.: 48; oligo 3)
5'-CAAGGATGAAGGTGGTGTAGA-3'

(SEQ. ID. NO.: 49; oligo 4)
5'-GTGTAGATCTTCTGGTGCACAGG-3'

were used for 3'-and 5'-race PCR with a human brain Marathon-Ready™ cDNA (Clontech, Cat# 7400-1) as template, according to manufacture's instructions. DNA fragments generated by the RACE PCR were cloned into the pCRII-TOPO™ vector (Invitrogen) and sequenced using the SP6/T7 primers (Stratagene) and some internal primers. The 3' RACE product contained a poly(A) tail and a completed open reading frame ending at a TAA stop codon. The 5' RACE product contained an incomplete 5' end; i.e., the ATG initiation codon was not present.

Based on the new 5' sequence, oligo 3 and the following primer:

5'-GCAATGCAGGTCATAGTGAGC-3' (SEQ. ID. NO.: 50; oligo 5)

were used for the second round of 5' RACE PCR and the PCR products were analyzed as above. A third round of 5' RACE PCR was carried out utilizing antisense primers:

5'-TGGAGCATGGTGACGGGAATGCAGAAG-3'
(SEQ. ID. NO.: 51; oligo 6) and

5'-GTGATGAGCAGGTCAGTACTGAGCGCCAAG-3'
(SEQ. ID. NO.: 52; oligo 7).

The sequence of the 5' RACE PCR products revealed the presence of the initiation codon ATG, and further round of 5' RACE PCR did not generate any more 5' sequence. The completed 5' sequence was confirmed by RT-PCR using sense primer 5'-GCAATGCAGGCGCTTAACATFAC-3' (SEQ. ID. NO.: 53; oligo 8)

and oligo 4 as primers and sequence analysis of the 650 bp PCR product generated from human brain and heart cDNA templates (Clontech, Cat# 7404-1). The completed 3' sequence was confirmed by RT-PCR using oligo 2 and the following antisense primer:

5'-TTGGGTTACAATCTGAAGGGCA-3' (SEQ. ID. NO.: 54; oligo 9)

and sequence analysis of the 670 bp PCR product generated from human brain and heart cDNA templates. (Clontech, Cat# 7404-1).

d. hRUP5 (Seq. Id. Nos. 9 & 10)

The full length hRUP5 was cloned by RT-PCR using a sense primer upstream from ATG, the initiation codon (SEQ. ID. NO.: 55), and an antisense primer containing TCA as the stop codon (SEQ. ID. NO.: 56), which had the following sequences:

5'-ACTCCGTGTCCAGCAGGACTCTG-3' (SEQ. ID. NO.: 55)

5'-TGCGTGTTCCTGGACCCTCACGTG-3' (SEQ. ID. NO.: 56)

and human peripheral leukocyte cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech) was used for the amplification in a 50 ul reaction by the following cycle with step 2 through step 4 repeated 30 times: 94° C. for 30 sec; 94° for 15 sec; 69° for 40 sec; 72° C. for 3 min; and 72° C. from 6 min. A 1.4 kb PCR fragment was isolated and cloned with the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the T7 DNA Sequenase™ kit (Amsham). See, SEQ. ID. NO.: 9.

e. hRUP6 (Seq. Id. Nos. 11 & 12)

The full length hRUP6 was cloned by RT-PCR using primers:

(SEQ. ID. NO.: 57)
5'-CAGGCCTTGATTTTAATGTCAGGGATGG-3' and

(SEQ. ID. NO.: 58)
5'-GGAGAGTCAGCTCTGAAAGAATTGAGG-3';

and human thymus Marathon-Ready™ cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech, according to manufacturer's instructions) was used for the amplification in a 50 ul reaction by the following cycle: 94° C. for 30sec; 94° C. for 5 sec; 66° C. for 40sec; 72° C. for 2.5 sec and 72° C. for 7 min. Cycles 2 through 4 were repeated 30 times. A 1.3 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (see, SEQ. ID. NO.: 11) using the ABI Big Dye Terminator™ kit (P.E. Biosystem).

f. hRUP7 (Seq. Id. Nos. 13 & 14)

The full length RUP7 was cloned by RT-PCR using primers:

(SEQ. ID. NO.: 59; sense)
5'-TGATGTGATGCCAGATACTAATAGCAC-3'
and

(SEQ. ID. NO.: 60; antisense)
5'-CCTGATTCATTTAGGTGAGATTGAGAC-3'

and human peripheral leukocyte cDNA (Clontech) as a template. Advantage™ cDNA polymerase (Clontech) was used for the amplification in a 50 ul reaction by the following cycle with step 2 to step 4 repeated 30 times: 94° C. for 2 minutes; 94° C. for 15 seconds; 60° C. for 20 seconds; 72° C. for 2 minutes; 72° C. for 10 minutes. A 1.25 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator™ kit (P.E. Biosystem). See, SEQ. ID. NO.: 13.

g. hARE-5 (Seq. Id. Nos. 5 & 6)

The full length hARE-5 was cloned by PCR using the hARE5 specific primers 5'-CAGCGCAGGGTGAAGCCTGAGAGC-3' SEQ. ID. NO.: 69 (sense, 5' of initiation codon ATG) and 5'-GGCACCTGCTGTGACCTGTGCAGG-3' SEQ. ID. NO.: 70 (antisense, 3' of stop codon TGA) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 96° C., 2 minutes; 96° C., 20 seconds; 58° C., 30 seconds; 72° C., 2 minutes; and 72° C., 10 minutes

A 1.1 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and

completely sequenced (SEQ. ID. NO.: 5) using the T7 DNA Sequenase™ kit (Amsham).

h. hARE-4 (Seq. Id. Nos.: 3 & 4)

The full length hARE-4 was cloned by PCR using the hARE-4 specific primers 5'-CTGGTGTGCTCCATGGCATCCC-3' SEQ.ID.NO.:67 (sense, 5' of initiation codon ATG) and 5'-GTAAGCCTCCCAGAACAGAGG-3' SEQ. ID. NO.: 68 (antisense, 3' of stop codon TGA) and human genomic DNA as template. Taq DNA polymerase (Stratagene) and 5% DMSO was used for the amplification by the following cycle with step 2 to step 3 repeated 35 times: 94° C., 3 minutes; 94° C., 30 seconds; 59° C., 2 minutes; 72° C., 10 minute

A 1.12 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (SEQ. ID. NO.: 3) using the T7 DNA Sequenase™ kit (Amsham).

i. hARE-3 (Seq. Id. Nos.: 1 & 2)

The full length hARE-3 was cloned by PCR using the hARE-3 specific primers 5'-gatcaagcttCCATCCTACTGAAACCATGGTC-3' SEQ.ID.NO65 (sense, lower case nucleotides represent Hind III overhang, ATG as initiation codon) and 5'-gatcagatctCAGTT CCAATATTCACACCACCGTC-3' SEQ. ID. NO.: 66 (antisense, lower case nucleotides represent Xba I overhang, TCA as stop codon) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 94° C., 3 minutes; 94° C., 1 minute; 55° C., 1 minute; 72° C., 2 minutes; 72° C., 10 minutes.

A 1.3 Kb PCR fragment of predicated size was isolated and digested with Hind III and Xba I, cloned into the pRC/CMV2 vector (Invitrogen) at the Hind III and Xba I sites and completely sequenced (SEQ. ID. NO.: 1) using the T7 DNA Sequenase™ kit (Amsham).

j. hRUP3 (Seq. Id. Nos.: 7 & 8)

The full length hRUP3 was cloned by PCR using the hRUP3 specific primers 5'-GTCCTGCCACTTCGAGACATGG-3' SEQ. ID.NO.:71 (sense, ATG as intiation codon) and 5'-GAAACTTCTCTCTGCCCCTTACCGTC-3'

SEQ.ID.NO.:72 (antisense, 3' of stop codon TAA) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 94° C., 3 minutes; 94° C., 1 minute; 58° C., 1 minute; 72° C., 2 minutes; 72° C., 10 minutes

A 1.0 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (SEQ. ID. NO.: 7)using the T7 DNA sequenase kit (Amsham).

Example 2

Receptor Expression

Although a variety of cells are available to the art for the expression of proteins, it is most preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, i.e., utilization of, e.g., yeast cells for the expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretary pathways that have evolved for mammalian systems—thus, results obtained in non-mammalian cells, while of potential use, are not as preferred as that obtained from mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular needs of the artisan. The general procedure for expression of the disclosed GPCRs is as follows.

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On day one, 1×10^7 293T cells per 150 mm plate were plated out. On day two, two reaction tubes will be prepared (the proportions to follow for each tube are per plate): tube A will be prepared by mixing 20 μ g DNA (e.g., pCMV vector, pCMV vector with receptor cDNA, etc.) in 1.2 ml serum free DMEM (Irvine Scientific, Irvine, Calif.); tube B will be prepared by mixing 120 μ l lipofectamine (Gibco BRL) in 1.2 ml serum free DMEM. Tubes A and B are admixed by inversions (several times), followed by incubation at room temperature for 30–45 min. The admixture can be referred to as the “transfection mixture”. Plated 293T cells are washed with $1 \times$ PBS, followed by addition of 10 ml serum free DMEM. 2.4 ml of the transfection mixture will then be added to the cells, followed by incubation for 4 hrs at 37° C./5% CO₂. The transfection mixture was then be removed by aspiration, followed by the addition of 25 ml of DMEM/10% Fetal Bovine Serum. Cells will then be incubated at 37° C./5% CO₂. After 72hr incubation, cells can then be harvested and utilized for analysis.

Example 3

Tissue Distribution of the Disclosed Human GPCRs

Several approaches can be used for determination of the tissue distribution of the GPCRs disclosed herein.

1. Dot-Blot Analysis

Using a commercially available human-tissue dot-blot format, endogenous orphan GPCRs were probed for a determination of the areas where such receptors are localized. cDNA fragments from the GPCRs of Example 1 (radiolabeled) were (or can be) used as the probe: radiolabeled probe was (or can be) generated using the complete receptor cDNA (excised from the vector) using a Prime-It II™ Random Primer Labeling Kit (Stratagene, #300385), according to manufacturer’s instructions. A human RNA Master Blot™ (Clontech, #7770-1) was hybridized with the endogenous human GPCR radiolabeled probe and washed under stringent conditions according manufacturer’s instructions. The blot was exposed to Kodak BioMax™ Autoradiography film overnight at –80° C. Results are summarized for several receptors in Table B and C (see FIGS. 1A and 1B for a grid identifying the various tissues and their locations, respectively). Exemplary dot-blot results are provided in FIGS. 2A and 2B for results derived using hCHN3 and hCHN8, respectively.

TABLE B

ORPHAN GPCR	Tissue Distribution (highest levels, relative to other tissues in the dot-blot)
hGPCR27	Fetal brain, Putamen, Pituitary gland, Caudate nucleus
hARE-1	Spleen, Peripheral leukocytes, Fetal spleen
hPPR1	Pituitary gland, Heart, salivary gland, Small intestine, Testis
hRUP3	Pancreas
hCHN3	Fetal brain, Putamen, Occipital cortex
hCHN9	Pancreas, Small intestine, Liver
hCHN10	Kidney, Thyroid

TABLE C

ORPHAN GPCR	Tissue Distribution (highest levels, relative to other tissues in the dot-blot)
hARE-3	Cerebellum left, Cerebellum right, Testis, Accumbens
hGPCR3	Corpus collusum, Caudate nucleus, Liver, Heart, Interventricular Septum
hARE-2	Cerebellum left, Cerebellum right, Substantia
hCHN8	Cerebellum left, Cerebellum right, Kidney, Lung

To ascertain the tissue distribution of hRUP3 mRNA, RT-PCR was performed using hRUP3-specific primers and

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human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) was utilized for the PCR reaction, using the following reaction cycles in a 40 ul reaction: 94° C. for 2 min; 94° C. for 15 sec; 55° C. for 30 sec; 72° C. for 1 min; 72° C., for 10 min. Primers were as follows:

(SEQ. ID. NO.: 61; sense)
5' -GACAGGTACCTTGCCATCAAG-3'

(SEQ. ID. NO.: 62; antisense)
5' -CTGCACAATGCCAGTGATAAGG-3'.

20 ul of the reaction was loaded onto a 1% agarose gel: results are set forth in FIG. 3.

As is supported by the data of FIG. 3, of the 16 human tissues in the cDNA panel utilized (brain, colon, heart, kidney, lung, ovary, pancreas, placenta, prostate, skeleton, small intestine, spleen, testis, thymus leukocyte, and liver) a single hRUP3 band is evident only from the pancreas. Additional comparative analysis of the protein sequence of hRUP3 with other GPCRs suggest that hRUP3 is related to GPCRs having small molecule endogenous ligand such that it is predicted that the endogenous ligand for hRUP3 is a small molecule.

b. hRUP4

RT-PCR was performed using hRUP4 oligo’s 8 and 4 as primers and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) was used for the amplification in a 40 ul reaction by the following cycles: 94° C. for 30 seconds, 94° C. for 10 seconds, 55° C. for 30 seconds, 72° C. for 2 minutes, and 72° C. for 5 minutes with cycles 2 through 4 repeated 30 times.

20 ul of the reaction were loaded on a 1% agarose gel to analyze the RT-PCR products, and hRUP4 mRNA was found expressed in many human tissues, with the strongest expression in heart and kidney. (see, FIG. 4). To confirm the authenticity of the PCR fragments, a 300 bp fragment derived from the 5' end of hRUP4 was used as a probe for the Southern Blot analysis. The probe was labeled with ³²P-dCTP using the Prime-It II™ Random Primer Labeling Kit (Stratagene) and purified using the ProbeQuant™ G-50 micro columns (Amersham). Hybridization was done overnight at 42° C. following a 12 hr pre-hybridization. The blot was finally washed at 65° C. with 0.1×SSC. The Southern blot did confirm the PCR fragments as hRUP4.

c. hRUP5

RT-PCR was performed using the following hRUP5 specific primers:

(SEQ. ID. NO.: 63; sense)
5' -CTGACTTCTTGTTCCTGGCAGCAGCGG-3'

(SEQ. ID. NO.: 64; antisense)
5' -AGACCAGCCAGGGCAGCTGAAGAGTG-3'

and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) was used for the amplification in a 40 ul reaction by the following cycles: 94° C. for 30 sec, 94° C. for 10 sec, 62° C. for 1.5 min, 72° C. for 5 min, and with cycles 2 through 3 repeated 30 times. 20 ul of the reaction were loaded on a 1.5% agarose gel to analyze the RT-PCR products, and hRUP5 mRNA was found expressed only in the peripheral blood leukocytes (data not shown).

d. hRUP6

RT-PCR was applied to confirm the expression and to determine the tissue distribution of hRUP6. Oligonucleotides used, based on an alignment of AC005871 and GPR66 segments, had the following sequences:

(SEQ. ID. NO.: 73; sense)
5' - CCAACACCAGCATCCATGGCATCAAG - 3'

(SEQ. ID. NO.: 74; antisense) 5
5' - GGAGAGTCAGCTCTGAAAGAATTCAGG - 3'

and the human multiple tissue cDNA panels (MTC, Clontech) were used as templates. PCR was performed using TaqPlus Precision™ polymerase (Stratagene; manufacturing instructions will be followed) in a 40 ul reaction by the following cycles: 94° C. for 30 sec; 94° C. 5 sec; 66° C. for 40 sec, 72° C. for 2.5 min, and 72° C. for 7 min. Cycles 2 through 4 were repeated 30 times.

20 ul of the reaction were loaded on a 1.2% agarose gel to analyze the RT-PCR products, and a specific 760 bp DNA fragment representing hRUP6 was expressed predominantly in the thymus and with less expression in the heart, kidney, lung, prostate small intestine and testis. (see, FIG. 5).

It is intended that each of the patents, applications, and printed publications mentioned in this patent document be hereby incorporated by reference in their entirety.

As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention and the claims that follow.

Although a variety of Vectors are available to those in the art, for purposes of utilization for both endogenous and non-endogenous human GPCRs, it is most preferred that the Vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on Oct. 13, 1998 (10801 University Blvd., Manassas, Va. 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

SEQUENCE LISTING

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<211> LENGTH: 419
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Met Val Phe Ser Ala Val Leu Thr Ala Phe His Thr Gly Thr Ser Asn
 1          5          10          15

Thr Thr Phe Val Val Tyr Glu Asn Thr Tyr Met Asn Ile Thr Leu Pro
 20          25          30

Pro Pro Phe Gln His Pro Asp Leu Ser Pro Leu Leu Arg Tyr Ser Phe
 35          40          45

Glu Thr Met Ala Pro Thr Gly Leu Ser Ser Leu Thr Val Asn Ser Thr
 50          55          60

Ala Val Pro Thr Thr Pro Ala Ala Phe Lys Ser Leu Asn Leu Pro Leu
 65          70          75          80

Gln Ile Thr Leu Ser Ala Ile Met Ile Phe Ile Leu Phe Val Ser Phe
 85          90          95

Leu Gly Asn Leu Val Val Cys Leu Met Val Tyr Gln Lys Ala Ala Met
100          105          110

Arg Ser Ala Ile Asn Ile Leu Leu Ala Ser Leu Ala Phe Ala Asp Met
115          120          125

Leu Leu Ala Val Leu Asn Met Pro Phe Ala Leu Val Thr Ile Leu Thr
130          135          140

Thr Arg Trp Ile Phe Gly Lys Phe Phe Cys Arg Val Ser Ala Met Phe
145          150          155          160

Phe Trp Leu Phe Val Ile Glu Gly Val Ala Ile Leu Leu Ile Ile Ser
165          170          175

Ile Asp Arg Phe Leu Ile Ile Val Gln Arg Gln Asp Lys Leu Asn Pro
180          185          190

Tyr Arg Ala Lys Val Leu Ile Ala Val Ser Trp Ala Thr Ser Phe Cys
195          200          205

Val Ala Phe Pro Leu Ala Val Gly Asn Pro Asp Leu Gln Ile Pro Ser
210          215          220

Arg Ala Pro Gln Cys Val Phe Gly Tyr Thr Thr Asn Pro Gly Tyr Gln
225          230          235          240

Ala Tyr Val Ile Leu Ile Ser Leu Ile Ser Phe Phe Ile Pro Phe Leu
245          250          255

Val Ile Leu Tyr Ser Phe Met Gly Ile Leu Asn Thr Leu Arg His Asn
260          265          270

Ala Leu Arg Ile His Ser Tyr Pro Glu Gly Ile Cys Leu Ser Gln Ala
275          280          285

Ser Lys Leu Gly Leu Met Ser Leu Gln Arg Pro Phe Gln Met Ser Ile
290          295          300

Asp Met Gly Phe Lys Thr Arg Ala Phe Thr Thr Ile Leu Ile Leu Phe
305          310          315          320

Ala Val Phe Ile Val Cys Trp Ala Pro Phe Thr Thr Tyr Ser Leu Val
325          330          335

Ala Thr Phe Ser Lys His Phe Tyr Tyr Gln His Asn Phe Phe Glu Ile
340          345          350

Ser Thr Trp Leu Leu Trp Leu Cys Tyr Leu Lys Ser Ala Leu Asn Pro
355          360          365

Leu Ile Tyr Tyr Trp Arg Ile Lys Lys Phe His Asp Ala Cys Leu Asp
370          375          380

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Met Met Pro Lys Ser Phe Lys Phe Leu Pro Gln Leu Pro Gly His Thr
385 390 395 400

Lys Arg Arg Ile Arg Pro Ser Ala Val Tyr Val Cys Gly Glu His Arg
405 410 415

Thr Val Val

<210> SEQ ID NO 3
<211> LENGTH: 1119
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

atgtagcca acagctcctc aaccaacagt tctgttctcc cgtgtcctga ctaccgacct 60
accacccgcc tgcacttggg ggtctacagc ttggtgctgg ctgccgggct cccctcaac 120
gcgctagccc tctgggtctt cctgcgcgcg ctgcgcgtgc actcgggtgg gagcgtgtac 180
atgtgtaacc tggcggccag cgacctgctc ttcacctctc cgctgccctg tegtctctcc 240
tactacgcac tgcaccactg gcccttcccc gacctctgt gccagacgac gggcgccatc 300
ttccagatga acatgtacgg cagctgcac ttctgatgc tcatcaacgt ggaccgctac 360
gccgcatcg tgcaccctg gcgactgcgc cacctgcggc ggcccccgct ggcgcggctg 420
ctctgcctgg gcgtgtgggc gctcactctg gtgtttgccc tgccccggc ccgcgtgcac 480
aggccctcgc gttgccgcta ccgggacctc gaggtgcgcc tatgcttcga gagcttcagc 540
gacgagctgt ggaaaggcag gctgctgccc ctctgctgctc tggccgaggc gctgggcttc 600
ctgctgcccc tggcggcggt ggtctactcg tcgggcccag tcttctggac gctggcgcgc 660
cccgacgcca cgcagagcca gcggcggcgg aagaccgtgc gcctcctgct ggctaacctc 720
gtcatcttcc tgctgtgctt cgtgccctac aacagcacgc tggcggctca cgggctgctg 780
cggagcaagc tgggtggcggc cagcgtgcct gcccgcatc gcgtgcgcgg ggtgctgatg 840
gtgatgggtc tgctggccgg cgccaactgc gtgctggacc cgctggtgta ctactttagc 900
gccgagggct tccgcaacac cctgcgcggc ctgggcactc cgcaccgggc caggacctcg 960
gccaccaacg ggacgcgggc ggcgctcgcg caatccgaaa ggtccgccgt caccaccgac 1020
gccaccaggc cggatgccgc cagtcagggg ctgctccgac cctccgactc cactctctg 1080
tcttccttca cacagtgtcc ccaggattcc gcctctga 1119

<210> SEQ ID NO 4
<211> LENGTH: 372
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Met Leu Ala Asn Ser Ser Ser Thr Asn Ser Ser Val Leu Pro Cys Pro
1 5 10 15

Asp Tyr Arg Pro Thr His Arg Leu His Leu Val Val Tyr Ser Leu Val
20 25 30

Leu Ala Ala Gly Leu Pro Leu Asn Ala Leu Ala Leu Trp Val Phe Leu
35 40 45

Arg Ala Leu Arg Val His Ser Val Val Ser Val Tyr Met Cys Asn Leu
50 55 60

Ala Ala Ser Asp Leu Leu Phe Thr Leu Ser Leu Pro Val Arg Leu Ser
65 70 75 80

Tyr Tyr Ala Leu His His Trp Pro Phe Pro Asp Leu Leu Cys Gln Thr

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

<210> SEQ ID NO 5

<211> LENGTH: 1107

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

```

atggccaact ccacagggt gaacgcctca gaagtcgcag gctcgttggg gttgatcctg    60
gcagctgtcg tggaggtggg ggcactgctg ggcaacggcg cgctgctggt cgtgggtgctg    120
cgcaagccgg gactgcgcga cgcgctctac ctggcgcacc tgtgcgtcgt ggacctgctg    180
gcgccgcct ccatcatgcc gctgggcctg ctggccgcac cgccgcccgg gctggggccgc    240
gtgcgcctgg gccccgcgc atgcgcgcgc gctcgttcc tctcgcgcgc tctgctgccc    300
gctgcacgc tcggggtggc cgcacttggc ctggcacgct accgcctcat cgtgcacccg    360
ctgcggccag gctcgcggcc gccgcctgtg ctctgtctca ccgcctgtg ggccgcggcg    420
ggactgctgg gcgcgctctc cctgctcggc ccgcccggc caccgcccc tgctcctgct    480

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cgtgctegg tctggtgg gggcctcggg cccttcggg cgctctgggc cctgctggcc 540
ttcgcgctgc ccgcctcct gctgctcggc gcctacggcg gcatcttcgt ggtggcgcgt 600
cgcgctgccc tgaggcccc acggccggcg cgcgggtccc gactccgctc ggactctctg 660
gatagccgcc tttccatctt gccgcgctc cggcctcgcc tgcccggggg caaggcggcc 720
ctggccccag cgctggcctt gggccaattt gcagcctgct ggctgcctta tggctgcgcg 780
tgcttgccgc ccgcagcgcg ggccgcggaa gccgaaggcg ctgtcacctg ggtcgcctac 840
tcggccttcg cggctcacc cttcctgtac gggctgctgc agcgccccgt gcgcttgga 900
ctgggcccgc tctctcgccg tgactgcct ggacctgtgc gggcctgcac tccgcaagcc 960
tggcaccgcg gggcactctt gcaatgcctc cagagacccc cagagggccc tgccgtaggc 1020
ccttctgagg ctccagaaca gacccccgag ttggcaggag ggccggagccc cgcataccag 1080
gggccacctg agagttctct ctctga 1107

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<210> SEQ ID NO 6

<211> LENGTH: 368

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

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

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Tyr Gly Cys Ala Cys Leu Ala Pro Ala Ala Arg Ala Ala Glu Ala Glu
 260 265 270
 Ala Ala Val Thr Trp Val Ala Tyr Ser Ala Phe Ala Ala His Pro Phe
 275 280 285
 Leu Tyr Gly Leu Leu Gln Arg Pro Val Arg Leu Ala Leu Gly Arg Leu
 290 295 300
 Ser Arg Arg Ala Leu Pro Gly Pro Val Arg Ala Cys Thr Pro Gln Ala
 305 310 315 320
 Trp His Pro Arg Ala Leu Leu Gln Cys Leu Gln Arg Pro Pro Glu Gly
 325 330 335
 Pro Ala Val Gly Pro Ser Glu Ala Pro Glu Gln Thr Pro Glu Leu Ala
 340 345 350
 Gly Gly Arg Ser Pro Ala Tyr Gln Gly Pro Pro Glu Ser Ser Leu Ser
 355 360 365

<210> SEQ ID NO 7
 <211> LENGTH: 1008
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

```

atggaatcat ctttctcatt tggagtgatc cttgctgtcc tggcctccct catcattgct    60
actaacacac tagtggctgt ggctgtgctg ctgttgatcc acaagaatga tgggtgctcagt    120
ctctgcttca ccttgaatct ggctgtggct gacaccttga ttggtgtggc catctctggc    180
ctactcacag accagctctc cagcccttct cggcccacac agaagaccct gtgcagcctg    240
cggatggcat ttgtcacttc ctccgcagct gcctctgtcc tcacggatcat gctgatcacc    300
tttgacaggt accttgccat caagcagccc ttcgctact tgaagatcat gagggggttc    360
gtggccgggg cctgcattgc cgggctgtgg ttagtgtctt acctcattgg ctctctccca    420
ctcggaatcc ccatgttcca gcagactgcc taaaagggc agtgcagctt ctttgctgta    480
tttaccctc acttegtgct gacctctcc tgcgttggtt tcttcccagc catgctctc    540
tttgtcttct tctactgca catgctcaag attgctcca tgcacagcca gcagattcga    600
aagatggaac atgcaggagc catggctgga ggttatcgat ccccacggac tcccagcgac    660
ttcaaagctc tccgtactgt gtctgttctc attgggagct ttgctctatc ctggaccccc    720
ttccttatca ctggcattgt gcaggtggcc tgccaggagt gtcacctcta cctagtgtg    780
gaacggatcc tgtggctgct cggcgtgggc aactccctgc tcaaccact catctatgcc    840
tattggcaga aggaggtgcg actgcagctc taccacatgg ccctaggagt gaagaagggtg    900
ctcacctcat tctctctctt tctctcggcc aggaattgtg gccagagag gccagggaa    960
agttcctgtc acatcgtcac tatctccagc tcagagtttg atggctaa    1008
  
```

<210> SEQ ID NO 8
 <211> LENGTH: 335
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

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

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

<210> SEQ ID NO 9

<211> LENGTH: 1413

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

```

atggacacta ccatggaagc tgacctgggt gccactggcc acaggccccg cacagagctt      60
gatgatgagg actcctacc ccaaggtggc tgggacacgg tcttctggt ggccctgctg      120
ctccttgggc tgccagccaa tgggttgatg gcgtggctgg ccggctccca ggcccggcat      180
ggagctggca cgcgtctggc gctgctcctg ctcagcctgg ccctctctga cttcttgttc      240
ctggcagcag cggccttcca gatcctagag atccggcatg ggggacactg gccgctgggg      300
acagctgect gccgcttcta ctacttcta tggggcgtgt cctactctc cggcctcttc      360
ctgctggccg ccctcagcct cgaccgctgc ctgctggcgc tgtgcccaca ctggtaccct      420
gggcaccgcc cagtcgcct gccctctgg gtctgcgcg gtgtctgggt gctggccaca      480

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ctcttcagcg tgcctggct ggtcttcccc gaggtgccc tctggtgta cgacctggtc 540
atctgctgg acttctggga cagcgaggag ctgtcgtga ggatgctgga ggtcctgggg 600
ggcttctgc ctttctcct gctgctcgtc tgccacgtgc tcacctcaggc cacagcctgt 660
cgcacctgcc accgccaaca gcagcccga gcctgcccgg gcttcgccc tgtggccagg 720
accattctgt cagcctatgt ggtcctgagg ctgccctacc agctggccc gctgctctac 780
ctggccttcc tgtgggacgt ctactctggc tacctgctct gggaggccct ggtctactcc 840
gactacctga tcctactcaa cagctgcctc agccccttcc tctgcctcat ggccagtgcc 900
gacctccgga cctgctgctg ctccgtgctc tcgtccttcg cggcagctct ctgagaggag 960
cggccgggca gcttcacgcc cactgagcca cagaccagc tagattctga gggccaact 1020
ctgccagagc cgatggcaga ggcccagtca cagatggatc ctgtggccc gcctcaggtg 1080
aaccacacac tccagccagc atcggatccc acagctcagc cacagctgaa ccctacggcc 1140
cagccacagt cggatcccac agcccagcca cagctgaacc tcatggccc gccacagtca 1200
gattctgtgg cccagccaca ggcagacact aacgtccaga cccctgcacc tgetgcccagt 1260
tctgtgccc gtccctgtga tgaagcttcc ccaacccat cctcgcctcc taccaggg 1320
gcccttgagg acccagccac acctcctgcc tctgaaggag aaagccccag cagcaccgg 1380
ccagaggcgg ccccgggccc aggccccacg tga 1413

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<210> SEQ ID NO 10

<211> LENGTH: 468

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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Met Asp Thr Thr Met Glu Ala Asp Leu Gly Ala Thr Gly His Arg Pro
 1             5             10             15
Arg Thr Glu Leu Asp Asp Glu Asp Ser Tyr Pro Gln Gly Gly Trp Asp
      20             25             30
Thr Val Phe Leu Val Ala Leu Leu Leu Leu Gly Leu Pro Ala Asn Gly
      35             40             45
Leu Met Ala Trp Leu Ala Gly Ser Gln Ala Arg His Gly Ala Gly Thr
      50             55             60
Arg Leu Ala Leu Leu Leu Leu Ser Leu Ala Leu Ser Asp Phe Leu Phe
      65             70             75             80
Leu Ala Ala Ala Ala Phe Gln Ile Leu Glu Ile Arg His Gly Gly His
      85             90             95
Trp Pro Leu Gly Thr Ala Ala Cys Arg Phe Tyr Tyr Phe Leu Trp Gly
      100            105            110
Val Ser Tyr Ser Ser Gly Leu Phe Leu Leu Ala Ala Leu Ser Leu Asp
      115            120            125
Arg Cys Leu Leu Ala Leu Cys Pro His Trp Tyr Pro Gly His Arg Pro
      130            135            140
Val Arg Leu Pro Leu Trp Val Cys Ala Gly Val Trp Val Leu Ala Thr
      145            150            155            160
Leu Phe Ser Val Pro Trp Leu Val Phe Pro Glu Ala Ala Val Trp Trp
      165            170            175
Tyr Asp Leu Val Ile Cys Leu Asp Phe Trp Asp Ser Glu Glu Leu Ser
      180            185            190
Leu Arg Met Leu Glu Val Leu Gly Gly Phe Leu Pro Phe Leu Leu Leu
      195            200            205

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

<210> SEQ ID NO 11

<211> LENGTH: 1248

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

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atgtcagggg tggaaaaact tcagaatgct tcctggatct accagcagaa actagaagat    60
ccattccaga aacacctgaa cagcaccgag gagtatctgg ccttcctctg cggacctcgg    120
cgcagccact tcttctccc cgtgtctgtg gtgtatgtgc caatttttgt ggtggggggtc    180
attggcaatg tcctggtgtg cctggtgatt ctgcagcacc aggctatgaa gacgcccacc    240
aactactacc tcttcagcct ggcgggtctct gacctcctgg tcttgcctct tggaatgccc    300
ctggaggtct atgagatgtg ggcgaactac cctttcttgt tcgggcccgt gggctgctac    360
ttcaagacgg ccctctttga gaccgtgtgc ttgcctcca tctcagcat caccaccgtc    420
agcgtggagc gctacgtggc catcctacac ccgttccggg ccaaactgca gagcaccggg    480
cgccgggccc tcaggatcct cggcatcgtc tggggcttct ccgtgctctt ctccctgccc    540
aacaccagca tccatggcat caagttccac tacttcccca atgggtccct ggtcccaggt    600

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tcggccacct gtacggatcat caagcccatg tggatctaca atttcatcat ccaggtcacc 660
tccttctctat tctacctctt ccccatgact gtcacatcagtg tcctctacta cctcatggca 720
ctcagactaa agaaagacaa atctcttgag gcagatgaag ggaatgcaaa tattcaaaga 780
ccctgcagaa aatcagtcaa caagatgctg tttgtcttg tcttagtggt tgctatctgt 840
tgggccccgt tccacattga ccgactcttc ttcagctttg tggaggagtg gagtgaatcc 900
ctggctgctg tgttcaacct cgtccatgtg gtgtcaggtg tcttcttcta cctgagctca 960
gctgtcaacc ccattatcta taacctactg tctcgcgct tccaggcagc attccagaat 1020
gtgatctctt ctttccacaa acagtggcac tcccagcatg acccacagtt gccacctgcc 1080
cagcggaaaca tcttctgac agaatgccac tttgtggagc tgaccgaaga tataggtccc 1140
caattcccat gtcagtcac catgcacaac tctcacctcc caacagccct ctctagttaa 1200
cagatgtcaa gaacaaacta tcaaagcttc cactttaaca aaacctga 1248

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<210> SEQ ID NO 12

<211> LENGTH: 415

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

```

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

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260	265	270
Leu Val Leu Val Phe Ala Ile Cys Trp Ala Pro Phe His Ile Asp Arg		
275	280	285
Leu Phe Phe Ser Phe Val Glu Glu Trp Ser Glu Ser Leu Ala Ala Val		
290	295	300
Phe Asn Leu Val His Val Val Ser Gly Val Phe Phe Tyr Leu Ser Ser		
305	310	315
Ala Val Asn Pro Ile Ile Tyr Asn Leu Leu Ser Arg Arg Phe Gln Ala		
325	330	335
Ala Phe Gln Asn Val Ile Ser Ser Phe His Lys Gln Trp His Ser Gln		
340	345	350
His Asp Pro Gln Leu Pro Pro Ala Gln Arg Asn Ile Phe Leu Thr Glu		
355	360	365
Cys His Phe Val Glu Leu Thr Glu Asp Ile Gly Pro Gln Phe Pro Cys		
370	375	380
Gln Ser Ser Met His Asn Ser His Leu Pro Thr Ala Leu Ser Ser Glu		
385	390	395
Gln Met Ser Arg Thr Asn Tyr Gln Ser Phe His Phe Asn Lys Thr		
405	410	415

<210> SEQ ID NO 13

<211> LENGTH: 1173

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

```

atgccagata ctaatagcac aatcaattta tcactaagca ctctgtgttac tttagcattt    60
tttatgtcct tagtagcttt tgctataatg ctaggaaatg ctttggtcat tttagctttt    120
gtggtggaca aaaaccttag acatcgaagt agttatTTTT ttcttaactt ggccatctct    180
gacttctttg tgggtgtgat ctccattcct ttgtacatcc ctcacacgct gttcgaatgg    240
gattttggaa aggaaatctg tgtatTTTtg ctactactg actatctgtt atgtacagca    300
tctgtatata acattgtcct catcagctat gatcgatacc tgtcagtctc aaatgctgtg    360
tcttatagaa ctcaacatac tggggctctg aagattgtta ctctgatggt ggccgTTTgg    420
gtgctggcct tcttagtgaa tgggccaatg attctagttt cagagtcttg gaaggatgaa    480
ggtagtgaat gtgaacctgg atTTTTtctg gaatggtaca tccttgccat cacatcattc    540
ttggaattcg tgatcccagt catcttagtc gcttatttca acatgaatat ttattggagc    600
ctgtggaagc gtgatcatct cagtaggtgc caaagccatc ctggactgac tgctgtctct    660
tccaacatct gtggacactc attcagaggt agactatctt caaggagatc tctttctgca    720
tcgacagaag ttctgcatc ctttcattca gagagacaga ggagaaagag tagtctcatg    780
ttttcctcaa gaaccaagat gaatagcaat acaattgctt ccaaaatggg ttcttctcc    840
caatcagatt ctgtagctct tcaccaaagg gaacatgTTg aactgcttag agccaggaga    900
ttagccaagt cactggccat tctcttaggg gTTTTtctg tttgctgggc tccatattct    960
ctgttcacaa ttgtcctttc atTTtattcc tcagcaacag gtctaaatc agTTTggtat   1020
agaattgcat tttgcttca gtggttcaat tcctttgtca atcctctttt gtattcattg   1080
tgtcacaagc gctttcaaaa ggctttcttg aaaatatttt gtataaaaaa gcaacctcta   1140
ccatcacaac acagtcggtc agtatcttct taa                                1173

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<210> SEQ ID NO 14

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<211> LENGTH: 390
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Met Pro Asp Thr Asn Ser Thr Ile Asn Leu Ser Leu Ser Thr Arg Val
 1           5           10           15
Thr Leu Ala Phe Phe Met Ser Leu Val Ala Phe Ala Ile Met Leu Gly
          20           25           30
Asn Ala Leu Val Ile Leu Ala Phe Val Val Asp Lys Asn Leu Arg His
          35           40           45
Arg Ser Ser Tyr Phe Phe Leu Asn Leu Ala Ile Ser Asp Phe Phe Val
          50           55           60
Gly Val Ile Ser Ile Pro Leu Tyr Ile Pro His Thr Leu Phe Glu Trp
          65           70           75           80
Asp Phe Gly Lys Glu Ile Cys Val Phe Trp Leu Thr Thr Asp Tyr Leu
          85           90           95
Leu Cys Thr Ala Ser Val Tyr Asn Ile Val Leu Ile Ser Tyr Asp Arg
          100          105          110
Tyr Leu Ser Val Ser Asn Ala Val Ser Tyr Arg Thr Gln His Thr Gly
          115          120          125
Val Leu Lys Ile Val Thr Leu Met Val Ala Val Trp Val Leu Ala Phe
          130          135          140
Leu Val Asn Gly Pro Met Ile Leu Val Ser Glu Ser Trp Lys Asp Glu
          145          150          155          160
Gly Ser Glu Cys Glu Pro Gly Phe Phe Ser Glu Trp Tyr Ile Leu Ala
          165          170          175
Ile Thr Ser Phe Leu Glu Phe Val Ile Pro Val Ile Leu Val Ala Tyr
          180          185          190
Phe Asn Met Asn Ile Tyr Trp Ser Leu Trp Lys Arg Asp His Leu Ser
          195          200          205
Arg Cys Gln Ser His Pro Gly Leu Thr Ala Val Ser Ser Asn Ile Cys
          210          215          220
Gly His Ser Phe Arg Gly Arg Leu Ser Ser Arg Arg Ser Leu Ser Ala
          225          230          235          240
Ser Thr Glu Val Pro Ala Ser Phe His Ser Glu Arg Gln Arg Arg Lys
          245          250          255
Ser Ser Leu Met Phe Ser Ser Arg Thr Lys Met Asn Ser Asn Thr Ile
          260          265          270
Ala Ser Lys Met Gly Ser Phe Ser Gln Ser Asp Ser Val Ala Leu His
          275          280          285
Gln Arg Glu His Val Glu Leu Leu Arg Ala Arg Arg Leu Ala Lys Ser
          290          295          300
Leu Ala Ile Leu Leu Gly Val Phe Ala Val Cys Trp Ala Pro Tyr Ser
          305          310          315          320
Leu Phe Thr Ile Val Leu Ser Phe Tyr Ser Ser Ala Thr Gly Pro Lys
          325          330          335
Ser Val Trp Tyr Arg Ile Ala Phe Trp Leu Gln Trp Phe Asn Ser Phe
          340          345          350
Val Asn Pro Leu Leu Tyr Pro Leu Cys His Lys Arg Phe Gln Lys Ala
          355          360          365
Phe Leu Lys Ile Phe Cys Ile Lys Lys Gln Pro Leu Pro Ser Gln His
          370          375          380
Ser Arg Ser Val Ser Ser

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385

390

<210> SEQ ID NO 15
 <211> LENGTH: 1128
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

```

atggcgaacg cgagcgagcc ggggtggcagc ggcggcggcg aggcggccgc cctgggcctc   60
aagctggcca cgctcagcct gctgctgtgc gtgagcctag cgggcaacgt gctgttcgcg   120
ctgctgatcg tgcgggagcg cagcctgcac cgcgccccgt actacctgct gctcgacctg   180
tgcttgccg acgggctgcg cgcgctcgcc tgctcccgg ccgtcatgct ggcggcgcgg   240
cgtgcggcgg ccgcggcggg ggcgcgcgcg ggcgcgctgg gctgcaagct gctcgccttc   300
ctggccgcgc tcttctgctt ccacgccgcc ttctgctgc tgggctgagg cgtcacccgc   360
tacctggcca tcgcgacca ccgcttctat gcagagcgcc tggccggctg gccgtgcgcc   420
gccatgctgg tgtgcgccgc ctgggcgctg gcgctggccg cggccttccc gccagtgctg   480
gacggcggtg gcgacgacga ggacgcgccg tgcgccctgg agcagcggcc cgacggcgcc   540
cccggcgcgc tgggcttctt gctgctgctg gccgtggctg tgggcccac gcacctcgtc   600
tacctccgcc tgctcttctt catccacgac cgcgcaaga tgcggcccgc gcgctggtg   660
cccgcgctca gccacgactg gaccttccac ggcccggggc ccaccggcca ggcggccgcc   720
aactggacgg cgggcttcgg ccgcgggccc acgcccccg cgcttgtggg catccggccc   780
gcagggccgg gccgcggcgc gcgcgcctc ctctgtctgg aagaattcaa gacggagaag   840
aggctgtgca agatgttcta cgcgctcag ctgctcttcc tgctcctctg ggggcctac   900
gtcgtggcca gctacctgcg ggtcctggtg cggcccggcg ccgtcccca ggectacctg   960
acggcctccg tgtggctgac cttcgcgcag gccggcatca acccgcctgt gtgcttctc  1020
ttcaacaggg agctgaggga ctgcttcagg gccagttcc cctgctgcca gagcccccg  1080
accaccaggg cgacctatcc ctgcgacctg aaaggcattg gtttatga   1128

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<210> SEQ ID NO 16
 <211> LENGTH: 375
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

```

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

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

<210> SEQ ID NO 17

<211> LENGTH: 1002

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

atgaacacca cagtgatgca aggcttcaac agatctgagc ggtgccccag agacactcgg 60
 atagtacagc tggattccc agccctctac acagtggttt tcttgaccgg catcctgctg 120
 aatactttgg ctctgtgggt gtttggtcac atccccagct cctccacctt catcatctac 180
 ctcaaaaaca ctttggtggc cgacttgata atgacactca tgcttcttt caaaatctc 240
 tctgactcac acctggcacc ctggcagctc agagcttttg tgtgctggtt ttcttcggtg 300
 atattttatg agaccatgta tgtgggcatc gtgctgtag ggctcatagc ctttgacaga 360
 ttctcaaga tcatcagacc tttgagaaat atttttctaa aaaaacctgt ttttgcaaaa 420
 acggtctcaa tcttcatctg gttctttttg ttcttcatct ccctgccaaa tacgatcttg 480
 agcaacaagg aagcaacacc atcgtctgtg aaaaagtgtg cttccttaaa ggggcctctg 540
 gggctgaaat ggcattcaat ggtaataaac atatgccagt ttatcttctg gactgttttt 600
 atcctaatac ttgtgtttta tgtggttatt gcaaaaaaag tatatgattc ttatagaaag 660

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tccaaaagta aggacagaaa aaacaacaaa aagctggaag gcaaagtatt tggtgtcgtg 720
gctgtcttct ttgtgtgttt tgctccattt cattttgccg gagttccata tactcacagt 780
caaaccaaca ataagactga ctgtagactg caaaatcaac tgtttattgc taaagaaaca 840
actctctttt tggcagcaac taacatttgt atggatccct taatatacat attcttatgt 900
aaaaaattca cagaaaagct accatgtatg caagggagaa agaccacagc atcaagccaa 960
gaaaatcata gcagtcagac agacaacata accttaggct ga 1002

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<210> SEQ ID NO 18

<211> LENGTH: 333

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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Met Asn Thr Thr Val Met Gln Gly Phe Asn Arg Ser Glu Arg Cys Pro
 1          5          10          15

Arg Asp Thr Arg Ile Val Gln Leu Val Phe Pro Ala Leu Tyr Thr Val
 20          25          30

Val Phe Leu Thr Gly Ile Leu Leu Asn Thr Leu Ala Leu Trp Val Phe
 35          40          45

Val His Ile Pro Ser Ser Ser Thr Phe Ile Ile Tyr Leu Lys Asn Thr
 50          55          60

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

Ser Asp Ser His Leu Ala Pro Trp Gln Leu Arg Ala Phe Val Cys Arg
 85          90          95

Phe Ser Ser Val Ile Phe Tyr Glu Thr Met Tyr Val Gly Ile Val Leu
100          105          110

Leu Gly Leu Ile Ala Phe Asp Arg Phe Leu Lys Ile Ile Arg Pro Leu
115          120          125

Arg Asn Ile Phe Leu Lys Lys Pro Val Phe Ala Lys Thr Val Ser Ile
130          135          140

Phe Ile Trp Phe Phe Leu Phe Phe Ile Ser Leu Pro Asn Thr Ile Leu
145          150          155          160

Ser Asn Lys Glu Ala Thr Pro Ser Ser Val Lys Lys Cys Ala Ser Leu
165          170          175

Lys Gly Pro Leu Gly Leu Lys Trp His Gln Met Val Asn Asn Ile Cys
180          185          190

Gln Phe Ile Phe Trp Thr Val Phe Ile Leu Met Leu Val Phe Tyr Val
195          200          205

Val Ile Ala Lys Lys Val Tyr Asp Ser Tyr Arg Lys Ser Lys Ser Lys
210          215          220

Asp Arg Lys Asn Asn Lys Lys Leu Glu Gly Lys Val Phe Val Val Val
225          230          235          240

Ala Val Phe Phe Val Cys Phe Ala Pro Phe His Phe Ala Arg Val Pro
245          250          255

Tyr Thr His Ser Gln Thr Asn Asn Lys Thr Asp Cys Arg Leu Gln Asn
260          265          270

Gln Leu Phe Ile Ala Lys Glu Thr Thr Leu Phe Leu Ala Ala Thr Asn
275          280          285

Ile Cys Met Asp Pro Leu Ile Tyr Ile Phe Leu Cys Lys Lys Phe Thr
290          295          300

Glu Lys Leu Pro Cys Met Gln Gly Arg Lys Thr Thr Ala Ser Ser Gln
305          310          315          320

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Glu Asn His Ser Ser Gln Thr Asp Asn Ile Thr Leu Gly
 325 330

<210> SEQ ID NO 19
 <211> LENGTH: 1122
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

atggccaaca ctaccggaga gcctgaggag gtgagcggcg ctctgtcccc accgtccgca 60
 tcagcttatg tgaagctggt actgctggga ctgattatgt gcgtgagcct ggcgggtaac 120
 gccatcttgt ccctgctggt gctcaaggag cgtgccctgc acaaggctcc ttactacttc 180
 ctgctggacc tgtgectggc cgatggcata cgctctgccg tctgcttccc ctttgtgctg 240
 gcttctgtgc gccacggctc ttcattggacc ttcagtgcac tcagctgcaa gattgtggcc 300
 tttatggcgc tgctcttttg cttccatgcg gccttcatgc tgttctgcat cagcgtcacc 360
 cgctacatgg ccatcgccca ccaccgcttc tacgccaagc gcatgacact ctggacatgc 420
 gcggctgtca tctgcatggc ctggaccctg tctgtggcca tggccttccc acctgtcttt 480
 gacgtgggca cctacaagtt tattcgggag gaggaccagt gcatctttga gcatcgctac 540
 ttcaaggcca atgacacgct gggcttcatg cttatgttgg ctgtgctcat ggcagctacc 600
 catgctgtct acggcaagct gctcctcttc gagtatcgtc accgcaagat gaagccagtg 660
 cagatggtgc cagccatcag ccagaactgg acattccatg gtcccggggc caccggccag 720
 gctgctgcca actggatcgc cggttttggc cgtgggcccc tgccaccaac cctgctgggt 780
 atccggcaga atgggcatgc agccagccgg cggctactgg gcatggacga ggtcaagggt 840
 gaaaagcagc tgggcccgat gttctacgcg atcacactgc tctttctgct cctctgggtca 900
 ccctacatcg tggcctgcta ctggcgagtg tttgtgaaag cctgtgctgt gccccaccgc 960
 tacctggcca ctgctgtttg gatgagcttc gccaggtg ccgtcaaccc aattgtctgc 1020
 ttctctgctca acaaggacct caagaagtgc ctgaccactc acgccccctg ctggggcaca 1080
 ggaggtgccc cggctcccag agaaccctac tgtgtcatgt ga 1122

<210> SEQ ID NO 20
 <211> LENGTH: 373
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

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

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

<210> SEQ ID NO 21

<211> LENGTH: 1053

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

atggcctttgg aacagaacca gtcaacagat tattattatg aggaaatga aatgaatggc	60
acttatgact acagtcaata tgaattgatc tgtatcaaag aagatgtcag agaatttgca	120
aaagttttcc tcctgtatt cctcacaata gctttcgtea ttggacttgc aggcaattcc	180
atggtagtgg caatttatgc ctattacaag aaacagagaa ccaaacaga tgtgtacatc	240
ctgaatttgg ctgtagcaga tttactcctt ctattcactc tgectttttg ggctgttaat	300
gcagttcatg ggtgggtttt agggaaaata atgtgcaaaa taacttcagc cttgtacaca	360
ctaaactttg tctctggaat gcagtttctg gcttgcacat gcatagacag atatgtggca	420
gtaactaatg tccccagcca atcaggagtg ggaaaacat gctggatcat ctgtttctgt	480
gtctggatgg ctgccatctt gctgagcata cccagctgg tttttatac agtaaatgac	540
aatgctaggt gcattcccat tttccccgc tacctaggaa catcaatgaa agcattgatt	600

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caaatgctag agatctgcat tggatttgta gtaccctttc ttattatggg ggtgtgctac 660
tttatcacgg caaggacact catgaagatg ccaaacatta aaatatctcg acccctaaaa 720
gttctgctca cagtcgttat agttttcatt gtcactcaac tgccttataa cattgtcaag 780
ttctgcccag ccatagacat catctactcc ctgatcacca gctgcaacat gagcaaacgc 840
atggacatcg ccatccaagt cacagaaagc attgcactct ttcacagctg cctcaaccca 900
atcctttatg tttttatggg agcatctttc aaaaactacg ttatgaaagt ggccaagaaa 960
tatgggtcct ggagaagaca gagacaaagt gtggaggagt ttccttttga ttctgagggt 1020
cctacagagc caaccagtac ttttagcatt taa 1053

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<210> SEQ ID NO 22

<211> LENGTH: 350

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

```

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

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

<210> SEQ ID NO 25

<211> LENGTH: 1113

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

atggcgaact atagccatgc agctgacaac attttgcaa atctctcgcc tctaacagcc 60
 tttctgaaac tgacttcctt gggtttcata ataggagtca gcgtggtggg caacctctg 120
 atctccattt tgctagttaa agataagacc ttgcatagag caccttacta cttcctgttg 180
 gatctttgct gttcagatat cctcagatct gcaatttggt tcccatttgt gttcaactct 240
 gtcaaaaatg gctctacctg gacttatggg actctgactt gcaaagtgat tgcctttctg 300
 ggggttttgg cctgtttcca cactgctttc atgctcttct gcatcagtgt caccagatac 360
 ttagctatcg cccatcaccg cttctataca aagaggctga ccttttgac gtgtctggct 420

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gtgatctgta tgggtgtggac tctgtctgtg gccatggcat ttcccccggt tttagacgtg 480
ggcacttact cattcattag ggaggaagat caatgcacct tccaacaccg ctcttcagg 540
gctaattgatt ccttaggatt tatgctgctt ctgctctca tcctcctagc cacacagctt 600
gtctacctca agctgatatt tttcgtccac gatcgaagaa aaatgaagcc agtccagttt 660
gtagcagcag tcagccagaa ctggactttt catggctctg gagccagtgg ccaggcagct 720
gccaatggc tagcaggatt tggaaggggt cccacaccac ccaccttgcg gggcatcagg 780
caaaatgcaa acaccacagg cagaagaagg ctattggctt tagacgagtt caaaatggag 840
aaaagaatca gcagaatgtt ctatataatg acttttctgt ttctaacctt gtggggcccc 900
tacctgggtg cctgttattg gagagttttt gcaagagggc ctgtagtacc aggggggattt 960
ctaacagctg ctgtctggat gagttttgcc caagcaggaa tcaatccttt tgtctgcatt 1020
ttctcaaaca gggagctgag gcgctgtttc agcacaaccc ttctttactg cagaaaatcc 1080
aggttaccaa gggaacctta ctgtgttata tga 1113

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<210> SEQ ID NO 26

<211> LENGTH: 370

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

```

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

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245				250				255							
Leu	Gly	Ile	Arg	Gln	Asn	Ala	Asn	Thr	Thr	Gly	Arg	Arg	Arg	Leu	Leu
			260								265				270
Val	Leu	Asp	Glu	Phe	Lys	Met	Glu	Lys	Arg	Ile	Ser	Arg	Met	Phe	Tyr
		275					280					285			
Ile	Met	Thr	Phe	Leu	Phe	Leu	Thr	Leu	Trp	Gly	Pro	Tyr	Leu	Val	Ala
	290					295					300				
Cys	Tyr	Trp	Arg	Val	Phe	Ala	Arg	Gly	Pro	Val	Val	Pro	Gly	Gly	Phe
305					310				315						320
Leu	Thr	Ala	Ala	Val	Trp	Met	Ser	Phe	Ala	Gln	Ala	Gly	Ile	Asn	Pro
			325						330					335	
Phe	Val	Cys	Ile	Phe	Ser	Asn	Arg	Glu	Leu	Arg	Arg	Cys	Phe	Ser	Thr
			340						345				350		
Thr	Leu	Leu	Tyr	Cys	Arg	Lys	Ser	Arg	Leu	Pro	Arg	Glu	Pro	Tyr	Cys
	355					360						365			
Val	Ile														
	370														

<210> SEQ ID NO 27
 <211> LENGTH: 1080
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

```

atgcaggtcc cgaacagcac cggcccggac aacgcgacgc tgcagatgct gcggaacccg    60
gcgatcgagg tggcctgcc cgtggtgtac tcgctggtgg cggcggtcag catcccgggc    120
aacctcttct ctctgtgggt gctgtgccgg cgcattggggc ccagatcccc gtcggtcatc    180
ttcatgatca acctgagcgt cacggacctg atgctggcca gcgtggtgcc ttccaaatc    240
tactaccatt gcaaccgcca ccaactgggta ttcgggggtgc tgctttgcaa cgtggtgacc    300
gtggcctttt acgcaaacat gtattccagc atcctcacca tgacctgtat cagcgtggag    360
cgcttctctg gggctctgta cccgctcagc tccaagcgt ggcgcgcggc tcgttacgcg    420
gtggccgcgt gtgcaggac ctggtgctg ctctgaccg ccctgtgccc gctggcgcgc    480
accgatctca cctaccgggt gcacgccttg ggcattcatc cctgcttcga cgtcctcaag    540
tggacgatgc tcccagcgt ggccatgtgg gccgtgttcc tcttcacat cttcatcctg    600
ctgttctca tccgcttctg gatcaccgtg gcttgttaca cggccacat cctcaagctg    660
ttgcgcacgg aggaggcga cggccgggag cagcggaggc gcgcgggtgg cctggccgcg    720
gtggtcttgc tggccttctg cacctgcttc gccccaaaca acttctgtgt cctggcgcac    780
atcgtgagcc gcctgttcta cggcaagagc tactaccacg tgtacaagct cacgctgtgt    840
ctcagctgcc tcaacaactg tctggaccgg tttgtttatt actttgcgtc ccgggaattc    900
cagctgcgcc tgcgggaata tttgggctgc cgccgggtgc ccagagacac cctggacacg    960
cgccgcgaga gcctcttctc cgccaggacc acgtccgtgc gctccgaggc cgggtgcgac   1020
cctgaaggga tggaggagc caccaggccc ggcctccaga ggcaggagag tgtgttctga   1080

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<210> SEQ ID NO 28
 <211> LENGTH: 359
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Met Gln Val Pro Asn Ser Thr Gly Pro Asp Asn Ala Thr Leu Gln Met

-continued

1	5	10	15
Leu Arg Asn Pro Ala Ile Ala Val Ala Leu Pro Val Val Tyr Ser Leu	20	25	30
Val Ala Ala Val Ser Ile Pro Gly Asn Leu Phe Ser Leu Trp Val Leu	35	40	45
Cys Arg Arg Met Gly Pro Arg Ser Pro Ser Val Ile Phe Met Ile Asn	50	55	60
Leu Ser Val Thr Asp Leu Met Leu Ala Ser Val Leu Pro Phe Gln Ile	65	70	80
Tyr Tyr His Cys Asn Arg His His Trp Val Phe Gly Val Leu Leu Cys	85	90	95
Asn Val Val Thr Val Ala Phe Tyr Ala Asn Met Tyr Ser Ser Ile Leu	100	105	110
Thr Met Thr Cys Ile Ser Val Glu Arg Phe Leu Gly Val Leu Tyr Pro	115	120	125
Leu Ser Ser Lys Arg Trp Arg Arg Arg Tyr Ala Val Ala Ala Cys	130	135	140
Ala Gly Thr Trp Leu Leu Leu Leu Thr Ala Leu Cys Pro Leu Ala Arg	145	150	155
Thr Asp Leu Thr Tyr Pro Val His Ala Leu Gly Ile Ile Thr Cys Phe	165	170	175
Asp Val Leu Lys Trp Thr Met Leu Pro Ser Val Ala Met Trp Ala Val	180	185	190
Phe Leu Phe Thr Ile Phe Ile Leu Leu Phe Leu Ile Pro Phe Val Ile	195	200	205
Thr Val Ala Cys Tyr Thr Ala Thr Ile Leu Lys Leu Leu Arg Thr Glu	210	215	220
Glu Ala His Gly Arg Glu Gln Arg Arg Arg Ala Val Gly Leu Ala Ala	225	230	235
Val Val Leu Leu Ala Phe Val Thr Cys Phe Ala Pro Asn Asn Phe Val	245	250	255
Leu Leu Ala His Ile Val Ser Arg Leu Phe Tyr Gly Lys Ser Tyr Tyr	260	265	270
His Val Tyr Lys Leu Thr Leu Cys Leu Ser Cys Leu Asn Asn Cys Leu	275	280	285
Asp Pro Phe Val Tyr Tyr Phe Ala Ser Arg Glu Phe Gln Leu Arg Leu	290	295	300
Arg Glu Tyr Leu Gly Cys Arg Arg Val Pro Arg Asp Thr Leu Asp Thr	305	310	315
Arg Arg Glu Ser Leu Phe Ser Ala Arg Thr Thr Ser Val Arg Ser Glu	325	330	335
Ala Gly Ala His Pro Glu Gly Met Glu Gly Ala Thr Arg Pro Gly Leu	340	345	350
Gln Arg Gln Glu Ser Val Phe	355		

<210> SEQ ID NO 29

<211> LENGTH: 1503

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

atggagcgtc cctgggagga cagcccaggc cgggaggggg cagctgaggg ctgcctgtg 60

ccagtcgccg ccggggcgcg ctccggtgcc gcggcgagtg gcacaggctg gcagccatgg 120

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gctgagtgcc cgggacccaa ggggaggggg caactgctgg cgaccgccgg ccctttgctg 180
cgctggcccc cccctctgcc tgccagctcc agccccgcc cgggagcggc gtccgctcac 240
tcggttcaag gcagcgcgac tgcgggtggc gcacgaccag ggccgagacc ttggggcgcg 300
cggcccatgg agtcggggct gctgcggccg gcgccggtga gcgaggtcat cgtcctgcat 360
tacaactaca cgggcaagct ccgcggtgcg agtaccagc cgggtgccgg cctgcgcgcc 420
gacgccgtgg tgtgcctggc ggtgtgcgcc ttcacgtgc tagagaatct agccgtgttg 480
ttggtgctcg gacgccacc gcgcttccac gctcccatgt tcctgctcct gggcagcctc 540
acgttgctcg atctgctggc aggcgccgcc tacgccgcca acatcctact gtcggggccg 600
ctcacgctga aactgtcccc cgcgctctgg ttcgcacggg agggaggcgt cttcgtggca 660
ctcactgctg ccgtgctgag cctcctggcc atcgcgctgg agcgcagcct caccatggcg 720
cgcagggggc ccgcgcccg ctccagtcgg gggcgcacgc tggcgatggc agccgcggcc 780
tggggcgctg cgctgctcct cgggctcctg ccagcgtggc gctggaattg cctgggtcgc 840
ctggacgctt gctccactgt cttgccgctc tacgccaagg cctacgtgct cttctgctg 900
ctgccttcg tgggcatcct ggccgcgatc tgtgactct acgcgcgcat ctactgccag 960
gtacgcgcca acgcgcggcg cctgccggca cggcccggga ctgcggggac cacctcgacc 1020
cgggcgcgct gcaagcccg ctctctggcc ttgctgcgca cgctcagcgt ggtgctcctg 1080
gcctttgtgg catgttgggg cccctcttc ctgctgctgt tgctcgacgt ggcgtgcccg 1140
gcgcgcacct gtcctgtact cctgcaggcc gatccctcc tgggactggc catggccaac 1200
tcacttctga accccatcat ctacacgctc accaaccgcg acctgcgcca cgcgctcctg 1260
cgctggtct gctgcggacg ccaactcctgc ggcagagacc cgagtggctc ccagcagtcg 1320
gcgagcgcgg ctgaggettc cgggggctcg cgcgctgccc tgccccggg ccttgatggg 1380
agcttcagcg gctcggagcg ctcatcgccc cagcgcgacg ggctggacac cagcggctcc 1440
acaggcagcc ccggtgcacc cacagccgcc cggactctgg tatcagaacc ggctgcagac 1500
tga 1503

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<210> SEQ ID NO 30

<211> LENGTH: 500

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

```

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

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115				120				125							
Gly	Ala	Ser	Tyr	Gln	Pro	Gly	Ala	Gly	Leu	Arg	Ala	Asp	Ala	Val	Val
130				135				140							
Cys	Leu	Ala	Val	Cys	Ala	Phe	Ile	Val	Leu	Glu	Asn	Leu	Ala	Val	Leu
145				150				155				160			
Leu	Val	Leu	Gly	Arg	His	Pro	Arg	Phe	His	Ala	Pro	Met	Phe	Leu	Leu
			165					170				175			
Leu	Gly	Ser	Leu	Thr	Leu	Ser	Asp	Leu	Leu	Ala	Gly	Ala	Ala	Tyr	Ala
			180					185				190			
Ala	Asn	Ile	Leu	Leu	Ser	Gly	Pro	Leu	Thr	Leu	Lys	Leu	Ser	Pro	Ala
			195				200					205			
Leu	Trp	Phe	Ala	Arg	Glu	Gly	Gly	Val	Phe	Val	Ala	Leu	Thr	Ala	Ser
	210					215					220				
Val	Leu	Ser	Leu	Leu	Ala	Ile	Ala	Leu	Glu	Arg	Ser	Leu	Thr	Met	Ala
225					230					235					240
Arg	Arg	Gly	Pro	Ala	Pro	Val	Ser	Ser	Arg	Gly	Arg	Thr	Leu	Ala	Met
			245						250					255	
Ala	Ala	Ala	Ala	Trp	Gly	Val	Ser	Leu	Leu	Leu	Gly	Leu	Leu	Pro	Ala
			260					265						270	
Leu	Gly	Trp	Asn	Cys	Leu	Gly	Arg	Leu	Asp	Ala	Cys	Ser	Thr	Val	Leu
		275					280					285			
Pro	Leu	Tyr	Ala	Lys	Ala	Tyr	Val	Leu	Phe	Cys	Val	Leu	Ala	Phe	Val
		290				295					300				
Gly	Ile	Leu	Ala	Ala	Ile	Cys	Ala	Leu	Tyr	Ala	Arg	Ile	Tyr	Cys	Gln
305					310					315					320
Val	Arg	Ala	Asn	Ala	Arg	Arg	Leu	Pro	Ala	Arg	Pro	Gly	Thr	Ala	Gly
			325						330					335	
Thr	Thr	Ser	Thr	Arg	Ala	Arg	Arg	Lys	Pro	Arg	Ser	Leu	Ala	Leu	Leu
			340					345				350			
Arg	Thr	Leu	Ser	Val	Val	Leu	Leu	Ala	Phe	Val	Ala	Cys	Trp	Gly	Pro
		355					360					365			
Leu	Phe	Leu	Leu	Leu	Leu	Leu	Leu	Asp	Val	Ala	Cys	Pro	Ala	Arg	Thr
	370					375					380				
Pro	Val	Leu	Leu	Gln	Ala	Asp	Pro	Phe	Leu	Gly	Leu	Ala	Met	Ala	Asn
385					390					395					400
Ser	Leu	Leu	Asn	Pro	Ile	Ile	Tyr	Thr	Leu	Thr	Asn	Arg	Asp	Leu	Arg
			405					410						415	
His	Ala	Leu	Leu	Arg	Leu	Val	Cys	Cys	Gly	Arg	His	Ser	Cys	Gly	Arg
		420						425					430		
Asp	Pro	Ser	Gly	Ser	Gln	Gln	Ser	Ala	Ser	Ala	Ala	Glu	Ala	Ser	Gly
		435					440					445			
Gly	Leu	Arg	Arg	Cys	Leu	Pro	Pro	Gly	Leu	Asp	Gly	Ser	Phe	Ser	Gly
	450					455					460				
Ser	Glu	Arg	Ser	Ser	Pro	Gln	Arg	Asp	Gly	Leu	Asp	Thr	Ser	Gly	Ser
465					470					475					480
Thr	Gly	Ser	Pro	Gly	Ala	Pro	Thr	Ala	Ala	Arg	Thr	Leu	Val	Ser	Glu
			485					490						495	
Pro	Ala	Ala	Asp												
			500												

<210> SEQ ID NO 31

<211> LENGTH: 1029

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 31

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atgcaagccg tgcacaatct cacctctgcg cctgggaaca ccagtctgtg caccagagac    60
tacaaaatca cccaggtcct ctteccactg ctctacactg tcctgttttt tggttggactt   120
atcacaaatg gcctggcgat gaggattttc tttcaaatcc ggagtaaadc aaactttatt   180
atTTTTctta agaacacagt cattttctgat cttctcatga ttctgacttt tccattcaaa   240
attcttagtg atgccaaact gggaacagga ccaactgagaa cttttgtgtg tcaagttacc   300
tccgtcatat tttatttcac aatgtatata agtatttcat tcctgggact gataactata   360
gatcgctacc agaagaccac caggccattt aaaacatcca accccaaaaa tctcttgggg   420
gctaagattc tctctgttgt catctgggca ttcattgttct tactctcttt gcctaactg   480
attctgacca acaggcagcc gagagacaag aatgtgaaga aatgctcttt ccttaaatca   540
gagttcgggc tagtctggca tgaatataga aattacatct gtcaagtcac tttctggatt   600
aatttcttaa ttgttattgt atgttataca ctattacaa aagaactgta ccggtcatac   660
gtaagaacga ggggtgtagg taaagtcccc aggaaaaagg tgaacgtcaa agttttcatt   720
atcattgctg tattctttat ttgttttgtt cctttccatt ttgcccgaat tccttacacc   780
ctgagccaaa cccgggatgt ctttgactgc actgctgaaa atactctgtt ctatgtgaaa   840
gagagcactc tgtggttaac ttccttaaata gcatgcctgg atccgttcat ctattttttc   900
ctttgcaagt ccttcagaaa ttccttgata agtatgctga agtgccccaa ttctgcaaca   960
tctctgtccc aggacaatag gaaaaaagaa caggatggtg gtgacccaaa tgaagagact  1020
ccaatgtaa                                     1029

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<210> SEQ ID NO 32

<211> LENGTH: 342

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

```

Met Gln Ala Val Asp Asn Leu Thr Ser Ala Pro Gly Asn Thr Ser Leu
  1           5           10           15
Cys Thr Arg Asp Tyr Lys Ile Thr Gln Val Leu Phe Pro Leu Leu Tyr
           20           25           30
Thr Val Leu Phe Phe Val Gly Leu Ile Thr Asn Gly Leu Ala Met Arg
           35           40           45
Ile Phe Phe Gln Ile Arg Ser Lys Ser Asn Phe Ile Ile Phe Leu Lys
           50           55           60
Asn Thr Val Ile Ser Asp Leu Leu Met Ile Leu Thr Phe Pro Phe Lys
           65           70           75           80
Ile Leu Ser Asp Ala Lys Leu Gly Thr Gly Pro Leu Arg Thr Phe Val
           85           90           95
Cys Gln Val Thr Ser Val Ile Phe Tyr Phe Thr Met Tyr Ile Ser Ile
           100          105          110
Ser Phe Leu Gly Leu Ile Thr Ile Asp Arg Tyr Gln Lys Thr Thr Arg
           115          120          125
Pro Phe Lys Thr Ser Asn Pro Lys Asn Leu Leu Gly Ala Lys Ile Leu
           130          135          140
Ser Val Val Ile Trp Ala Phe Met Phe Leu Leu Ser Leu Pro Asn Met
           145          150          155          160
Ile Leu Thr Asn Arg Gln Pro Arg Asp Lys Asn Val Lys Lys Cys Ser
           165          170          175

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Phe Leu Lys Ser Glu Phe Gly Leu Val Trp His Glu Ile Val Asn Tyr
 180 185 190
 Ile Cys Gln Val Ile Phe Trp Ile Asn Phe Leu Ile Val Ile Val Cys
 195 200 205
 Tyr Thr Leu Ile Thr Lys Glu Leu Tyr Arg Ser Tyr Val Arg Thr Arg
 210 215 220
 Gly Val Gly Lys Val Pro Arg Lys Lys Val Asn Val Lys Val Phe Ile
 225 230 235 240
 Ile Ile Ala Val Phe Phe Ile Cys Phe Val Pro Phe His Phe Ala Arg
 245 250 255
 Ile Pro Tyr Thr Leu Ser Gln Thr Arg Asp Val Phe Asp Cys Thr Ala
 260 265 270
 Glu Asn Thr Leu Phe Tyr Val Lys Glu Ser Thr Leu Trp Leu Thr Ser
 275 280 285
 Leu Asn Ala Cys Leu Asp Pro Phe Ile Tyr Phe Phe Leu Cys Lys Ser
 290 295 300
 Phe Arg Asn Ser Leu Ile Ser Met Leu Lys Cys Pro Asn Ser Ala Thr
 305 310 315 320
 Ser Leu Ser Gln Asp Asn Arg Lys Lys Glu Gln Asp Gly Gly Asp Pro
 325 330 335
 Asn Glu Glu Thr Pro Met
 340

<210> SEQ ID NO 33
 <211> LENGTH: 1077
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

atgtcggctct gctaccgtcc cccagggaac gagacactgc tgagctggaa gacttcgctg 60
 gccacaggca cagccttctt gctgctggcg gcgctgctgg ggctgcctgg caacggcttc 120
 gtgggtgtgga gcttgccggg ctggcggcct gcacgggggc gaccgctggc ggccacgctt 180
 gtgctgcacc tggcgctggc cgacggcgcg gtgctgctgc tcacgcccgt ctttgtggcc 240
 ttctgacctt ggcaggcctg gccgctgggc caggcgggct gcaaggcggg gtactacgtg 300
 tgcgcgctca gcatgtacgc cagcgtgctg ctcaccggcc tgctcagcct gcagcgtgct 360
 ctgcagtcac cccgcccctt cctggcgcct cggtgcgca gcccggcctt ggcccgcgcg 420
 ctgctgctgg cggctctggc ggccgcccct ttgctgcgcg tcccggccgc cgtctaccgc 480
 cacctgtgga gggaccgct atgccagctg tgccaccgct cgccgggtcca cgccgcccgc 540
 cacctgagcc tggagactct gaccgctttc gtgcttctt tcgggctgat gctcggctgc 600
 tacagcgtga cgctggcacg gctgcggggc gcccgctggg gctccgggcg gcacggggcg 660
 cgggtgggccc ggctggtgag cgccatcgtg cttgctcttg gcttgccttg ggccccctac 720
 cacgcagtca accttctgca ggccgctgca gcgctggctc caccggaagg ggccttgccg 780
 aagctgggcg gagccggcca ggccggcgca gcgggaacta cggccttggc cttcttcagt 840
 tctagcgtca acccggtgct ctacgtcttc accgctggag atctgctgcc ccgggcaggt 900
 ccccgcttcc tcacgggct cttcgaagcc tctggggagg cccgaggggg cggccgctct 960
 agggaaggga ccatggagct ccgaactacc cctcagctga aagtgggtgg gcagggccgc 1020
 ggcaatggag acccgggggg tgggatggag aaggacggtc cggaatggga cctttga 1077

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<210> SEQ ID NO 34
<211> LENGTH: 358
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34
Met Ser Val Cys Tyr Arg Pro Pro Gly Asn Glu Thr Leu Leu Ser Trp
 1           5           10           15
Lys Thr Ser Arg Ala Thr Gly Thr Ala Phe Leu Leu Leu Ala Ala Leu
      20           25           30
Leu Gly Leu Pro Gly Asn Gly Phe Val Val Trp Ser Leu Ala Gly Trp
      35           40           45
Arg Pro Ala Arg Gly Arg Pro Leu Ala Ala Thr Leu Val Leu His Leu
      50           55           60
Ala Leu Ala Asp Gly Ala Val Leu Leu Leu Thr Pro Leu Phe Val Ala
      65           70           75           80
Phe Leu Thr Arg Gln Ala Trp Pro Leu Gly Gln Ala Gly Cys Lys Ala
      85           90           95
Val Tyr Tyr Val Cys Ala Leu Ser Met Tyr Ala Ser Val Leu Leu Thr
      100          105          110
Gly Leu Leu Ser Leu Gln Arg Cys Leu Ala Val Thr Arg Pro Phe Leu
      115          120          125
Ala Pro Arg Leu Arg Ser Pro Ala Leu Ala Arg Arg Leu Leu Leu Ala
      130          135          140
Val Trp Leu Ala Ala Leu Leu Leu Ala Val Pro Ala Ala Val Tyr Arg
      145          150          155          160
His Leu Trp Arg Asp Arg Val Cys Gln Leu Cys His Pro Ser Pro Val
      165          170          175
His Ala Ala Ala His Leu Ser Leu Glu Thr Leu Thr Ala Phe Val Leu
      180          185          190
Pro Phe Gly Leu Met Leu Gly Cys Tyr Ser Val Thr Leu Ala Arg Leu
      195          200          205
Arg Gly Ala Arg Trp Gly Ser Gly Arg His Gly Ala Arg Val Gly Arg
      210          215          220
Leu Val Ser Ala Ile Val Leu Ala Phe Gly Leu Leu Trp Ala Pro Tyr
      225          230          235          240
His Ala Val Asn Leu Leu Gln Ala Val Ala Ala Leu Ala Pro Pro Glu
      245          250          255
Gly Ala Leu Ala Lys Leu Gly Gly Ala Gly Gln Ala Ala Arg Ala Gly
      260          265          270
Thr Thr Ala Leu Ala Phe Phe Ser Ser Ser Val Asn Pro Val Leu Tyr
      275          280          285
Val Phe Thr Ala Gly Asp Leu Leu Pro Arg Ala Gly Pro Arg Phe Leu
      290          295          300
Thr Arg Leu Phe Glu Gly Ser Gly Glu Ala Arg Gly Gly Gly Arg Ser
      305          310          315          320
Arg Glu Gly Thr Met Glu Leu Arg Thr Thr Pro Gln Leu Lys Val Val
      325          330          335
Gly Gln Gly Arg Gly Asn Gly Asp Pro Gly Gly Gly Met Glu Lys Asp
      340          345          350
Gly Pro Glu Trp Asp Leu
      355

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<210> SEQ ID NO 35
<211> LENGTH: 1005

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<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

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atgctgggga tcatggcatg gaatgcaact tgcaaaaact ggctggcagc agaggctgcc      60
ctggaaaagt actacctttc cattttttat gggattgagt tcgttgtggg agtccttgga     120
aataccattg ttgtttacgg ctacatcttc tctctgaaga actggaacag cagtaatatt     180
tatctcttta acctctctgt ctctgactta gcttttctgt gcacctccc catgctgata     240
aggagttatg ccaatggaaa ctggatatat ggagacgtgc tctgcataag caaccgatat     300
gtgcttcatg ccaacctcta taccagcatt ctctttctca cttttatcag catagatcga     360
tacttgataa ttaagatcc tttccgagaa caccttctgc aaaagaaaga gtttgctatt     420
ttaatctcct tggccatttg ggttttagta accttagagt tactacccat acttcccctt     480
ataaatcctg ttataactga caatggcacc acctgtaatg attttgcaag ttctggagac     540
cccaactaca acctcattta cagcatgtgt ctaacactgt tggggttcct tattcctctt     600
tttgtgatgt gtttctttta ttacaagatt gctctcttcc taaagcagag gaataggcag     660
gttgctactg ctctgccctt tgaaaagcct ctcaacttgg tcatcatggc agtggtaatc     720
ttctctgtgc tttttacacc ctatcacgtc atgcggaatg tgaggatcgc ttcacgcctg     780
gggagttgga agcagtatca gtgcactcag gtcgtcatca actcctttta cattgtgaca     840
cggcctttgg cctttctgaa cagtgtcatc aaccctgtct tctattttct tttgggagat     900
cacttcaggg acatgctgat gaatcaactg agacacaact tcaaatccct tacatccttt     960
agcagatggg ctcatgaact cctactttca ttcagagaaa agtga                       1005

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<210> SEQ ID NO 36

<211> LENGTH: 334

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

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Met Leu Gly Ile Met Ala Trp Asn Ala Thr Cys Lys Asn Trp Leu Ala
 1           5           10          15
Ala Glu Ala Ala Leu Glu Lys Tyr Tyr Leu Ser Ile Phe Tyr Gly Ile
          20          25          30
Glu Phe Val Val Gly Val Leu Gly Asn Thr Ile Val Val Tyr Gly Tyr
          35          40          45
Ile Phe Ser Leu Lys Asn Trp Asn Ser Ser Asn Ile Tyr Leu Phe Asn
          50          55          60
Leu Ser Val Ser Asp Leu Ala Phe Leu Cys Thr Leu Pro Met Leu Ile
          65          70          75          80
Arg Ser Tyr Ala Asn Gly Asn Trp Ile Tyr Gly Asp Val Leu Cys Ile
          85          90          95
Ser Asn Arg Tyr Val Leu His Ala Asn Leu Tyr Thr Ser Ile Leu Phe
          100         105         110
Leu Thr Phe Ile Ser Ile Asp Arg Tyr Leu Ile Ile Lys Tyr Pro Phe
          115         120         125
Arg Glu His Leu Leu Gln Lys Lys Glu Phe Ala Ile Leu Ile Ser Leu
          130         135         140
Ala Ile Trp Val Leu Val Thr Leu Glu Leu Leu Pro Ile Leu Pro Leu
          145         150         155         160
Ile Asn Pro Val Ile Thr Asp Asn Gly Thr Thr Cys Asn Asp Phe Ala
          165         170         175

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Ser Ser Gly Asp Pro Asn Tyr Asn Leu Ile Tyr Ser Met Cys Leu Thr
 180 185 190

Leu Leu Gly Phe Leu Ile Pro Leu Phe Val Met Cys Phe Phe Tyr Tyr
 195 200 205

Lys Ile Ala Leu Phe Leu Lys Gln Arg Asn Arg Gln Val Ala Thr Ala
 210 215 220

Leu Pro Leu Glu Lys Pro Leu Asn Leu Val Ile Met Ala Val Val Ile
 225 230 235 240

Phe Ser Val Leu Phe Thr Pro Tyr His Val Met Arg Asn Val Arg Ile
 245 250 255

Ala Ser Arg Leu Gly Ser Trp Lys Gln Tyr Gln Cys Thr Gln Val Val
 260 265 270

Ile Asn Ser Phe Tyr Ile Val Thr Arg Pro Leu Ala Phe Leu Asn Ser
 275 280 285

Val Ile Asn Pro Val Phe Tyr Phe Leu Leu Gly Asp His Phe Arg Asp
 290 295 300

Met Leu Met Asn Gln Leu Arg His Asn Phe Lys Ser Leu Thr Ser Phe
 305 310 315 320

Ser Arg Trp Ala His Glu Leu Leu Leu Ser Phe Arg Glu Lys
 325 330

<210> SEQ ID NO 37

<211> LENGTH: 1296

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

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acgcgggagc agttcatcgc tctgtaccgg ctgcgaccgc tcgtctacac cccagagctg 120

ccgggacgcg ccaagctggc cctcgtgctc accggcgtgc tcatcttcgc cctggcgctc 180

tttgcaatg ctctggtgtt ctacgtggtg acccgcagca aggccatgcg caccgtcacc 240

aacatcttta tctgctcctt ggcgctcagt gacctgctca tcaccttctt ctgcattccc 300

gtcaccatgc tccagaacat ttccgacaac tggctggggg gtgctttcat ttgcaagatg 360

gtgccatttg tccagtctac cgctgttggt acagaaatgc tcactatgac ctgcattgct 420

gtggaaaggc accagggact tgtgcatcct ttaaaaatga agtggcaata caccaaccga 480

agggctttca caatgctagg tgtggtctgg ctggtggcag tcatcgtagg atcaccatg 540

tggcacgtgc aacaactga gatcaaatat gacttcctat atgaaaagga acacatctgc 600

tgcttagaag agtggaccag cctgtgacac cagaagatct acaccacctt catccttgct 660

atcctcttcc tctgctctct tatgggtgatg cttattctgt acagtaaaat tggttatgaa 720

ctttggataa agaaaagagt tggggatggt tcagtgtctc gaactattca tggaaaagaa 780

atgtccaaaa tagccaggaa gaagaaacga gctgtcatta tgatggtgac agtgggtggct 840

ctctttgctg tgtgctgggc accattccat gttgtccata tgatgattga atacagtaat 900

tttggaaagg aatatgatga tgtcacaatc aagatgattt ttgctatcgt gcaaattatt 960

ggattttcca actccatctg taatccatt gtctatgcat ttatgaatga aaacttcaaa 1020

aaaaatgttt tgtctgcagt ttgttattgc atagtaaata aaaccttctc tccagcacia 1080

aggcatggaa attcaggaat tacaatgatg cggaagaaag caaagtttct cctcagagag 1140

aatccagtgg aggaaaccaa aggagaagca ttcagtgatg gcaacattga agtcaaattg 1200

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tgtgaacaga cagaggagaa gaaaaagctc aaacgacatc ttgctctctt taggtctgaa 1260
 ctggctgaga attctccttt agacagtggg cattaa 1296

<210> SEQ ID NO 38
 <211> LENGTH: 431
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Met Gln Ala Leu Asn Ile Thr Pro Glu Gln Phe Ser Arg Leu Leu Arg
 1 5 10 15
 Asp His Asn Leu Thr Arg Glu Gln Phe Ile Ala Leu Tyr Arg Leu Arg
 20 25 30
 Pro Leu Val Tyr Thr Pro Glu Leu Pro Gly Arg Ala Lys Leu Ala Leu
 35 40 45
 Val Leu Thr Gly Val Leu Ile Phe Ala Leu Ala Leu Phe Gly Asn Ala
 50 55 60
 Leu Val Phe Tyr Val Val Thr Arg Ser Lys Ala Met Arg Thr Val Thr
 65 70 75 80
 Asn Ile Phe Ile Cys Ser Leu Ala Leu Ser Asp Leu Leu Ile Thr Phe
 85 90 95
 Phe Cys Ile Pro Val Thr Met Leu Gln Asn Ile Ser Asp Asn Trp Leu
 100 105 110
 Gly Gly Ala Phe Ile Cys Lys Met Val Pro Phe Val Gln Ser Thr Ala
 115 120 125
 Val Val Thr Glu Met Leu Thr Met Thr Cys Ile Ala Val Glu Arg His
 130 135 140
 Gln Gly Leu Val His Pro Phe Lys Met Lys Trp Gln Tyr Thr Asn Arg
 145 150 155 160
 Arg Ala Phe Thr Met Leu Gly Val Val Trp Leu Val Ala Val Ile Val
 165 170 175
 Gly Ser Pro Met Trp His Val Gln Gln Leu Glu Ile Lys Tyr Asp Phe
 180 185 190
 Leu Tyr Glu Lys Glu His Ile Cys Cys Leu Glu Glu Trp Thr Ser Pro
 195 200 205
 Val His Gln Lys Ile Tyr Thr Thr Phe Ile Leu Val Ile Leu Phe Leu
 210 215 220
 Leu Pro Leu Met Val Met Leu Ile Leu Tyr Ser Lys Ile Gly Tyr Glu
 225 230 235 240
 Leu Trp Ile Lys Lys Arg Val Gly Asp Gly Ser Val Leu Arg Thr Ile
 245 250 255
 His Gly Lys Glu Met Ser Lys Ile Ala Arg Lys Lys Lys Arg Ala Val
 260 265 270
 Ile Met Met Val Thr Val Val Ala Leu Phe Ala Val Cys Trp Ala Pro
 275 280 285
 Phe His Val Val His Met Met Ile Glu Tyr Ser Asn Phe Glu Lys Glu
 290 295 300
 Tyr Asp Asp Val Thr Ile Lys Met Ile Phe Ala Ile Val Gln Ile Ile
 305 310 315 320
 Gly Phe Ser Asn Ser Ile Cys Asn Pro Ile Val Tyr Ala Phe Met Asn
 325 330 335
 Glu Asn Phe Lys Lys Asn Val Leu Ser Ala Val Cys Tyr Cys Ile Val
 340 345 350
 Asn Lys Thr Phe Ser Pro Ala Gln Arg His Gly Asn Ser Gly Ile Thr

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355	360	365	
Met Met Arg Lys Lys Ala Lys Phe Ser Leu Arg Glu Asn Pro Val Glu			
370	375	380	
Glu Thr Lys Gly Glu Ala Phe Ser Asp Gly Asn Ile Glu Val Lys Leu			
385	390	395	400
Cys Glu Gln Thr Glu Glu Lys Lys Lys Leu Lys Arg His Leu Ala Leu			
	405	410	415
Phe Arg Ser Glu Leu Ala Glu Asn Ser Pro Leu Asp Ser Gly His			
	420	425	430
<210> SEQ ID NO 39			
<211> LENGTH: 24			
<212> TYPE: DNA			
<213> ORGANISM: Homo sapiens			
<400> SEQUENCE: 39			
ctgtgtacag cagttcgcag agtg			24
<210> SEQ ID NO 40			
<211> LENGTH: 24			
<212> TYPE: DNA			
<213> ORGANISM: Homo sapiens			
<400> SEQUENCE: 40			
gagtgccagg cagagcaggt agac			24
<210> SEQ ID NO 41			
<211> LENGTH: 31			
<212> TYPE: DNA			
<213> ORGANISM: Homo sapiens			
<400> SEQUENCE: 41			
cccgaattcc tgcttgctcc cagcttggcc c			31
<210> SEQ ID NO 42			
<211> LENGTH: 32			
<212> TYPE: DNA			
<213> ORGANISM: Homo sapiens			
<400> SEQUENCE: 42			
tgtggatcct gctgtcaaag gtcccattcc gg			32
<210> SEQ ID NO 43			
<211> LENGTH: 20			
<212> TYPE: DNA			
<213> ORGANISM: Homo sapiens			
<400> SEQUENCE: 43			
tcacaatgct aggtgtggtc			20
<210> SEQ ID NO 44			
<211> LENGTH: 22			
<212> TYPE: DNA			
<213> ORGANISM: Homo sapiens			
<400> SEQUENCE: 44			
tgcatagaca atgggattac ag			22
<210> SEQ ID NO 45			
<211> LENGTH: 511			
<212> TYPE: DNA			
<213> ORGANISM: Homo sapiens			

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<400> SEQUENCE: 45

tcacaatgct aggtgtggc tggctggg cagtcacgt aggatcacc atgtggcacg 60
 tgcaacaact tgagatcaaa tatgacttcc tatatgaaaa ggaacacatc tgctgcttag 120
 aagagtggac cagccctgtg caccagaaga tctacaccac cttcatcctt gtcacacctt 180
 tcctcctgcc tcttatggg atgcttattc tgtacgtaaa attgggtatg aactttggat 240
 aaagaaaaga gttggggatg gttcagtgc tgcgaactatt catggaaaag aaatgtccaa 300
 aatagccagg aagaagaaac gagctgtcat tatgatggg acagtgggg ctctctttgc 360
 tgtgtgctgg gcaccattcc atgttgcca tatgatgatt gaatacagta attttgaaaa 420
 ggaatatgat gatgtcaca tcaagatgat tttgctatc gtgcaaatta ttggattttc 480
 caactccatc tgtaatccca ttgtctatgc a 511

<210> SEQ ID NO 46

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

ctgcttagaa gagtggacca g 21

<210> SEQ ID NO 47

<211> LENGTH: 22

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

ctgtgcacca gaagatctac ac 22

<210> SEQ ID NO 48

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

caaggatgaa ggtggtgtag a 21

<210> SEQ ID NO 49

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

gtgtagatct tctggtgcac agg 23

<210> SEQ ID NO 50

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

gcaatgcagg tcatagttag c 21

<210> SEQ ID NO 51

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

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tggagcatgg tgacgggaat gcagaag	27
<210> SEQ ID NO 52 <211> LENGTH: 27 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <400> SEQUENCE: 52	
gtgatgagca ggtcactgag cgccaag	27
<210> SEQ ID NO 53 <211> LENGTH: 23 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <400> SEQUENCE: 53	
gcaatgcagg cgcttaacat tac	23
<210> SEQ ID NO 54 <211> LENGTH: 22 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <400> SEQUENCE: 54	
ttgggttaca atctgaagg ca	22
<210> SEQ ID NO 55 <211> LENGTH: 23 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <400> SEQUENCE: 55	
actccgtgtc cagcaggact ctg	23
<210> SEQ ID NO 56 <211> LENGTH: 24 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <400> SEQUENCE: 56	
tgcgtgttcc tggaccctca cgtg	24
<210> SEQ ID NO 57 <211> LENGTH: 29 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <400> SEQUENCE: 57	
caggccttgg attttaatgt cagggatgg	29
<210> SEQ ID NO 58 <211> LENGTH: 27 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <400> SEQUENCE: 58	
ggagagtcag ctctgaaaga attcagg	27
<210> SEQ ID NO 59 <211> LENGTH: 27 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <400> SEQUENCE: 59	

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tgatgtgatg ccagatacta atagcac 27

<210> SEQ ID NO 60
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

cctgattcat ttaggtgaga ttgagac 27

<210> SEQ ID NO 61
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

gacaggtacc ttgccatcaa g 21

<210> SEQ ID NO 62
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

ctgcacaatg ccagtataa gg 22

<210> SEQ ID NO 63
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

ctgacttett gttcctggca gcagcgg 27

<210> SEQ ID NO 64
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

agaccagcca gggcacgctg aagagtg 27

<210> SEQ ID NO 65
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

gatcaagctt ccacccact gaaacctgg tc 32

<210> SEQ ID NO 66
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

gatcagatct cagttccaat attcacacca ccgtc 35

<210> SEQ ID NO 67
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 67
ctggtgtgct ccatggcatc cc 22

<210> SEQ ID NO 68
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68
gtaagcctcc cagaacgaga gg 22

<210> SEQ ID NO 69
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69
cagcgcaggg tgaagcctga gagc 24

<210> SEQ ID NO 70
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70
ggcacctgct gtgacctgtg cagg 24

<210> SEQ ID NO 71
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71
gtcctgccac ttcgagacat gg 22

<210> SEQ ID NO 72
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72
gaaacttctc tgcccttacc gtc 23

<210> SEQ ID NO 73
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73
ccaacaccag catccatggc atcaag 26

<210> SEQ ID NO 74
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74
ggagagtcag ctctgaaaga attcagg 27

What is claimed is:

1. A method for identifying a compound for regulating insulin concentration in the blood of a mammal comprising the steps of:

contacting one or more candidate compounds with a host cell that expresses a receptor comprising the amino acid sequence of SEQ ID NO: 8; and

measuring the ability of the compound or compounds to inhibit or stimulate said receptor, wherein said inhibition or stimulation of said receptor is indicative of a compound for regulating insulin concentration in the blood of a mammal.

2. The method of claim 1 wherein said compound for regulating insulin concentration in the blood of a mammal is a therapeutic for treating diabetes.

3. The method of claim 1 wherein the compound for regulating insulin concentration in the blood of a mammal is selected from agonist, partial agonist, and inverse agonist of the receptor.

4. The method of claim 1 wherein said host cell comprises an expression vector, said expression vector comprising a polynucleotide, said polynucleotide comprising a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 8.

5. The method of claim 1 where said host cell is produced by a method comprising:

transfecting a cell with an expression vector, said expression vector comprising a polynucleotide, said polynucleotide comprising a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 8;

wherein said host cell, under appropriate culture conditions, produces a polypeptide comprising said amino acid sequence of SEQ ID NO: 8.

6. A method for identifying a compound for regulating glucose concentration in the blood of a mammal comprising the steps of:

contacting one or more candidate compounds with a host cell that expresses a receptor comprising the amino acid sequence of SEQ ID NO: 8; and

measuring the ability of the compound or compounds to inhibit or stimulate said receptor, wherein said inhibition or stimulation of said receptor is indicative of a compound for regulating glucose concentration in the blood of a mammal.

7. The method of claim 6 wherein said host cell comprises an expression vector, said expression vector comprising a polynucleotide, said polynucleotide comprising a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 8.

8. The method of claim 6 where said host cell is produced by a method comprising:

transfecting a cell with an expression vector, said expression vector comprising a polynucleotide, said polynucleotide comprising a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 8;

wherein said host cell, under appropriate culture conditions, produces a polypeptide comprising said amino acid sequence of SEQ ID NO: 8.

9. A method for identifying a compound for regulating glucagon concentration in the blood of a mammal comprising the steps of:

contacting one or more candidate compounds with a host cell that expresses a receptor comprising the amino acid sequence of SEQ ID NO: 8; and

measuring the ability of the compound or compounds to inhibit or stimulate said receptor, wherein said inhibition or stimulation of said receptor is indicative of a compound for regulating glucagon concentration in the blood of a mammal.

10. The method of claim 9 wherein said host cell comprises an expression vector, said expression vector comprising a polynucleotide, said polynucleotide comprising a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 8.

11. The method of claim 9 where said host cell is produced by a method comprising:

transfecting a cell with an expression vector, said expression vector comprising a polynucleotide, said polynucleotide comprising a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 8;

wherein said host cell, under appropriate culture conditions, produces a polypeptide comprising said amino acid sequence of SEQ ID NO: 8.

12. A method for identifying a compound for inhibiting or stimulating a receptor comprising:

a) the amino acid sequence of SEQ ID NO: 8;

b) a mutant of SEQ ID NO: 8, wherein lysine is substituted for leucine at amino acid residue 224;

c) an amino acid sequence encoded by a nucleotide sequence that hybridizes to the complete complement of SEQ ID NO: 7 at 42° C., followed by washing in 0.1× SSC at 65° C.;

d) an amino sequence encoded by the nucleotide sequence of SEQ ID NO: 7;

e) a G protein-coupled receptor having at least 95% identity to the amino acid sequence of SEQ ID NO: 8, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels; or

f) a G protein-coupled receptor encoded by a nucleotide sequence having at least 95% identity to the nucleotide sequence of SEQ ID NO: 7, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels,

comprising the steps of:

i) contacting one or more candidate compounds with a host cell or membrane thereof,

wherein said host cell or membrane expresses a receptor comprising:

a) the amino acid sequence of SEQ ID NO: 8;

b) a mutant of SEQ ID NO: 8, wherein lysine is substituted for leucine at amino acid residue 224;

c) an amino acid sequence encoded by a nucleotide sequence that hybridizes to the complete complement of SEQ ID NO: 7 at 42° C., followed by washing in 0.1× SSC at 65° C.;

d) an amino sequence encoded by the nucleotide sequence of SEQ ID NO: 7;

e) a G protein-coupled receptor having at least 95% identity to the amino acid sequence of SEQ ID NO: 8, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels; or

f) a G protein-coupled receptor encoded by a nucleotide sequence having at least 95% identity to the nucleotide sequence of SEQ ID NO: 7, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels; and

ii) measuring the ability of the compound or compounds to inhibit or stimulate said receptor.

13. The method of claim 12, wherein the compound is selected from agonist, partial agonist, and inverse agonist of the receptor.

14. The method of claim 13, wherein the compound is an agonist of the receptor.

15. The method of claim 13, wherein the compound is a partial agonist of the receptor.

16. The method of claim 13, wherein the compound is an inverse agonist of the receptor.

17. The method of claim 12, wherein said host cell comprises an expression vector, said expression vector comprising a polynucleotide, said polynucleotide comprising:

a) a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 8;

b) a nucleotide sequence encoding a polypeptide comprising a mutant of SEQ ID NO: 8, wherein lysine is substituted for leucine at amino acid residue 224;

c) a nucleotide sequence that hybridizes to the complete complement of SEQ ID NO:7 at 42° C., followed by washing in 0.1×SSC at 65° C.;

d) the nucleotide sequence of SEQ ID NO: 7;

e) a nucleotide sequence encoding a G protein-coupled receptor having at least 95% identity to the amino acid sequence of SEQ ID NO: 8, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels; or

f) a nucleotide sequence having at least 95% identity to the nucleotide sequence of SEQ ID NO: 7, wherein said nucleotide sequence encodes a G protein-coupled receptor capable of modulating insulin or glucagon levels.

18. The method of claim 12, wherein said host cell is produced by a method comprising:

transfecting a cell with an expression vector, said expression vector comprising a polynucleotide, said polynucleotide comprising:

a) a nucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 8;

b) a nucleotide sequence encoding a polypeptide comprising a mutant of SEQ ID NO: 8, wherein lysine is substituted for leucine at amino acid residue 224;

c) a nucleotide sequence that hybridizes to the complete complement of SEQ ID NO:7 at 42° C., followed by washing in 0.1×SSC at 65° C.;

d) the nucleotide sequence of SEQ ID NO: 7;

e) a nucleotide sequence encoding a G protein-coupled receptor having at least 95% identity to the amino acid sequence of SEQ ID NO: 8, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels; or

f) a nucleotide sequence having at least 95% identity to the nucleotide sequence of SEQ ID NO: 7, wherein said nucleotide sequence encodes a G protein-coupled receptor capable of modulating insulin or glucagon levels,

wherein said host cell, under appropriate culture conditions, produces a polypeptide comprising:

a) the amino acid sequence of SEQ ID NO: 8;

b) a mutant of SEQ ID NO: 8, wherein lysine is substituted for leucine at amino acid residue 224;

c) an amino acid sequence encoded by a nucleotide sequence that hybridizes to the complete complement of SEQ ID NO:7 at 42° C., followed by washing in 0.1×SSC at 65° C.;

d) an amino sequence encoded by the nucleotide sequence of SEQ ID NO: 7;

e) a G protein-coupled receptor having at least 95% identity to the amino acid sequence of SEQ ID NO: 8, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels; or

f) a G protein-coupled receptor encoded by a nucleotide sequence having at least 95% identity to the nucleotide sequence of SEQ ID NO:7, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels.

19. The method of claim 12, wherein the receptor comprises the amino acid sequence of SEQ ID NO: 8.

20. The method of claim 12, wherein the receptor is a mutant of SEQ ID NO: 8, wherein lysine is substituted for leucine at amino acid residue 224.

21. The method of claim 12, wherein the ability of the compound or compounds to inhibit or stimulate said receptor is measured by measuring the activity of a second messenger.

22. The method of claim 21, wherein the second messenger is selected from the group consisting of adenylyl cyclase and phospholipase C.

23. The method of claim 12, wherein the ability of the compound or compounds to inhibit or stimulate said receptor is measured by measuring the level of a second messenger.

24. The method of claim 23, wherein the second messenger is selected from the group consisting of cAMP, diacyl glycerol, and inositol 1,4,5-triphosphate.

25. The method of claim 12, wherein the ability of the compound or compounds to inhibit or stimulate said receptor is measured by measuring the binding of GTPγS to a membrane comprising said G protein-coupled receptor.

26. The method of claim 12, wherein the host cell is a mammalian host cell.

27. The method of claim 12, wherein the host cell is a yeast host cell.

28. The method of claim 12, wherein the host cell comprises a reporter system comprising multiple cAMP responsive elements operably linked to a reporter gene.

29. The method of claim 12, wherein said receptor is a constitutively activated receptor.

30. The method according to claim 12, wherein said method comprises identifying a compound for inhibiting or stimulating a receptor comprising:

a) a G protein-coupled receptor having at least 98% identity to the amino acid sequence of SEQ ID NO: 8, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels; or

b) a G protein-coupled receptor encoded by a nucleotide sequence having at least 98% identity to the nucleotide sequence of SEQ ID NO:7, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels, comprising the steps of:

contacting one or more candidate compounds with a host cell or membrane thereof,

wherein said host cell or membrane expresses a receptor comprising:

a) a G protein-coupled receptor having at least 98% identity to the amino acid sequence of SEQ ID NO: 8, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels; or

b) a G protein-coupled receptor encoded by a nucleotide sequence having at least 98% identity to the nucleotide sequence of SEQ ID NO:7, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels, and measuring the ability of the compound or compounds to inhibit or stimulate said receptor.

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31. The method of claim 17, wherein said host cell comprises an expression vector, said expression vector comprising a polynucleotide, said polynucleotide comprising:

- a) a nucleotide sequence encoding a G protein-coupled receptor having at least 98% identity to the amino acid sequence of SEQ ID NO: 8, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels; or
- b) a nucleotide sequence having at least 98% identity to the nucleotide sequence of SEQ ID NO: 7, wherein said nucleotide sequence encodes a G protein-coupled receptor capable of modulating insulin or glucagon levels.

32. The method of claim 18, wherein said host cell is produced by a method comprising:

- transfecting a cell with an expression vector, said expression vector comprising a polynucleotide, said polynucleotide comprising:
 - a) a nucleotide sequence encoding a G protein-coupled receptor having at least 98% identity to the amino acid sequence of SEQ ID NO: 8, wherein said G

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protein-coupled receptor is capable of modulating insulin or glucagon levels; or

- b) a nucleotide sequence having at least 98% identity to the nucleotide sequence of SEQ ID NO: 7, wherein said nucleotide sequence encodes a G protein-coupled receptor capable of modulating insulin or glucagon levels,

wherein said host cell, under appropriate culture conditions, produces a polypeptide comprising:

- a) a G protein-coupled receptor having at least 98% identity to the amino acid sequence of SEQ ID NO: 8, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels; or
- b) a G protein-coupled receptor encoded by a nucleotide sequence having at least 98% identity to the nucleotide sequence of SEQ ID NO: 7, wherein said G protein-coupled receptor is capable of modulating insulin or glucagon levels.

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