Title: CADHERIN MATERIALS AND METHODS

Abstract

DNA sequences encoding novel cadherins, designated cadherins-4 through -12, are disclosed along with methods and materials for the recombinant production of the same. Antibody substances specific for the novel cadherins and cadherin peptides are disclosed as useful for modulating the natural binding and/or regulatory activities of the cadherins.
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CADHERIN MATERIALS AND METHODS

This application is a continuation-in-part of U.S. Patent Application Serial No. 07/872,643 filed on April 17, 1992.

FIELD OF THE INVENTION

The present invention relates, in general, to materials and methods relevant to cell-cell adhesion. More particularly, the invention relates to novel Ca^{2+}-dependent cell adhesion proteins, referred to as cadherins, and to polynucleotide sequences encoding the cadherins. The invention also relates to methods for inhibiting binding of the cadherins to their natural ligands/antiligands.

BACKGROUND

In vivo, cell-cell adhesion plays an important role in a wide range of events including morphogenesis and organ formation, leukocyte extravasation, tumor metastasis and invasion, and the formation of cell junctions. Additionally, cell-cell adhesion is crucial for the maintenance of tissue integrity, e.g., of the intestinal epithelial barrier, of the blood brain barrier and of cardiac muscle.

Intercellular adhesion is mediated by specific cell adhesion molecules. Cell adhesion molecules have been classified into at least three superfamilies including the immunoglobulin (Ig) superfamily, the integrin superfamily and the cadherin superfamily. All cell types that form solid tissues express some members of the cadherin superfamily suggesting that cadherins are involved in selective adhesion of most cell types.

Cadherins have been generally described as glycosylated integral membrane proteins that have an N-terminal extracellular domain that determines binding specificity (the N-terminal 113 amino acids appear to be directly involved in binding), a hydrophobic membrane-spanning domain and a C-terminal cytoplasmic domain (highly conserved among the members of the superfamily) that interacts with the cytoskeleton through catenins and other cytoskeleton-associated proteins. Some cadherins lack a cytoplasmic domain, however, and
appear to function in cell-cell adhesion by a different mechanism than cadherins that do have a cytoplasmic domain. The cytoplasmic domain is required for the binding function of the extracellular domain in cadherins that do have a cytoplasmic domain. Binding between members of the cadherin family expressed on different cells is mainly homophilic (i.e., a member of the cadherin family binds to cadherins of its own or a closely related subclass) and Ca\(^{2+}\)-dependent. For recent reviews on cadherins, see Takeichi, *Annu. Rev. Biochem.*, 59: 237-252 (1990) and Takeichi, *Science*, 251, 1451-1455 (1991).

The first cadherins to be described (E-cadherin in mouse epithelial cells, L-CAM in avian liver, uvomorulin in the mouse blastocyst, and CAM 120/80 in human epithelial cells) were identified by their involvement in Ca\(^{2+}\)-dependent cell adhesion and by their unique immunological characteristics and tissue localization. With the later immunological identification of N-cadherin, which was found to have a different tissue distribution from E-cadherin, it became apparent that a new family of Ca\(^{2+}\)-dependent cell-cell adhesion molecules had been discovered.

an antibody generated to bovine aortic endothelial cells recognized an intercellular junctional molecule designated V-cadherin which had a similar molecular weight to known cadherins and was able to inhibit Ca²⁺-dependent cell endothelial cell adhesion. The article did not disclose any sequence information for the protein recognized by the antibody.


The determination of the tissue expression of the various cadherins reveals that each subclass of cadherins has a unique tissue distribution pattern. For example, E-cadherin is found in epithelial tissues while N-cadherin is found in nonepithelial tissues such as neural and muscle tissue. The unique expression pattern of the different cadherins is particularly significant when the role each subclass of cadherins may play in vivo in normal events (e.g., the maintenance of the intestinal epithelial barrier) and in abnormal events (e.g., tumor metastasis or inflammation) is considered. Suppression of cadherin function has been implicated in the progression of various cancers. See Shimoyama et al., Cancer Res., 52: 5770-5774 (1992). Different subclasses or combinations of subclasses of cadherins are likely to be responsible for different cell-cell adhesion events in which therapeutic detection and/or intervention may be desirable. Studies have also suggested that cadherins may have some regulatory activity in addition to adhesive activity. Matsunaga et al., Nature, 334, 62-64 (1988) reports that N-cadherin has neurite outgrowth promoting activity and Mahoney et al., Cell, 67,
853-868 (1991) reports that the Drosophila fat tumor suppressor gene, another member of the cadherin superfamily, appear to regulate cell growth. Expression of the cytoplasmic domain of N-cadherin without its extracellular domain has been shown in Kintner et al., Cell, 69: 229-236 (1992) to disrupt embryonic cell adhesion and in Fugimori et al., Mol. Biol. Cell, 4: 37-47 (1993) to disrupt epithelial cell adhesion. Thus, therapeutic intervention in the regulatory activities of cadherins expressed in specific tissues may also be desirable.

There thus continues to exist a need in the art for the identification and characterization of additional cadherins participating in cell-cell adhesion and/or regulatory events. Moreover, to the extent that cadherins might form the basis for the development of therapeutic and diagnostic agents, it is essential that the genes encoding the proteins be cloned. Information about the DNA sequences and amino acid sequences encoding the cadherins would provide for the large scale production of the proteins and for the identification of the cells/tissues naturally producing the proteins, and would permit the preparation of antibody substances or other novel binding molecules specifically reactive with the cadherins that may be useful in modulating the natural ligand/antiligand binding reactions in which the cadherins are involved.

**SUMMARY OF THE INVENTION**

The present invention provides materials and methods that are relevant to cell-cell adhesion. In one of its aspects, the present invention provides purified and isolated polynucleotide sequences (e.g., DNA and RNA, both sense and antisense strands) encoding novel cadherins, cadherin-4 through -12. Preferred polynucleotide sequences of the invention include genomic and cDNA sequences as well as wholly or partially synthesized DNA sequences, and biological replicas thereof (i.e., copies of purified and isolated DNA sequences made in vivo or in vitro using biological reagents). Biologically active vectors comprising the polynucleotide sequences are also contemplated.
The scientific value of the information contributed through the disclosures of the DNA and amino acid sequences of the present invention is manifest. For example, knowledge of the sequence of a cDNA encoding a cadherin makes possible the isolation by DNA/DNA hybridization of genomic DNA sequences that encode the protein and that specify cadherin-specific expression regulating sequences such as promoters, enhancers and the like. DNA/DNA hybridization procedures utilizing the DNA sequences of the present invention also allow the isolation of DNAs encoding heterologous species proteins homologous to the rat and human cadherins specifically illustrated herein.

According to another aspect of the invention, host cells, especially eucaryotic and procaryotic cells, are stably transformed or transfected with the polynucleotide sequences of the invention in a manner allowing the expression of cadherin polypeptides in the cells. Host cells expressing cadherin polypeptide products, when grown in a suitable culture medium, are particularly useful for the large scale production of cadherin polypeptides, fragments and variants; thereby enabling the isolation of the desired polypeptide products from the cells or from the medium in which the cells are grown.

The novel cadherin proteins, fragments and variants of the invention may be obtained as isolates from natural tissue sources, but are preferably produced by recombinant procedures involving the host cells of the invention. The products may be obtained in fully or partially glycosylated, partially or wholly de-glycosylated or non-glycosylated forms, depending on the host cell selected or recombinant production and/or post-isolation processing.

Cadherin variants according to the invention may comprise polypeptide analogs wherein one or more of the specified (i.e., naturally encoded) amino acids is deleted or replaced or wherein one or more nonspecified amino acids are added: (1) without loss, and preferably with enhancement, of one or more of the biological activities or immunological characteristics specific for a
cadherin; or (2) with specific disablement of a particular ligand/antiligand binding function of a cadherin.

Also contemplated by the present invention are antibody substances [e.g., monoclonal and polyclonal antibodies, chimeric and humanized antibodies, and antibody domains including Fab, Fab', and F(\(ab')_2\), single chain antibodies, and Fv or single variable domains] and other binding proteins or peptides specifically react with cadherins of the invention. Antibody substances can be developed using isolated natural, recombinant or synthetic cadherin polypeptide products or host cells expressing such products on their surfaces. The antibody substances may be utilized for purifying polypeptides of the invention, for determining the tissue expression of the polypeptides and as antagonists of the ligand/antiligand binding activities of the cadherins. Specifically illustrating antibody substances of the invention are the monoclonal antibodies produced by the hybridomas designated 30Q8A, 30Q4H, 45A5G, 30S2F and 45C6A which were all deposited with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852 on April 6, 1993 and were respectively assigned ATCC Deposit Nos. HB11316, HB11317, HB11318, HB11319 and HB11320. Also illustrating antibody substances of the invention is the monoclonal antibody produced by the hybridoma designated 30T11G which was deposited with the ATCC on April 8, 1993 and was assigned ATCC Deposit No. HB11324.

The DNA and amino acid sequence information provided by the present invention makes possible the systematic analysis of the structure and function of the cadherins described herein and definition of those molecules with which the cadherins will interact on extracellular and intracellular levels. The idiotypes of anti-cadherin monoclonal antibodies of the invention are representative of such molecules and may mimic natural binding proteins (peptides and polypeptides) through which the intercellular and intracellular activities of cadherins are modulated. Alternately, they may represent new classes of
modulators of cadherin activities. Anti-idiotypic antibodies, in turn, may represent new classes of biologically active cadherin equivalents.

Methods for modulating cadherin activity may involve contacting a cadherin with an antibody (or antibody fragment), another polypeptide or peptide ligand (including peptides derived from cadherins or other proteins, or a novel peptide), or a small molecule ligand that specifically binds to a portion (extracellular or cytoplasmic) of the cadherin.

Numerous aspects and advantages of the present invention will be apparent upon consideration of the following detailed description thereof, reference being made to the drawing wherein:

FIGURE 1 is a bar graph illustrating the binding of polymorphonuclear neutrophils and T cells to fusion proteins comprising extracellular subdomains of cadherin-5.

DETAILED DESCRIPTION

The present invention is illustrated by the following examples wherein Example 1 describes the isolation of cDNA sequences encoding rat cadherins-4 through -11 and -13; Example 2 describes the isolation of cDNA sequences encoding the human homologs of rat cadherins-4, -5, -6, -8, -10, -11 and -13 and the isolation of a human cadherin not identified in rat, cadherin-12;

Example 3 characterizes the relationship of cadherins of the invention to previously identified cadherins in terms of amino acid sequence and structure. The generation of polyclonal and monoclonal antibodies specific for cadherins of the invention is described in Example 4. Example 5 describes the construction of expression constructs comprising cadherin-4, -5 and -8 sequences, transfection of mammalian cells with the constructs and results of cell-cell adhesion assays performed with the transfected cells. Example 6 presents the results of assays for cadherin mRNA and protein expression in various mammalian tissues, cells and cell lines. The results of in vitro transendothelial migration assays involving

Example 1

Partial cDNA clones encoding nine novel cadherins were isolated from rat brain and retina by PCR. Eight of the novel rat cadherin cDNAs were isolated using degenerate PCR primers based on highly conserved regions of the cytoplasmic domain of known cadherins and one was isolated using degenerate PCR primers based on moderately conserved regions of the extracellular domain of known cadherins.

A. Preparation of Rat cDNA

Total RNAs were prepared from rat brain by the guanidium isothiocyanate/cesium chloride method described in Maniatis et al., pp. 196 in Molecular Cloning: A Laboratory Manual, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory (1982). Brain poly(A)* RNAs were then isolated using an Invitrogen (San Diego, CA) FastTrack kit. Rat retina poly(A)* RNA was purchased from Clonetics (Palo Alto, CA). cDNA was synthesized from the poly(A)* RNA of both rat brain and retina using a cDNA synthesis kit (Boehringer Mannheim Corporation, Indianapolis, IN).
B. Design and Synthesis of PCR Primers

Corresponding to Cadherin Cytoplasmic Domain

A first pair of degenerate oligonucleotide primers, listed below in IUPAC nomenclature, was designed to correspond to highly conserved sequences in the cytoplasmic domain of mouse N-, E-, and P-cadherins. Underlined sequences at the end of each oligonucleotide indicate an EcoR1 site added to the primers to facilitate cloning of the fragments generated by PCR.

Degenerate Primer 1

**TAPPYD** (SEQ ID NO: 1)

5' GAATTCACNGCNCCNCCNTAYGA 3' (SEQ ID NO: 2)

Degenerate Primer 2

**FKKLAD** (SEQ ID NO: 3)

3' AARTTYTTRYRANCNCTCTTAAG 5' (SEQ ID NO: 4)

The degenerate oligonucleotides were synthesized using the Applied Biosystems model 380B DNA synthesizer (Foster City, CA).

C. Design and Synthesis of PCR Primers

Corresponding to Cadherin Extracellular Domain

A second pair of degenerate oligonucleotide primers, listed below in IUPAC nomenclature, was designed to correspond to moderately conserved sequences in the third subdomain of the extracellular domain of mouse N-, E-, and P-cadherins. The extracellular domains of the mouse N-, E- and P-cadherins have been characterized as having five internal subdomains, some of which may be involved in cadherin interaction with Ca^{2+}. Underlined sequences at the end of each oligonucleotide indicate an EcoR1 site added to the primers to facilitate cloning of the fragments generated by PCR.
Degenerate Primer 3
\[ K(P/G)(L/I/V)D(F/Y)E \quad (\text{SEQ ID NO: 5}) \]
\[ 5' \text{GAATTCAARSSNNTNGAYTWYG} \text{A} 3' \quad (\text{SEQ ID NO: 6}) \]

Degenerate Primer 4
\[ (N/D)E(A/P)\text{PXF} \quad (\text{SEQ ID NO: 7}) \]
\[ 3' \text{TRCTYSGNNGNNNAARCTTAAG} 5' \quad (\text{SEQ ID NO: 8}) \]

D. Cloning of cDNA Encoding Eight Novel Rat Cadherins

PCR amplification reactions of rat brain and retina cDNA were carried out either with degenerate primers 1 and 2 or with degenerate primers 3 and 4 under conditions essentially the same as those described in Saiki et al., *Science*, 239, 487-491 (1988). Briefly, 100 ng of brain or retina first strand cDNA was used as template for amplification by Taq DNA polymerase (International Biotechnology, New Haven, CT) using 10 \( \mu \text{g} \) of each primer set per reaction. PCR reactions were initiated by adding 2 units of Taq DNA polymerase to the reaction solution, after which 35 PCR reaction cycles were carried out. Reaction cycles consisted of denaturation performed at 94 °C for 1.5 minutes, oligonucleotide annealing at 45 °C for 2 minutes, and elongation at 72 °C for 3 minutes. The resulting PCR fragments were separated by agarose gel electrophoresis, and DNA bands of the expected size were extracted from the gel and digested with *EcoR*1. The fragments were then cloned into the M13 vector (Boehringer Mannheim Corp., Indianapolis, IN) and *E. coli* JM101 cells were transformed with the resulting constructs. Individual clones were then isolated and sequenced. Sequencing of the DNAs was carried out using a sequenase kit (United States Biochemicals, Cleveland, OH) and the resulting DNA and deduced amino acid sequences of the clones were compared to sequences of known cadherins using the Microgenie program (Beckman, Fullerton, CA).
Ten representative cDNA clones encoding cadherins were identified from the PCR reaction based on degenerate primers 1 and 2. Two clones corresponded to rat N-, and E-cadherins, but eight clones encoded previously undescribed cadherins, and were designated cadherins-4 through -11. The DNA and deduced amino acid sequences of the eight rat cytoplasmic domain cDNA clones are respectively set out in SEQ ID NOs: 9 and 10 (cadherin-4), SEQ ID NOs: 11 and 12 (cadherin-5), SEQ ID NOs: 13 and 14 (cadherin-6), SEQ ID NOs: 15 and 16 (cadherin-7), SEQ ID NOs: 17 and 18 (cadherin-8), SEQ ID NOs: 19 and 20 (cadherin-9), SEQ ID NOs: 21 and 22 (cadherin-10) and SEQ ID NOs: 23 and 24 (cadherin-11).

An additional novel cadherin was identified from the PCR reaction based on degenerate primers 3 and 4, and it was designated cadherin-13. The DNA and deduced amino acid sequences of the rat cadherin-13 fragment are respectively set out in SEQ ID NOs: 25 and 26.

The PCR reaction based on degenerate primers 3 and 4 also amplified sequences which were later determined to be fragments of the extracellular domains of rat cadherins 4, -5, -6, -8, -9, -10, -11 and -13. The DNA and amino acid sequences of these extracellular fragments are respectively set out in SEQ ID NOs: 27 and 28 (cadherin-4), SEQ ID NOs: 29 and 30 (cadherin-6), SEQ ID NOs: 31 and 32 (cadherin-8), SEQ ID NOs: 33 and 34 (cadherin-9), SEQ ID NOs: 35 and 36 (cadherin-10), SEQ ID NOs: 37 and 38 (cadherin-11), SEQ ID NOs: 39 and 40 (cadherin-13).

Larger cadherin-8 and -10 cDNAs were isolated from a rat brain cDNA library made in Uni-ZAP vector (Stratagene, La Jolla, CA) using labelled cadherin-8 extracellular domain PCR fragment (SEQ ID NO: 17) or cadherin-10 extracellular domain fragment (SEQ ID NO: 21) as probes. Two types of cadherin-8 cDNA clones were isolated. The first type encodes a full length cadherin, but the second type encodes a truncated protein the sequence of which diverges from the first type of cadherin-8 clone near the N-terminus of the fifth
extracellular subdomain (EC5). The truncated clone contains a short stretch of unique sequence in the N-terminus of EC5 but lacks the remainder of EC5, the transmembrane domain and the cytoplasmic domain. DNA and deduced amino acid sequences of the full length clone are respectively set out in SEQ ID NOs: 41 and 42 and the DNA and deduced amino acid sequences of the truncated cadherin-8 clone are set out in SEQ ID NOs: 43 and 44. The cadherin-10 cDNA clone that was isolated has an open reading frame which begins at a region corresponding to the middle of the first extracellular domain (EC1) of previously identified cadherins. The DNA and deduced amino acid sequences of the cadherin-10 clone are set out in SEQ ID NOs: 45 and 46.

**Example 2**

Full length cDNAs encoding human homologs of rat cadherins-4, -8, -11 and -13 and partial cDNAs encoding human homologs of rat cadherins-6 and -10 were isolated from a human fetal brain cDNA library (λZapII vector, Stratagene). A full length cDNA encoding a human homolog of rat cadherin-5 was isolated from a human placental cDNA library (λgt11 vector, Dr. Millan, La Jolla Cancer Research Foundation, La Jolla, CA).

Probes for screening the human fetal brain and placental cDNA libraries were amplified by PCR from human brain cDNA (Dr. Taketani, Kansain Medical University, Moriguchi, Osaka, Japan) using the primers described in Example 1B-C. Probes consisting of human cadherin-4, -5, -6, -8, -10 and -11 sequences were generated using degenerate primers 1 and 2 and probes consisting of human cadherin-13 sequence were generated using degenerate primers 3 and 4. Amplification of the human fetal brain cDNA with degenerate primers 3 and 4 also generated a PCR fragment encoding a cadherin not isolated from rat, designated cadherin-12.

PCR fragments encoding human cadherins-4, -5, -6, -8, -10, -11, -12 and -13 were labelled with ³²p and used to probe the human fetal brain and
placental cDNA libraries according to the plaque hybridization method described in Ausubel et al., Eds., *Current Protocols in Molecular Biology*, Sections 6.1.1 to 6.1.4 and 6.2.1 to 6.2.3, John Wiley & Sons, New York (1987). Positives were plaque-purified and inserts were cut out using an in vivo excision method. The inserts were then subcloned into the M13 vector (Boehringer Mannheim) for sequencing.

Inserts consisting of full length cDNAs encoding human homologs of rat cadherins-4, -8, -11, -12 (putative) and -13 and partial cDNAs encoding human homologs of rat cadherins-6 and -10 were identified in clones from the human fetal brain cDNA library and a full length cDNA encoding a human homolog of rat cadherin-5 was identified in a clone from the human placental cDNA library. The DNA and deduced amino acid sequences of the human homologs are respectively set out in SEQ ID NOS: 47 and 48 (cadherin-4), SEQ ID NOS: 49 and 50 (cadherin-5), SEQ ID NOS: 51 and 52 (cadherin-6), SEQ ID NOS: 53 and 54 (cadherin-8), SEQ ID NOS: 55 and 56 (cadherin-10), SEQ ID NOS: 57 and 58 (cadherin-11), SEQ ID NOS: 59 and 60 (cadherin-12), and SEQ ID NOS: 61 and 62 (cadherin-13).

**Example 3**

Comparison of the full-length sequences of the novel human cadherins described in Examples 1 and 2 with sequences of previously described cadherins and cadherin-related proteins provides support for the proposal that cadherins can be divided into at least three subgroups based on amino acid sequence identity and/or domain structure. Identity values for one possible alignment of the sequences of the extracellular domains of selected human cadherins are presented in Table 1 below.
Based on such sequence alignments and on the fact that certain combinations of cadherin sequences seem to have conserved stretches of amino acids when aligned, one subgroup of cadherins may include E-cadherin, N-cadherin, P-cadherin and cadherin-4, while a second subgroup may include cadherin-5, cadherin-8, cadherin-11 and cadherin-12. Cadherins-6, -7, -9 and -10 may also be included with the second subgroup based on their partial amino acid sequences disclosed herein. The amino acid sequence of cadherin-4 exhibits especially high amino acid sequence identity with that of R-cadherin (92%), indicating that cadherin-4 may be the human homolog of chicken R-cadherin. All cadherins in these two subgroups have a similar structure. Following an initiation codon, each has a signal sequence, prosequence, proteolytic cleavage site of precursor protein, an extracellular domain (which comprises five subdomains EC1-5), a transmembrane sequence and a cytoplasmic domain. For cadherin-5, these sequences/domains appear to correspond to about the following amino acid positions of SEQ ID NO: 50: 1-24 (signal sequence), 25-43 (prosequence), 44-147 (EC1), 148-254 (EC2), 255-368 (EC3), 369-475 (EC4), 476-589 (EC5), 590-616 (transmembrane sequence) and 617-780 (cytoplasmic domain).
Cadherin-13, T-cadherin and V-cadherin may be representative of a third subgroup of cadherins. Cadherin-13 consists of a cadherin-like extracellular domain, but has no domains that would correspond to the typical transmembrane or cytoplasmic domains of other cadherins. Even though about 10% of the clones obtained by PCR using degenerate primers 3 and 4 were cadherin-13 clones, none of the clones included sequences corresponding to a cytoplasmic domain. An attempt to isolate a cDNA that contained this region by PCR using a primer corresponding to the most C-terminal region of cadherin-13 available and a mixed oligonucleotide primer corresponding to a well-conserved amino acid sequence of the cytoplasmic domain of cadherins failed to generate any product with the anticipated molecular weight. A similar protein, T-cadherin, has been identified in chicken which also lacks the typical cadherin cytoplasmic domain. The amino acid sequence identity between the two molecules is about 80%. Cadherin-13 may be the human homologue of chicken T-cadherin or may be a closely related molecule. Human cadherin-13 and avian T-cadherin may also both be closely related to V-cadherin. A 29-amino acid amino terminal sequence of bovine V-cadherin is similar to the start of the precursor region of cadherin-13 (93%) and T-cadherin (79%). V-cadherin is a 135 KD protein which appears to be restricted in tissue distribution to endothelium. In contrast, mature T-cadherin has a molecular weight of 95 KD and shows a wide tissue distribution. Both V-cadherin and T-cadherin are linked to the cell membrane through phosphoinositol.

Example 4

Polyclonal and/or monoclonal antibodies specific for cadherins of the invention were generated.

A. Generation of Polyclonal Antibodies

Bacterial fusion proteins consisting of maltose binding protein fused to portions of cadherin extracellular subdomains (either human cadherin-4, -5 or
-11, or rat cadherin-8) were generated and subsequently used for the generation of polyclonal antibodies.

A cDNA fragment corresponding to a 40 KD portion of the extracellular domain of human cadherin-5 (nucleotides 535 to 1527 of SEQ ID NO: 49) was synthesized by PCR from the full-length human cadherin-5 cDNA described in Example 2. The fragment was subcloned into the multicloning site (EcoR1-XbaI) of the pMAL-RI plasmid vector [New England Biolabs Inc. (NEB), Beverly, MA]. The resulting construct encodes maltose binding protein fused to the extracellular domain of cadherin-5. Constructs encoding maltose binding protein fused to the three N-terminal subdomains of human cadherin-4, rat cadherin-8 and human cadherin-11 were generated by similar methods.

E. coli NM522 cells (Stratagene) were then transformed with one of the fusion protein constructs and grown in quantity. After disruption of E. coli cells, the individual fusion proteins were purified by affinity column chromatography using amylose resin (NEB) according to the instructions of the manufacturer. When subjected to SDS-PAGE, the purified fusion proteins each showed essentially one band of the expected size.

A total of five hundred µg of a fusion protein in Freund's complete adjuvant was injected into rabbits at four subcutaneous sites. Subsequent injections were carried out at three week intervals using 100 µg of the fusion protein in Freund's incomplete adjuvant also at four subcutaneous sites. The resulting polyclonal sera generated from immunization of rabbits with cadherin-4, -5 or -8 fusion protein were collected and tested for specificity on L cells transfected with the appropriate cadherin sequence (see Example 5). Polyclonal serum generated from immunization of rabbits with cadherin-11 was also collected.

Immunoblotting of various cell types showed that the anti-cadherin-4 polyclonal serum reacts with protein of about 130 KD in L cells transfected with full length cadherin-4 cDNA and in rat brain. Cadherin-5-specific serum reacts with a protein of about 135 KD in L cells transfected with
a full length cadherin-5 DNA and with a protein of about 135 KD in human umbilical vein endothelial cells (HUVECs). The serum does not react with MDCK cells that expressed high levels of E-cadherin. In bovine aortic endothelial cells, the anti-cadherin-5 serum reacts with a protein of about 120 KD. Additionally, the anti-cadherin-5 serum reacts with a protein which has the same molecular weight in rat brain endothelial cells in culture. The cadherin-8 polyclonal antibody detected a strong band of about 90 KD and a weak band of about 130 KD in rat brain.

B. Generation of Monoclonal Antibodies Specific for Human Cadherin-5

Monoclonal antibodies to cadherin-5 were prepared using bacterial fusion proteins containing subdomains of the extracellular domain of human cadherin-5 as immunogens. The fusion proteins prepared included maltose binding protein and the extracellular subdomains 1-2 (EC1-2) or extracellular subdomains 2-4 (EC2-4) of cadherin-5 in the bacterial expression vector pMAL (NEB). The two fusion proteins were expressed in bacteria and purified on amylose-sepharose as described in foregoing section on generation of polyclonal antibodies. The purified fusion proteins were used separately to immunize mice at two subcutaneous sites (100 µg of fusion protein per mouse in Freund’s complete adjuvant). The mice then were subcutaneously immunized with Freund’s incomplete adjuvant.

The spleen from each mouse was removed sterility and treated in the same manner. Briefly, a single-cell suspension was formed by grinding the spleen between the frosted ends of two glass microscope slides submerged in serum free RPMI 1640 supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 100 units/ml penicillin and 100 µg/ml streptomycin (RPMI) (Gibco, Canada). The cell suspension was filtered through a sterile 70-mesh cell strainer, and washed twice by centrifuging at 200 g for 5 minutes and resuspending the pellet in 20 ml serum free RPMI. Thymocytes taken from 3 naive Balb/c mice were prepared in a similar manner. NS-1 myeloma cells, kept in log phase in
RPMI with 11% fetal bovine serum (FBS) (HyClone Laboratories, Inc., Logan, UT) for three days prior to fusion, were centrifuged at 200 g for 5 minutes, and the pellet was washed twice as described for the mouse spleen cells.

After washing, the spleen cells and myeloma cells were brought to a final volume of 10 ml in serum free RPMI, and 10 μl of that final volume was diluted 1:100 in serum free RPMI. Twenty μl of each dilution was removed, mixed with 20 μl 0.4% trypan blue stain in 0.85% saline, loaded onto a hemacytometer and counted. Two x 10^8 spleen cells were combined with 4 x 10^7 NS-1 cells, centrifuged and the supernatant was aspirated. The cell pellets were dislodged by tapping the tube and 2 ml of 37°C PEG 1500 (50% in 75 mM Hepes, pH 8.0) (Boehringer Mannheim) was added with stirring over the course of 1 minute, followed by adding 14 ml of serum free RPMI over 7 minutes. An additional 16 ml RPMI was added and the cells were centrifuged at 200 g for 10 minutes. After discarding the supernatant, the pellet was resuspended in 200 ml RPMI containing 15% FBS, 100 mM sodium hypoxanthine, 0.4 mM aminopterin, 16 mM thymidine (HAT) (Gibco), 25 units/ml IL-6 (Boehringer Mannheim) and 1.5 x 10^6 thymocytes/ml (plating medium). The suspension was dispensed into ten 96-well flat bottom tissue culture plates at 200 ml/well. Cells in plates were fed on days 2, 4, and 6 days post-fusion by aspirating approximately 100 ml from each well with an 18 G needle, and adding 100 ml/well plating medium described above except containing 10 units/ml IL-6 and lacking thymocytes.

Fusions 30 (from a mouse immunized with EC2-4) and 45 (from a mouse immunized with EC1-2) were screened initially by antibody capture ELISA, testing for presence of mouse IgG. Secondary screening of fusions 30 and 45 consisted of assays using plates coated with a monolayer of fixed endothelial cells for ELISAs. HUVEcs, Lewis rat brain endothelial cells (LeBCE), and bovine aortic endothelial cells (BAE) were allowed to grow in 96-well flat bottom tissue culture microtiter plates until the bottom of well was completely covered with a monolayer of cells. Plates were washed twice with
100 μl/well of Ca²⁺/Mg²⁺ free PBS (CMF-PBS) and aspirated completely. Cells were then fixed with 100 μl/well of 3% ρ-Formaldehyde, 1% Sucrose in CMF-PBS at room temperature for 30 minutes. Cells were then permeabilized with approximately 250 μl/well of CSK buffer (0.5% Triton 100, 100mM NaCl, 10mM PIPES, 2mM MgCl) and incubated at room temperature for 30 minutes. Plates were blocked with 250 μl/well of 2% BSA in 1X CMF-PBS (blocking solution) and incubated at 37°C for 60 minutes. Blocking solution was aspirated and 50 to 100 μl/well of supernatant from fusion plates was added. Plates were incubated at room temperature for 60 minutes and then were washed one time with 250 μl/well of 0.5% BSA in CMF-PBS (wash solution 1) and two times with 250 μl/well of CMF-PBS (wash solution 2). One hundred fifty μl of horseradish peroxidase conjugated goat anti-mouse IgG(fc) (Jackson ImmunoResearch, West Grove, PA) diluted 1:3500 in PBST was added and plates were incubated at room temperature for 60 minutes. Plates were washed as before and 150 μl substrate consisting of 1mg/ml o-phenylene diamine (Sigma) and 0.1 ml/ml 30% H₂O₂ in 100mM Citrate, pH 4.5 was added. The color reaction was stopped after 30 minutes with the addition of 50 μl of 15% H₂SO₄. A₄₉₀ was read on a plate reader (Dynatech). About 20 positive wells were identified for each fusion and were subsequently cloned.

Hybridomas were screened in cloning steps in an ELISA assay by testing for reactivity of monoclonals to the cadherin-5 EC2-4 fusion protein and excluding maltose binding protein reactive monoclonals. Immulon 4 plates (Dynatech, Cambridge, MA) were coated at 4°C with 50 μl/well fusion protein diluted to 0.1 μg/well (for fusion protein) and to 0.2 μg/well (for maltose binding protein alone) in 50mM carbonate buffer, pH 9.6. Plates were washed 3 times with PBS, 0.05% Tween 20 (PBST) and 50 μl hybridoma culture supernatant was added. After incubation at 37°C for 30 minutes, and washing as above, 50 μl of horseradish peroxidase conjugated goat anti-mouse IgG(fc) (Jackson ImmunoReseach, West Grove, PA) diluted 1:3500 in PBST was added. Plates
were incubated at 37°C for 30 minutes and washed 4 times with PBST. One hundred μl substrate consisting of 1 mg/ml o-phenylene diamine (Sigma Chemical Co., St. Louis, MO) and 0.1 μl 30% H₂O₂ in 100 mM citrate, pH 4.5 was added. The color reaction was stopped after 5 minutes with the addition of 50 μl of 15% H₂SO₄. Absorbance at 490 nm was determined using a plate reader.

The hybridomas designated 30Q8A (ATCC HB11316), 30Q4H (ATCC HB11317), 45A5G (HB11318), 30S2F (HB11319), 45C6A (HB11320), 30T11G (ATCC HB11324), 30M8G, 30O6E and 30R1A were identified as reactive with endothelial cells and with the cadherin-5 EC2-4 fusion protein. The hybridomas were cloned twice by limiting dilution and grown in ascites. The monoclonal antibodies produced by the hybridomas were isotyped in an ELISA assay. The results of the assay are presented in Table 2 below.

C. Subdomain Specificity of C5 Specific Monoclonal Antibodies

To determine if the hybridomas produced monoclonal antibodies reactive with unique epitopes of the extracellular domain of C5, the monoclonal antibodies were purified, biotinylated, and tested in a cross competition ELISA. Immulon IV 96-well plates were coated with either EC1-2 or EC2-4 cadherin-5 fusion protein at 0.2 μg/ml in 50 μl 50mM NaCO₃, pH 9.6 overnight at 4°C. The wells were aspirated and washed three times with PBS/0.05% Tween 20. The plate was then blocked with 50 μl/well PBS, 2% BSA (Sigma) for 30 minutes at 37°C. Monoclonal antibodies were purified from hybridoma supernatants over a protein A-Sepharose column and the eluted antibody was dialyzed against 0.1M NaCO₃ pH 8.2. One mg/ml of antibody was reacted with 60 μl of a 1 mg/ml stock solution in DMSO of NHS-biotin (Pierce Chemical Co., Rockford, IL) for 1 hour at room temperature and the reaction was stopped by dialysis overnight at 4°C against CMF/PBS. The biotinylated antibodies in PBS/0.05% Tween 20 were then added as primary antibody (50 μl/well) to a plate coated with fusion protein and incubated for 30 minutes at 37°C. The plate was then aspirated and washed three times with PBS/0.05% Tween 20. Peroxidase-conjugated
streptavidin in PBS/Tween was added 50 µl/well and incubated for 30 minutes at 37°C. The plate was aspirated and washed three times in PBS/0.05% Tween 20, and o-phenylenediamine in 100mM citrate buffer and hydrogen peroxide was added at 100 µl/well. The plate was developed at room temperature for 5-15 minutes. The reaction was stopped with 50 µl/well 15% sulfuric acid and the plate was read on a plate reader. Results of the assay are presented in Table 2 below.

To confirm subdomain specificity, the cadherin-5 fusion proteins EC1-2 and EC2-4 were run on SDS-PAGE (10%) and immunoblotted with the cadherin-5 specific monoclonal antibodies.

Table 2 below set outs the domain specificity and isotype of the cadherin-5 specific monoclonal antibodies.

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>C5 Subdomain</th>
<th>Isotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>30Q4H</td>
<td>2</td>
<td>IgG_{2b}</td>
</tr>
<tr>
<td>45A5G</td>
<td>2</td>
<td>IgG_{1}</td>
</tr>
<tr>
<td>45C6A</td>
<td>2</td>
<td>IgG_{1}</td>
</tr>
<tr>
<td>30S2F</td>
<td>3-4</td>
<td>IgG_{1}</td>
</tr>
<tr>
<td>30Q8A</td>
<td>3-4</td>
<td>IgG_{2b}</td>
</tr>
<tr>
<td>30T11G</td>
<td>3-4</td>
<td>IgG_{1}</td>
</tr>
</tbody>
</table>

Competition assays were carried out as described above for assays for binding to cadherin-5 EC2-4 fusion protein except that unlabelled primary cadherin-5 specific monoclonal antibodies (or mouse IgG) were added 30 minutes prior to addition of biotinylated cadherin-5 specific monoclonal antibodies. Monoclonal antibodies produced by the hybridomas 30M8G, 30O6E and 30RIA compete for a site that is near or identical to the binding site of the antibody produced by hybridoma 30Q4H.
Example 5

Human cadherins-4 and -5 and rat cadherin -8 were expressed in mouse fibroblast L cells (ATCC CCL1.3) which do not normally express cadherins.

A. Construction of Expression Vectors

The cDNA sequences encoding human cadherins-4 and -5 which are described in Example 2 and the cDNA sequence encoding rat cadherin-8 which is described in Example 1 were subcloned into the multicloning site of expression vector pRC/RSV (Invitrogen).

Cadherin-4 DNA sequences were isolated by an in vivo excision procedure from the λZapII clone (described in Example 2) containing the entire coding sequence of cadherin-4. Using a helper virus, the sequences were excised from λZapII in the form of Bluescript plasmid. The plasmid was then cut with HindIII and blunt-ended with T4 polymerase. The resulting DNA fragment was redigested with SpeI to generate a cadherin-4 cDNA fragment having a blunt end and a SpeI sticky end. The fragment was purified by agarose gel electrophoresis and subcloned into the pRC/RSV expression vector that had been previously digested with SpeI and XbaI (the XbaI end was blunt-ended with T4 polymerase).

The λgt11 clone containing the entire coding sequence of cadherin-5 (described in Example 2) was cut with EcoRI and the resulting fragment containing the cadherin-5 sequences was purified by agarose gel electrophoresis. The purified fragment was then subcloned into the EcoRI site of the Bluescript plasmid. Cadherin-5 sequences were cut from the resulting construct with HincII and XbaI and subcloned into the NotI-XbaI site of the pRC/RSV vector.

The full length cDNA encoding rat cadherin-8 was excised from the Uni-ZAP clone described in Example 1 by digestion with KpnI, followed by blunt-ending and re-digestion with SpeI. The cadherin-8 encoding fragment was purified by agarose gel electrophoresis and was subcloned into the pRC/RSV vector which had been digested with XbaI, blunt-ended and redigested with SpeI.
B. Transfection of L Cells

Mouse fibroblast L cells were transfected with the human cadherin-4 and -5 and rat cadherin-8 expression constructs by a Ca\textsuperscript{2+} phosphate precipitation method and stable transfectants were obtained by G418 selection. Cadherin-4 and -8 transfectant cells showed a morphology similar to that of parental L cells (fibroblastic), but cadherin-5 transfectant cells exhibited a flattened morphology. Neuro 2a cells (ATCC CCL131) were also transfected by a Ca\textsuperscript{2+} phosphate precipitation procedure with the cadherin-4 and cadherin-8 expression constructs. Cadherin-4 transfectants showed epithelial structure, suggesting that cadherin-4 has activity in epithelial structure formation and may be involved in the neural tissue development.

C. Northern and Western Blot Assays of Cadherin mRNA and Protein Expression in Transfected Cells

Both cadherin-4, -5 and -8 transfectants showed mRNA of the expected size of 3.5 kb, 3.2 kb and 3 kb, respectively, in Northern blot analysis using the appropriate full length human cDNAs as a probe. (See Example 6A for a description of the Northern blot assay.)

For Western blots, cadherin-4, -5 and -8 transfectants were washed with PBS and SDS-PAGE sample buffer was added directly to the cells. SDS-PAGE (Laemmli) was carried out and and gels were blotted electrophoretically onto PVDF membrane. The membranes were incubated in TBS containing 5% skim milk for 2 hours at room temperature and then were incubated with the appropriate polyclonal antibody in TBS containing 0.05% Tween 20 for 1 hour at room temperature. After four washes (of 5 minutes each) with TBS containing 0.05% Tween 20, the membranes were incubated with alkaline phosphatase conjugated anti-rabbit IgG antibody (Promega Corp., Madison, WI) in TBS containing 0.05% Tween 20 for 1 hour at room temperature. The membranes were then washed again four times with TBS containing 0.05% Tween 20 at room temperature and developed by using Promega Western blue. Cadherin-4, -5 and
8 polyclonal antibodies each reacted with a band of about 130 KD.

D. Calcium Protection from Trypsin Digestion

Since cadherins have been shown to be protected from trypsin digestion by Ca\(^{2+}\), the effect of Ca\(^{2+}\) on trypsin treatment (0.01% soybean trypsin for 30 minutes at 37°C) of human cadherin-4 and -5 and rat cadherin-8 expressed on the surface of transfected L cells was examined. Two mM Ca\(^{2+}\) protected the cadherin-4 from the trypsin digestion, but cadherin-5 and cadherin-8 were digested easily even in the presence of 1-5 mM of Ca\(^{2+}\).

E. Cell-Cell Adhesion Assay

The cell-cell adhesion activity of the transfected cells was assayed by a re-aggregation assay as described in Yoshida-Noro et al., *Devel. Biol.*, 101, 19-27 (1984). Briefly, transfecants were grown to near confluency and then dispersed into single cells with mild trypsin treatment (0.01% for 15 minutes) in the presence of 2 mM Ca\(^{2+}\). After washing, the trypsinized cells were incubated in Hepes buffered saline (HBS) containing 2 mM CaCl\(_2\), 1% BSA and 20 μg/ml deoxyribonuclease on a rotary shaker at 50 rpm for 30 to 60 minutes and then cell aggregation was monitored. Cadherin-4 transfecnt cells aggregated within 30 minutes and formed relatively large aggregates, whereas cadherin-5 transfecnt cells did not aggregate under the same conditions. However, cadherin-5 transfecnts gradually re-aggregated and formed relatively small aggregate after prolonged incubation (4-5 hours or more). Similarly, cadherin-8 transfecnts did not show significant cell adhesion activity. Parental L cells did not show cell adhesion under the same conditions. The sensitivity of cadherin-5 and cadherin-8 to trypsin digestion may account for the reduced cell adhesion seen in the reaggregation assay because the transfected L cells are initially dispersed with trypsin in the assay.

Example 6
The expression of mRNAs encoding cadherins of the invention was examined in rat brain, kidney, liver, lung and skin and in various human cells by Northern blot analysis. The expression of cadherin protein was also examined in endothelial cells and leukocytes by immunofluorescence or immunoblotting.

A. Northern Blot Assays of Rat Tissue and Human Cells

Poly(A)^+ RNA from rat brain, kidney, liver, lung and skin was prepared as described in Example 1 for rat brain. The RNA preparations were then electrophoresed in an 0.8% agarose gel under denaturing conditions and transferred onto a nitrocellulose filter. Northern blot analyses were carried out according to a method described in Thomas, *Proc. Natl. Acad. Sci. USA*, 77, 5201-5202 (1980). Filters were hybridized with rat cadherin PCR fragments (described in Example 1) labeled with $^{32}$P, including fragments corresponding to cadherins-4 through -11. The final hybridization wash was in 0.2X standard saline citrate containing 0.1% sodium dodecyl sulfate at 65°C for 10 minutes.

Cadherin-4 and cadherin-8 through -10 mRNAs were detected only in rat brain. The cadherin-8 PCR fragment hybridized to a major band of about 3.5 kb and a minor band of about 4.5 kb in rat brain. The mRNAs detected may be alternative splicing products and may correspond to the truncated and full length cadherin-8 clones described in Example 1. Cadherin-6 and -7 probes gave weak signals on rat brain mRNA even after prolonged exposure. Cadherins-5, -6 and -11 mRNAs were detected in rat brain and other rat tissues including cadherin-5 mRNA in lung and kidney, cadherin-6 mRNA in kidney, and cadherin-11 mRNA in liver.

The expression of cadherin-8 and -11 in cultured human SK-N-SH neuroblastoma cells (ATCC HTB11), U251MG glioma cells and Y79 retinoblastoma cells (ATCC HTB18) was also assayed by Northern blot. Human cDNAs encoding cadherins-8 and -11 (described in Example 2) were labelled with $^{32}$P and used as probes of poly(A)^+ RNA prepared from the cells using an Invitrogen FastTrack kit.
The Northern blot procedure detected cadherin-8 RNA in the neuroblastoma and retinoblastoma cell lines, while cadherin-11 RNA was detected only in neuroblastoma cells. These results indicate that at least some of the cadherins of the invention are expressed in neurons and glial cells and/or their precursor cells.

Cadherin-5 RNA was detected by Northern blot assay of HUVECs (Clonetics), but was not detected in A431 human epidermoid carcinoma cells (ATCC CRL1555) or IMR90 human fibroblast cells (ATCC CCL186).

B. Immunofluorescence of Endothelial Cells and Immunoblotting of Leukocytes

Cultured endothelial cells isolated from bovine aorta, bovine brain microvasculature and human umbilical vein were subjected to immunofluorescence microscopy using anti-C5 polyclonal antibodies. Cadherin-5 protein at the cell junctions which was in close association with the peripheral actin microfilaments was labelled.

In contrast, when freshly isolated leukocytes (human PMN, lymphocytes and monocytes) or the monocyte-like cell line U937 were analyzed for the expression of cadherin-5 by immunoblotting using polyclonal antibodies and a monoclonal antibody (30O6E) to cadherin-5, no cadherin-5 was detected. Furthermore, using a pan-cadherin antibody [Geiger et al., J. Cell Science, 97: 607-614 (1990)] specific for the cytoplasmic tail, no other cadherins were detected in these cell populations.

Example 7

Three in vitro transendothelial migration assays were utilized to show that cadherin-5 may participate in the movement of leukocytes across the intercellular junctions of endothelium.
A. Transmigration Assays

The migration of leukocytes (either human polymorphonuclear neutrophils or rat T cells) was followed for specific periods of time (15 minutes for PMNs and 2 hours for T cells). Immunofluorescent labeling of leukocytes using antibodies to specific cellular markers was used to distinguish between leukocytes and endothelium. The polyclonal antibodies described in Example 4 were used to measure changes in the distribution of cadherin-5. An antibody (Novocastra Laboratories Ltd., United Kingdom) to PE-CAM1 (CD31) which is an intercellular junction molecule in endothelium was used as a control.

The role of cadherin-5 in the transmigration of polymorphonuclear neutrophils (PMNs) across HUVECs was analyzed. The system utilized, which is described in Furie et al., J. Immunol., 143: 3309-3317 (1989), has been characterized with regard to electrical resistance of the endothelium and the adhesion molecules used in transmigration. HUVECs were isolated in the absence of growth factor and cultured on human amniotic connective tissue in a two-chamber system. PMN migration on IL1β-treated HUVECs has previously been shown to involve E-selectin and β2 integrins (CD11/CD18). See Furie et al., J. Immunol., 148: 2395-2484 (1992).

In the first assay, transmigration of PMNs was followed as an 11 minute time course on HUVECs pretreated for four hours with IL1β (1.5 U/ml) (Collaborative Research Inc., Beford, MA). Prior to addition of neutrophils, antibodies to cadherin-5 heavily labelled the cell junctions of the HUVECs in a continuous pattern. Pretreatment of the endothelial monolayer with IL1β had no effect on the distribution of cadherin-5 in the HUVEC monolayer compared to a control untreated culture. In the second assay, chemotaxis of PMNs across HUVECs was stimulated by leukotriene B4 (LTB4) (Sigma) which was placed in the bottom chamber at 10^{-7}M while neutrophils were added to the upper chamber. Chemotaxis of PMNs to LTB4 across the endothelial monolayer was previously shown to be blocked by antibodies to CD11a, CD11b and ICAM-1. [See Furie
In both assays, PMNs were identified with anti-CD45 antibody (Becton Dickinson, San Jose, CA).

In both assays during the 11-minute time course, the majority of the PMNs that adhered also transmigrated. Addition of neutrophils caused a rapid redistribution and regional loss of cadherin-5 even at the earliest time point (3 minutes). CD31 was also lost at sites of disruption of the monolayer, but in general appeared to be more stable during the transmigration process. The loss of cadherin-5 is probably the result of proteases released from the neutrophils during transmigration.

In a third assay, CD4 antigen activated rat T cells were utilized instead of PMNs (for a two-hour time course). Rat brain microvascular endothelium was grown on Transwell 5 micron polycarbonate membranes (Costar, Cambridge, MA). T cells were identified using an anti-CD4 antibody (Serotec, Indianapolis, IN). In this assay, the loss of cadherin-5 immunolabeling did not occur during transendothelial migration even though 10% of the T cells had crossed the endothelium after two hours. These results demonstrate differential effects of PMN versus T cells on intercellular junctions during transendothelial migration. Analysis by confocal microscopy suggests that CD4 antigen-activated T cells and PMNs have a ligand that is able to interact with cadherin-5 on the endothelium during transmigration. Photomicrographs from confocal analysis show that during leukocyte transendothelial migration leukocytes can be found spanning the intercellular junction. The leukocyte separates the cell junction and cadherin-5 remains on adjacent cells even though the endothelial cells are not in contact.

B. Adhesion of PMNs and T Cells to Cadherin-5

To quantitate the binding of PMNs and activated T-cells to cadherin-5, a cell-substrate adhesion assay was developed. This assay utilized plate-bound fusion proteins containing various extracellular subdomains of cadherin-5 (EC1-2 or EC2-4, see Example 4) and measured the binding of dye-
labelled leukocytes to cadherin-5 protein using a cytofluor 2300 (Millipore, Bedford, MA).

The purified fusion proteins were absorbed to styrene plates and the binding of dye-labeled leukocytes to the fusion proteins was compared to binding to maltose binding protein and heat denatured bovine serum albumin (BSA) which was used to block nonspecific binding. The fusion proteins were dissolved in PBS containing Ca²⁺ and Mg²⁺, diluted into coating buffer and incubated overnight at 4°C. The plates were blocked with heat denatured BSA and then incubated with calciem (Molecular Probes, Eugene, OR)-labelled cells for 1 hour at 37°C. Results of the assay are presented in FIGURE 1 wherein the relative fluorescence values reported are the mean value of three samples.

PMNs bound to fusion proteins comprising the EC2-4 of cadherin-5, but preferentially bound to fusion proteins comprising EC1-2. These results are consistent with presence of cadherin subdomain 2 sequences in both fusion proteins. CD4 antigen activated T cells bound EC2-4 fusion protein. All these results, which indicate that PMNs interact with a more terminal or exposed subdomain of cadherin-5, are consistent with the rate that these cell types cross the endothelium, PMNs transmigrate in a few minutes and T cells require 30-60 minutes. The binding of U937 cells could be blocked in a dose dependent manner by polyclonal antisera made to the cadherin-5 EC2-4 subdomains.

The results presented in the foregoing paragraph in combination with the results presented in Example 6B that leukocytes do not express cadherins suggests that the counter ligand to which cadherin-5 binds on leukocytes is a distantly related cadherin or is not a cadherin. Cadherin binding has previously been thought to be homotypic.
Example 8

Expression of cadherin-5 in the blood-brain barrier in the endothelium of the cerebral cortex was assayed by Western blot and immunocytochemistry.

A SDS lysate was prepared by boiling bovine or macaque capillaries in SDS sample buffer for 2 minutes and then drawing the extract through a 25 G syringe needle. The extract was centrifuged in a microfuge for 15 minutes at 4°C. Protein concentration in the supernatant was determined by the BCA method (Pierce) using bovine serum albumin as a standard. Samples of the supernatent (75μg) were separated by SDS-PAGE (Laemmli) and electrophoretically transferred to nitrocellulose. The nitrocellulose was blocked with 5% milk and 10% FBS in Tris-buffered saline, pH 8.0, containing 0.05% Tween 20. Cadherin-5 specific monoclonal antibodies (30Q4H and 45C6A) were added. After washing to remove unbound antibody, the filters were incubated with alkaline phosphatase-conjugated anti-mouse IgG (Promega, Madison, WI). Reactive bands were visualized by addition of NBT/BCIP (Sigma, St. Louis, MO). Expression of cadherin-5 was detected in the freshly isolated bovine and macaque capillaries.

The Western blot results were confirmed by immunocytochemistry using the cadherin-5 antibodies 30Q4H and 45C6A. Macaque cerebral cortex was incubated in 15% sucrose in PBS for 30 minutes at 4°C and embedded in OCT compound (Tissue-Tek, Elkhart, IN) in cryomolds and quickly frozen. Six micron sections were cut and placed on glass slides. The slides were washed with PBS and fixed in 3% p-formaldehyde for 5 minutes. To permeabilize the tissue sections the slides were immersed in -20°C acetone for 10 minutes and air dried. The sections were blocked with 2% goat serum and 1% BSA in PBS for 30 minutes and then incubated with the primary antisera for 1 hour at room temperature. The sections were rinsed 3 times in PBS containing 0.1% BSA and incubated with biotinylated anti-rabbit or anti-mouse IgG (Vector Laboratories,
Burlingame, CA) in 1% BSA in PBS for 30 minutes. After rinsing 3 times, strepavidin-conjugated with horseradish peroxidase (Vector Laboratories) was added for 30 minutes and washed 3 times. Immunolabeling was detected by reaction with diaminobenzoic acid in the presence of NiCl₂. The monoclonal antibody 45C6A only appeared to label larger vessels and the monoclonal antibody 30Q4H labeled both large and microvessels. The cell junctions of cerebral capillaries were labelled with the anti-cadherin-5 antibodies in a localized site.

These results and the results presented in Example 7 suggest cadherin-5 is involved in maintenance of the blood-brain barrier and that cadherin-5 peptides or cadherin-5 specific monoclonal antibodies may be able to open the blood-brain barrier.

Example 9

Patent Cooperation Treaty (PCT) International Publication No. WO 91/04745 discusses fragments of cell adhesion molecules and antibodies to cell adhesion molecules which are purported to disrupt microvascular and endothelial cell tight junctions.

Three cadherin-5 peptides corresponding to the cell binding domain [HAV region, Blaschuk et al., Devel. Biol., 139: 227-229 (1990)], the calcium binding region A1 and the calcium binding region B1 of E-cadherin [Ringwald et al., EMBO J., 6: 3647-3653 (1987)] were tested for the ability to affect the permeability of brain endothelium. The peptides utilized had the following sequences:

Peptide 1 (Amino acids 114 to 128 of SEQ ID NO: 50)

LTAVIVDKDTGENLE,
Peptide 2 (Amino acids 132 to 145 of SEQ ID NO: 50) SFTIKVHDVNDNWP, and

Peptide 3 (Amino acids 168 to 178 of SEQ ID NO: 50) SVTAVDADDPT, respectively.

Permeability was measured using a two-chamber culture system (Costar). Rat brain microvascular endothelium was grown on 12 mm Transwell filters with 3 micron pores (Costar) in the culture system. When the monolayers were confluent, two weeks after plating, \(^3\)H-inulin (201 mCi/g) (New England Nuclear, Boston, MA) was added to the upper chamber. Cadherin-5 peptide at 100 \(\mu\)g/ml was added to both the upper and lower chambers. Radioactivity appearing in the bottom chamber was measured at 15 minute intervals over a two hour time course carried out at 37°C and was compared to the radioactivity appearing in the bottom chamber of cultures where no peptide was added or where no endothelial cells were present.

Both peptides 1 and 3 increased endothelium permeability in comparison to control cultures. The increase in permeability obtained with peptide 3 was 2.5-fold and the increase with peptide 1 was 1.5-fold over the controls. Peptide 2 had no effect on permeability.

**Example 10**

The functional properties of cadherins involve not only specific intercellular interactions, but also involve intracellular interactions with the cytoskeleton. Immunoprecipitation experiments utilizing the cadherin-5-specific rabbit polyclonal antibodies and the monoclonal antibody 30Q8A (see Example 4) were performed to determine with which proteins cadherin-5 interacts on an intracellular level.
Endothelial cells were metabolically labeled overnight with 50 μCi/ml of [³⁵S]-methionine and were then extracted with 0.5% Triton X-100 in 10mM HEPES pH 7.4, 0.15M NaCl, 2mM EDTA, 2mM EGTA, 1mM phenanthroline and protease inhibitors. The inhibitors included 1mM PMSF, 10 μg/ml aprotinin, leupeptin, pepstatin A, antipain, soybean trypsin inhibitor, 100 μg/ml chymostatin and TPCK, 40 μg/ml of TPCK and bestatin, 50 μg/ml of benzamidine, 1mM o-vanadate and 20mM NaF. After 20 minutes on ice, the cells were scraped and centrifuged in a microfuge for 30 minutes at 4°C. The supernatant was precleared and either polyclonal anti-cadherin-5 or normal rabbit serum was added and incubated overnight at 4°C. Protein A-sepharose (Pharmacia, Piscataway, NJ) was added for 2 hours at 4°C and centrifuged. A first low stringency wash with 10mM HEPES pH 7.4, 0.15M NaCl, 2mM EDTA and 2mM EGTA containing 1% Triton X-100, 0.5% DOC and 0.2% SDS was performed. A second high stringency wash was performed with the same buffer containing 2% SDS. A final wash was then performed with Tris-buffered saline, and the samples were boiled and analyzed on SDS/PAGE (7%). Three bands with molecular weights of 104 KD, 95 KD, and 82 KD were identified as associated with cadherin-5.

Three intracellular proteins, termed catenins, have previously been identified by their ability to bind to the cytoplasmic domain of E-cadherin. These proteins have been designated α, β, and γ catenins and have molecular weights of 102 KD, 88 KD and 80 KD, respectively [Ozawa et al., EMBO J. 8: 1711-1717 (1989)]. The association of catenins with E-cadherin seem to be required for E-cadherin function because deletion of the cytoplasmic domain of E-cadherin results in loss of cell adhesion function and catenin binding. The molecular cloning of α-catenin has shown it to be a vinculin-like protein [Nagafuki et al., Cell, 65: 849-857 (1991); Herrenkenecht et al., Proc. Natl. Acad. Sci. USA, 88: 9156-9160 (1991)]. The amino acid sequence of the Xenopus β-catenin [McCrea et al., Science, 254: 1359-1361 (1991)] exhibits 63% similarity to the human

To identify whether plakoglobin was one of the proteins complexed to cadherin-5, an unlabeled lysate of bovine aortic endothelial cells was made and immunoprecipitation was carried out as described above using anti-cadherin-5 antibody. The unlabelled immunoprecipitates were separated by SDS/PAGE and then electrophoretically transferred to nitrocellulose. The membrane was blocked with 5% milk in Tris-buffered saline, pH 8.0, containing 0.05% Tween 20 (TBST) and then was incubated with the murine monoclonal antibody PG5.1 (IBI Research Products, Cambridge, MA) to plakoglobin in blocking solution (1:20) for 1 hour at room temperature. The membrane was washed with TBST and then incubated with goat anti-mouse IgG conjugated to alkaline phosphatase. An 82 KD protein was identified using NBT/BCIP under both low and high stringency wash conditions. These results demonstrate that plakoglobin is tightly associated with the cytoplasmic domain of cadherin-5 in endothelium. Immunofluorescence studies of regenerated endothelium show that cadherin-5 and plakoglobin are localized to the cell junctions and are coordinately regulated.

The interaction of cadherin-5 with plakoglobin may be a target for modulation of cadherin-5 activity.
While the present invention has been described in terms of preferred embodiments, it is understood that variations and improvements will occur to those skilled in the art. Thus, only such limitations as appear in the appended claims should be placed on the scope of the invention.
SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Suzuki, Shintaro

(ii) TITLE OF INVENTION: CADHERIN MATERIALS AND METHODS

(iii) NUMBER OF SEQUENCES: 62

(iv) CORRESPONDENCE ADDRESS:
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(v) COMPUTER READABLE FORM:
    (A) MEDIUM TYPE: Floppy disk
    (B) COMPUTER: IBM PC compatible
    (C) OPERATING SYSTEM: PC-DOS/MS-DOS
    (D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
    (A) APPLICATION NUMBER:
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    (C) CLASSIFICATION:

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    (A) APPLICATION NUMBER: US 07/872,643
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 6 amino acids
    (B) TYPE: amino acid
    (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

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

Thr Ala Pro Pro Tyr Asp
1  5

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 23 base pairs
    (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA

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

GAATTCA CG CNCG CNCTA YGA

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

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

Phe Lys Lys Leu Ala Asp

1 5

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

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

GAATTCTCG CNARYTTYT RAA

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION: /note= "The amino acid at this position is a proline or a glycine."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 3
(D) OTHER INFORMATION: /note= "The amino acid at this position is a leucine, an isoleucine or a valine."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION: /note= "The amino acid at this position is a phenylalanine or a tyrosine."
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Lys Xaa Xaa Asp Xaa Glu
1 5

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GAATTCAARS SNNTNGAYTW YGA

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "The amino acid at this position is an asparagine or an aspartic acid."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 3
(D) OTHER INFORMATION: /note= "The amino acid at this position is an alanine or a proline."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Xaa Glu Xaa Pro Xaa Phe
1 5

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GAATTCAAN NNGGNGSYT CRT

23
(2) INFORMATION FOR SEQ ID NO:9:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 117 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:
TCCCTGCTGG TCTTCGACTA CGAAGGCAGC GTTCTCTCTG CAGGCTCTGT CAGCTCCCTG 60
AACTCTCCA GCTCCGGGGT TCAAGATTAC GACTTCTGA ATGACTGGGG GCCCGGG 117

(2) INFORMATION FOR SEQ ID NO:10:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:
Ser Leu Leu Val Phe Asp Tyr Glu Gly Ser Gly Ser Thr Ala Gly Ser 1 5 10 15
Val Ser Ser Leu Asn Ser Ser Ser Ser Gly Asp Gln Asp Tyr Asp Tyr 20 25 30
Leu Asn Asp Trp Gly Pro Arg 35

(2) INFORMATION FOR SEQ ID NO:11:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:
ACACTGCACA TCTACGGCTA CGAGGGCACA GAGTCATCG CAGAGTCCTC CAGCTCCCTG 60
AGCAGCAATT CCTGAGCCATC TGACATCGAC TATGACTTCC TCAATGACTG GGGACCCAGG 120

(2) INFORMATION FOR SEQ ID NO:12:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Thr Leu His Ile Tyr Gly Tyr Glu Gly Thr Glu Ser Ile Ala Glu Ser
1       5       10        15
Leu Ser Ser Leu Ser Thr Asn Ser Ser Asp Ser Asp Ile Asp Tyr Asp
20      25        30
Phe Leu Asn Asp Trp Gly Pro Arg
35      40

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TCCTGGCGCA CCTATGCCTA CGAAGGAACCT GCCTCGGTGG CCGACTCCCT GAGCTCAGTA 60
GAATCAGTGA CCAGAGATG AGACCAAGAT TATGACTATT TGAGTGACTG GGGCCCTCGA 120

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Ser Leu Ala Thr Tyr Ala Tyr Glu Gly Thr Gly Ser Val Ala Asp Ser
1       5       10        15
Leu Ser Ser Leu Glu Ser Val Thr Asp Gly Asp Gln Asp Tyr Asp
20      25        30
Tyr Leu Ser Asp Trp Gly Pro Arg
35      40

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TCGCTCAGA CTATGCAATT GAAAGGAAAT GGCTCAGTAG CTGAATCTCT CAGTTCTTTA

60

GATTCTAACA GCTCGAACTC TGATCAGAAT TATGACTACC TTATGACTG GGGTCCCTCCT

120

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Ser Leu Gln Thr Tyr Ala Phe Glu Gly Asn Gly Ser Val Ala Glu Ser
1  5 10 15

Leu Ser Ser Leu Asp Ser Asn Ser Ser Asn Ser Asp Gln Asn Tyr Asp
20 25 30

Tyr Leu Ser Asp Trp Gly Pro Arg
35 40

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TCCATTCCAAGTTATGGCTA TGAAGCCGA GGGTCTGTGG CTGGCTCTCT CAGCTCGTGG

60

GAGTCCACCA CATCAGACTC AGACCAAGT TTTGACTACC TCAGTGACTG GGGTCCCCGC

120

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Ser Ile Gln Ile Tyr Gly Tyr Glu Gly Ser Val Ala Gly Ser
1  5 10 15

Leu Ser Ser Leu Glu Ser Thr Thr Ser Asp Ser Asp Gln Asn Phe Asp
20 25 30
Tyr Leu Ser Asp Trp Gly Pro Arg
35
40

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TCCTGGGCA CTTACGCCTA TGAAGGAAT GATTCTGTG CCAATTCTCT CAGCTCCTTA
60
GAATCTCTCA CAGCTGATTT TACCCAGGAT TATGACTACC TTAGTGACTG GGGGCCACGC
120

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Ser Leu Ala Thr Tyr Ala Tyr Glu Gly Asn Asp Ser Val Ala Asn Ser
1 5 10 15
Leu Ser Ser Leu Glu Ser Leu Thr Ala Asp Cys Asn Gln Asp Tyr Asp
20 25 30
Tyr Leu Ser Asp Trp Gly Pro Arg
35 40

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

TCGCTGGCTA CCTATGCTTA TGAAGGAAAC GACTCTGTG CTGAATCTCT CAGCTCCTTA
60
GAATCAGGTA CGACTGAAG AGACCAAAAC TACGATTACC TTGAGAATG GGGGCCCTGG
120
(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:22:
Ser Leu Ala Thr Tyr Ala Tyr Glu Gly Asn Asp Ser Val Ala Glu Ser
1 5 10 15
Leu Ser Ser Leu Glu Ser Gly Thr Thr Glu Gly Asp Gln Asn Tyr Asp
20 25 30
Tyr Leu Arg Glu Trp Gly Pro Arg
35 40

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:23:
TCCATCCAAA TCTATGGTTA TGGGGCCAGG GGTCCCGTG CTGGGTCCTT GAGCTCCTT 60
GAATCTGCCA CCACGATTC GGACCTGGAC TACGACTATC TACGAAACTG GGGACCTCGG 120

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:24:
Ser Ile Gln Ile Tyr Gly Tyr Glu Gly Arg Gly Ser Val Ala Gly Ser
1 5 10 15
Leu Ser Ser Leu Glu Ser Ala Thr Thr Asp Ser Asp Leu Asp Tyr Asp
20 25 30
Tyr Leu Gln Asn Trp Gly Pro Arg
35 40
(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 150 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:
AAGCGGTTTG ATTACGAGAT CTCTGCCCTT CACACCCCTGC TGATCAAGTG GAGAATGAG 60
GACCCATTTG TACCAGACGT CTCCCTATGGC CCCAGCTCCA CGGCCACTGT CCACATCAG 120
GTCTTGGATG TCAAAGGAGG ACCAGTCTTC 150

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:
Lys Arg Phe Asp Tyr Glu Ile Ser Ala Phe His Thr Leu Leu Ile Lys 1 5 10 15
Val Glu Asn Glu Pro Leu Val Pro Asp Val Ser Tyr Gly Pro Ser 20 25 30
Ser Thr Ala Thr Val His Ile Thr Val Leu Asp Val Asn Glu Gly Pro 35 40 45
Val Phe 50

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 150 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:
AAGGCTATGG ATTATGAGCT GAACGTGCC TCCATGCTGA CCATAATGGT GTCCAACCAG 60
GGGCCCCCTGG CCCAGGGGAT CCAGATGCTC TTCCAGTCCA CAGTTGGGCT AACCATCTCT 120
GTCACCCGATG TCAAAGGAGG CCCCTACTTC 150
(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:
Lys Gly Met Asp Tyr Glu Leu Asn Arg Ala Ser Met Leu Thr Ile Met 1 5 10 15
Val Ser Asn Gln Ala Pro Leu Ala Ser Gly Ile Gln Met Ser Phe Gln 20 25 30
Ser Thr Val Gly Val Thr Ile Ser Val Thr Asp Val Asn Glu Ala Pro 35 40 45
Tyr Phe 50

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 153 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:
AAACGACTGG ATTTTGAACT CATCCAGCAG TACACGGTCC ACATCGAGGC CACAGACCCC 60
ACTATCACAG TCGGATACCT GAGGACGACT GCAGGCAAAAA ACAAAAGCCAA GATCATCATC 120
AATGTCCTAG ATGTGGATGA GCCCCCTGTT TTC 153

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:
Lys Arg Leu Asp Phe Glu Leu Ile Gln Gln Tyr Thr Phe His Ile Glu 1 5 10 15
Ala Thr Asp Pro Thr Ile Arg Leu Gly Tyr Leu Ser Ser Thr Ala Gly 20 25 30
Lys Asn Lys Ala Lys Ile Ile Ile Asn Val Leu Asp Val Asp Glu Pro 35 40 45
Pro Val Phe
50

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 153 base pairs
    (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:
AAGGTTTGGG ATTTTGAAAA GAAGAAAGTG TATA GCCCTTA AAGTGGAAAGC CTCCAAT CCT
60
TATGGTGGAC CACG ATCTGCTT CTACCTGGGG CCTTCAAAAG ATTC A GCACAC GTTTAGAATT
120
GTGGTGAGG ATGTAGATGA ACCTCTG GCC TTC
153

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 51 amino acids
    (B) TYPE: amino acid
    (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:
Lys Gly Leu Asp Phe Glu Lys Lys Lys Val Tyr Thr Leu Lys Val Glu
1       5      10    15
Ala Ser Asn Pro Tyr Val Glu Pro Arg Phe Leu Tyr Leu Gly Pro Phe
20
Lys Asp Ser Ala Thr Val Arg Ile Val Val Glu Asp Val Asp Glu Pro
35      40     45
Pro Ala Phe
50

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 153 base pairs
    (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:
AAGCCTCTGG ACTTGGAGAC CAAAAATCC TATATCTCTGA AGTGGAAGGC AGCCAATAC
60
CAGATG ACC CAGTCTTTGC TGGCAGGGGA CCCCTTAAG ATACAGCAAC AGTCAAAATT
120
GTGGTGGAGG ATGCGTATGA GCCCTCGGT TTC
153
(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xii) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Asp Ala Leu Asp Phe Glu Thr Lys Lys Ser Tyr Thr Leu Lys Val Glu 1 5 10 15
Ala Ala Asn Ile His Ile Asp Pro Arg Phe Ser Gly Arg Gly Pro Phe 20 25 30
Lys Asp Thr Ala Thr Val Lys Ile Val Val Glu Asp Ala Asp Glu Pro 35 40 45
Pro Val Phe 50

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 152 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xii) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

AAGGGGTGG ACTATGAAGG CAAAACAAGT TATACCTGC GCATAGAAGC TGCAAATCGA 60
GATGCTGATC CCCGTTTCT GAGCTTGGA TCATTCACTG ACACAAACA ACATGAAGA 120
ATTGTGGAAAG AGCGGGATGA ACCCGGTACT C 152

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xii) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Lys Gly Val Asp Tyr Glu Ala Lys Thr Ser Tyr Thr Leu Arg Ile Glu 1 5 10 15
Ala Ala Asn Arg Asp Ala Asp Pro Arg Phe Leu Ser Leu Gly Pro Phe 20 25 30
Ser Asp Thr Thr Thr Val Lys Ile Ile Val Glu Asp Val Asp Glu Pro 35 40 45
(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 153 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

AGGCCACCTG ACTATGAGAA CGGRAAGACTA TATACACTGA AGGTGGAGGC AGAAATACCC 60
CATGTGGATC CACGGTCTTA CTTATAGGG CCAATAAAG ATACAACAAT TGTTAAAATC 120
TCCATAGAAG AGTGGATGA GCCACCCCCC TTT 153

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Lys Pro Leu Asp Tyr Glu Asn Arg Arg Leu Tyr Thr Leu Lys Val Glu 1 5 10 15
Ala Glu Asn Thr His Val Asp Pro Arg Phe Tyr Tyr Leu Gly Pro Phe 20 25 30
Lys Asp Thr Thr Ile Val Lys Ile Ser Ile Glu Asp Val Asp Glu Pro 35 40 45
Pro Pro Phe 50

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 153 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

AGGGGTGTGG ATTATGAAAC CAAAAGAC ACA TTACGCTTGA AGTGGAGGC GGCACATGA 60
CACATTGATC CAAAGTCTCATGCAAGAG GCTTCAAGG ACACAGTGAC TGTCAGATT 120
GCAGTAGAAG ATGCCAATGA GCCCCCTCCC TTC 153
(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Arg Gly Val Asp Tyr Glu Thr Lys Arg Ala Tyr Ser Leu Lys Val Glu
1  5  10
Ala Ala Asn Val His Ile Asp Pro Lys Phe Ile Ser Asn Gly Pro Phe
20  25  30
Lys Asp Thr Val Thr Val Lys Ile Ala Val Glu Asp Ala Asn Glu Pro
35  40  45
Pro Pro Phe
50

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3136 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GGCACGAGCG CAAGCGCGGC AGGCGTCGCC CCAGAATTAG TGGATGGATT TGGAAATCTCC 60
CTGCTTCTTC CAAAGCTCCG CACTGCACAT TTACGGAGAG CACGTAGGGT GACACCCGGA
120
GGCGTACTTT TAGGCTGCAG ACAGTGAGCC CAGCGGCGCA GCTCGCGCAT TCCGGACCCAG
180
GCTCCACAGC TCCGAGAGCC ATGAAACCGA TCCGGGAGAG ACTACCGCTTC GCGCGGGGAT
240
CGTGAGAGAT TACCGCCTCT CGGGAGACTGA CCCCCAGCCTT CTTCGAGCCAT TTATGAATCC
300
AGAGGTGTGA GATTTTTTTC CGGATCCCCG AGGCGCGACTT GAGAAAATTC AATGAAGGG
360
AAAGTCATGG GATGTGGTGC TTGGGAAAAAG TCAGTGGAGA TGCTCTGTTTC CCGGCTCTCT
420
GAACCCGCTG CAGAGCGTCG ATGTGCCGCT TGAGCAGGTC TGGAGATAG GATGCCCTTCG
480
GACCGCGGCT CAAAAATATA ATTTGCTCTAT TTTGCGCTTG ATTTGCTTCAA ATGGTGGGAG
540
CATGGCCAGAA AGGCTAGGGG AGACCTTTTT GCCCTCCTTC ACTCCATTAA TATATATTAG
600
GATTACTCTT CCCCTTTTTG TGTACACTGGC TCCGATGAAT CAGGCTCACG TTTTAACTAC
660
TGGATCGGGT TTGGGACTAA GAGGCGAGAG TGGAAATATG CAGGTTTCTGG ACGGCTCCA
720
AAGGGCGTGG GCGGGGAGTC AAAATTTGTT TGCAGGAGAA TTTTCTGGAC CGTACGGGAT
780
TCTGTTGGC CAGGTACACA CAGATCTTGA TCCGGGAGC AAAAAATCA AGTATATCCT
ATCGGGTGAT GGAAGCGGCA CAAATTTTCA AATAAAGCAT ATAACCTGAG ACATCTCAATGC 900
TATCAAAAGA CTTGACCCAG AGGAAAAAGGC TGAATATACG TTAACAGCTC AGGCAGTGGGA 960
CTGGGAGACA AACCAACCTC TCGAGGCTCC TTTGGAAATT ATTATTAAGG TTCAAGACAT 1020
CAACAGCAAT GCCCGGAGCT TTCTCAATGG ACCTTACCTT GCTACTGGTC CAGAGATGTC 1080
CATTTGGGTG ACTACTGCTCA CTAATTGAAAC GGCACAGTAG CGTGACAGTC CATTTTATGG 1140
AAACAGTCCAG AAGTTGTCCCT ACAGCATTTT ACAGAGGACAG CCGTTATTTT CCATGAGGCC 1200
TGAAACAGCT ATATTTAAAA CTGGAACCTTC TAAACATGGAC AGAGAGCGCA AGAGAGGATA 1260
CTTGGTTGTAA ATTTAAGCAG GAGATATGGG TGGGCATCCG GTGTTTGCTG CTGAGGCACAC 1320
GACACTCACA GTGACCGCTTA CCGATGTGAA TGAAATACCT CCAGAAAAATG CTCAAGGTTT 1380
GTATCCTCCT CAAGTCACAG AACAGTTGGA TTTGGGACCT CCGACTCTAC CAGTTAAAGG 1440
CAAGTACCCAG GATATTGGTG AAAATTGACA ATCTTTCTCTAT GACATCATTT GAGAGATGGG 1500
GACAGCTACA TTTGAAATCTA CTCTTCAGTC CACAGGCAAG CATGGTTGTTA TAAACGTAAAG 1560
AAAGCCTCTG GACTTTGAGA CCAAAAATCT CATACTCTCTG AAGTGGAGG CAGCAAAATAT 1620
CCACATCGAC CCAAGTTTTCA GTGCGAACGG ACCCTTAAAA CATACACGCAA AGGTAAAGGT 1680
TGTTGTAGAG GATGCTCGTG AGCCCTCGGT CTTCTCTTCTA CCGACTTACT TCTTTGAGGT 1740
TCATGAAAAT GCTGGCTTGA ACTCTGGTAT TGGGCAAGTG ACAGCAGTGG ACCCTGATAT 1800
CACCCTCAGC CCAATAGGCT TTTCCATTGGA CGCAGCACACT GACTTGGAGA GACAGTCTAA 1860
CATCAATCGA GATGATGGGA AGATAACACT GCGGACCCCCA CTGAGACAGG AACTAGTGTT 1920
GTGCCACACA ATTTCACTCA TTCTCAGTGA GATCGAGAAC CACAGTCAGA TATTCGGAGT 1980
GCCGGTTTCA ATAAAGTGGC TGAGATGTCA TGACACGCGC CCTGAATTCG GTGGCAAGTA 2040
TGAGCCATTT TTAATGGAAC ATGGAAAACC CGGGCAGCTC ATTCAACAGC TAAGGGCCAT 2100
GGCAAAAGAC GACATCCCCCA ATTTCTGTTGA AGTCTTTCCTA CAGTTAAAGGT 2160
CAACACCACA AATTTGACCA TCAAGAAAATG CGAAGATAAT TCCCTGAGCA TTCTGCGAAA 2220
ACATATAAGG TCAACCGGCC AGAGCAAGAG AGTCACCTTT CTGCCCTATTG TGATCAAGTG 2280
CAGTGGGAAAC CCCCCCTCTGA TGGACCCGAG TACCCTGACC ATCCCGGCTCT GTGGCGTAG 2340
CAATGACGCG GTGCGCTCAGT CGCTGAACTCT CGAAGCTTTT GCTCTTTCCTA TGGGGTCAG 2400
TAGGGGGGCG TTTAATGTCA TTAGGCTCGT CATTATTTTG TCTGGCTGCTA TGTGCTTCT 2460
GTGCTTACCC CTGGGCCGCC ATAAATATGA ACCACTAAAT ATCAGAGATG AGAAGAGGT 2520
TGAGAAACAC ATCATTGCCT ATGAGCGAGA AAGAGCGGCG GAGGAAGCA CAGAGGCTTT 2580
TGACATTCCA ATTTTGGAAC ACCAGATGGA AATTAYGCTC TTTTTACCCG GTAAGGATT 2640
TAACACAGAT TTGGCAATTGA TGCCCGAGGA AGGGCTTGGCT CCAGTTCCAA ATGTTGTGGGA 2700
TGTCATGAAA TTTTAAATAG TAAATGCTCA TGAGCAGAAT AATGACCCCA CGGGCCGACC 2760
ATATGACTCC ATTCAGATTT ATGCTATGAG AGGCCAGGCT TCTGTGCGTCA GCTCTCTTCAG 2820
CTGTTGGGAG TCCACCACTC CAGACTTACA CCAAATTTTT GACTTCCCTA GTGACCTGAGG 2880
-51-

TCCCCGCTTT TACAGAGCATG GCGAActCCA CTCTGTGCTT GAAAGTGACA AAGAAACTTG  2940
ACAGTGGATT ACAATAATAA TCAATGGGAC TGAGATTCT GGAATTTCT AGGGTCACCT  3000
CCCTTAGATG CAACAAATTG GCCTATCTGT TTTAGAGGCA AGTTAGACAC CAATCTCTA  3060
TAAACTCAAC CACATTTTAA TGCTGAACCA AAAAAATATAA TAAAAATAAA AAGTAGATA  3120
TTAGAGGTTG AAAAA  3136

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 799 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Met Pro Glu Arg Leu Ala Glu Thr Leu Leu Asp Leu Trp Thr Thr Pro Leu
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Ile Ile Leu Trp Ile Thr Leu Pro Ser Phe Val Tyr Met Ala Pro Met
20  25  30
Asn Gln Ala His Val Leu Thr Thr Gly Ser Pro Leu Glu Leu Ser Arg
35  40  45
Gln Ser Glu Glu Met Arg Ile Leu Asn Arg Ser Lys Arg Gly Trp Val
50  55  60
Trp Asn Gln Met Phe Val Leu Glu Glu Phe Ser Gly Pro Glu Pro Ile
65  70  75  80
Leu Val Gly Arg Leu His Thr Asp Leu Asp Pro Gly Ser Lys Lys Ile
85  90  95
Lys Tyr Ile Leu Ser Gly Asp Gly Ala Gly Thr Ile Phe Gln Ile Asn
100 105 110
Asp Ile Thr Gly Asp Ile His Ala Ile Lys Arg Leu Asp Arg Glu Glu
115 120 125
Lys Ala Glu Tyr Thr Leu Thr Ala Gln Ala Val Asp Trp Glu Thr Asn
130 135 140
Lys Pro Leu Glu Pro Ser Glu Phe Ile Lys Val Gln Asp Ile
145 150 155
Asn Asp Asn Ala Pro Glu Phe Leu Asn Gly Pro Tyr His Ala Thr Val
160 165 170 175
Pro Glu Met Ser Ile Leu Gly Thr Ser Val Thr Asn Val Thr Ala Thr
180 185 190
Asp Ala Asp Asp Pro Val Tyr Gly Asn Ser Ala Lys Leu Val Tyr Ser
195 200 205
Ile Leu Glu Gly Gln Pro Tyr Phe Ser Ile Glu Pro Glu Thr Ala Ile
210 215 220
Ile Lys Thr Ala Leu Pro Asn Met Asp Arg Glu Ala Lys Glu Glu Tyr
225 230 235 240
Leu Val Val Ile Gln Ala Lys Asp Met Gly Gly His Ser Gly Gly Leu
245 250 255
Ser Gly Thr Thr Thr Leu Thr Val Thr Leu Thr Asp Val Asn Asp Asn
260 265 270
Pro Pro Lys Phe Ala Gln Ser Leu Tyr His Phe Ser Val Pro Glu Asp
275 280 285
Val Val Leu Gly Thr Ala Ile Gly Arg Val Lys Ala Asn Asp Gln Asp
290 295 300
Ile Gly Glu Asn Ala Gln Ser Ser Tyr Asp Ile Ile Asp Gly Asp Gly
305 310 315 320
Thr Ala Leu Phe Glu Ile Thr Ser Asp Ala Gln Ala Gln Asp Gly Val
325 330 335
Ile Arg Leu Arg Lys Pro Leu Asp Phe Glu Thr Lys Lys Ser Tyr Thr
340 345 350
Leu Lys Val Glu Ala Ala Asn Ile His Ile Asp Pro Arg Phe Ser Gly
355 360 365
Arg Gly Pro Phe Lys Asp Thr Ala Thr Val Lys Ile Val Val Glu Asp
370 375 380
Ala Asp Glu Pro Pro Val Phe Ser Ser Pro Thr Tyr Leu Leu Glu Val
385 390 395 400
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405 410 415
Asp Pro Asp Ile Thr Ser Ser Pro Ile Arg Phe Ser Ile Asp Arg His
420 425 430
Thr Asp Leu Glu Arg Glu Ile Asn Ala Asp Asp Gly Lys Ile
435 440 445
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450 455 460
Ser Ile Ile Ala Thr Glu Arg Asn His Ser Gln Ile Ser Arg Val
465 470 475 480
Pro Val Ala Ile Lys Val Leu Asp Val Asn Asn Ala Pro Glu Phe
485 490 495
Ala Ser Glu Tyr-Glu Ala Phe Leu Cys Glu Asn Gly Lys Pro Gly Gln
500 505 510
Val Ile Gln Thr Val Ser Ala Met Asp Lys Asp Asp Pro Lys Asn Gly
515 520 525
His Phe Phe Leu Tyr Ser Leu Pro Glu Met Val Asn Asn Pro Asn
530 535 540
Phe Thr Ile Lys Asp Gln Ser Asn Ser Leu Ser Ile Leu Ala Lys
545 550 555 560
His Asn Gly Phe Asn Arg Glu Gln Asn Gnu Val Tyr Leu Leu Pro Ile
565 570 575
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580 585 590
Thr Ile Arg Val Cys Gly Cys Ser Asn Asp Gly Val Val Gln Ser Cys
595          600          605
Asn Val Glu Ala Tyr Val Leu Pro Ile Gly Leu Ser Met Gly Ala Leu
610          615          620
Ile Ala Ile Leu Ala Cys Ile Ile Leu Leu Leu Val Ile Val Val Leu
625          630          635          640
Phe Val Thr Leu Arg Arg His Lys Asn Glu Pro Leu Ile Ile Lys Asp
645          650          655
Asp Glu Asp Val Arg Glu Asn Ile Ile Arg Tyr Asp Glu Gly Gly
660          665          670
Gly Glu Glu Thr Glu Ala Phe Asp Ile Ala Thr Leu Gln Asn Pro
675          680          685
Asp Gly Ile Asn Gly Phe Leu Pro Arg Lys Asp Ile Lys Pro Asp Leu
690          695          700
Gln Phe Met Pro Arg Gln Gly Leu Ala Pro Val Pro Asn Gly Val Asp
705          710          715          720
Val Asp Glu Phe Ile Asn Val Arg Leu His Glu Ala Asp Asn Asp Pro
725          730          735
Thr Ala Pro Tyr Asp Ser Ile Gln Ile Tyr Gly Tyr Glu Gly Arg
740          745          750
Gly Ser Val Ala Gly Ser Leu Ser Ser Leu Glu Ser Thr Thr Ser Asp
755          760          765
Ser Asp Gln Asn Phe Asp Tyr Leu Ser Asp Trp Gly Pro Arg Phe Lys
770          775          780
Arg Leu Gly Leu Tyr Ser Val Gly Gly Ser Asp Lys Glu Thr
785          790          795

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 3043 base pairs
   (B) TYPE: nucleic acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

GGCACGAGGC CAAGCCGGG AGCCGCTCGG CCCGAATTAG TGATGGATT TGGAAATCTCC
CTGCTCTCCT CRAGCTCGCC CACTGCCACT TTAGGCGAG ACCTGACGCT CAACAGCGGA
GGCTGCTTT TAGGCTGCGG ACACTGAGCC CAGGGCGGCGA CCTGCAGCTG TCCGCAGCAG
GGCTCCACAC TCAGGAGGCC ATGAACCGCG TGCGAGGAGG ACTACGCTGC GGGCGGGGAT
GGCTGGACAT TACGCGCTCT GGGAACTGA CCCCAACGCTC CTTGAGCCAT TTAGAATCC
AGAGCTGTTG GATTTTTTCC CGCATCCCGG AGCCGACCT GAGAATTTG AATGAAAGG
AAAGCTGATG GATCGCGCTC TGTTAGACG TGCTCTGTTT CCGGCTCTCT

60
120
180
240
300
360
420
GAACCGTG GG CAGAGCTGTA AGTARAGGCC CTCACTGCTG TGATGRAATTG GATGGGCTTG

GACCAGGAGG AAAAAAATA ATTGCTCAT ATGTTCGGAC ATGGAATTAA CTGGTGGGAC

CAAGGCAGAA AGGCTAGTGG AGAGGCCTTTTG GAACTCTGGG ACTCCATCTAA TAATATTAGT

GATTACCTT CCCTCTTTTG TGGCATGAGCG TCGATGAGAT CAGGCTCAG CTTTTACTAC

TGATCCCCCT TTGGAACTAA CGAGCCGAGG TGAAGAAATTG CGGATTTTGA ACCGCTCCAA

AACAGGTTG GGTTGGAAATC AATGTTGTTTG TCTGGAGAGAA TTZTTCTGGA CTCGATCGCT

TCCTGTTGGC CCGTACCAA CAGAATGAGA TCCCTTTCCC CCAAATTTG CAAATAGCTCT

ATCGGGGTG ATGAGCGGAGA CAAATTTTAA ACAAAACGAT ATAAACTGAG ACATCATGTG

TATAAATAA CTTGAGCAGG AGGAAAGGAC TAGATATACG TTAACAGGCT AGGCAGTGG

CTGGGAGACA AACAAACCTC TGACAGGCTCC TTCTGAGATT ATTATAGGTT TCTGAAGCATT

CAACGCAAAT CCCCCCGAGT TTCTCATATTG ACCTTACCAT GCTACTCTTG CAGAGATGTGC

CATCCTGTGGT CATCATTCTCA CTAATAAAGC GCCGAACGTG CATCTTATATG

AACAGTACAA AAGTGGTTTT AAGATATCTT CGAGGAGCAA CAGTTATTTT CAAATGAGCC

TGAAACAGCT AATAAAATCA CTGCCCTTCC TTAACATGGG AGAGAGGCCA AGAGGAAATA

CCCTGTTGTA ATACAAAGCA AAGATATGGG TGGGCATTC CGGGTCGCTG CTGGAGAC

GACACTCACT GTACGCTTAA CCAGTGTGAA TGACAACTAC CCAAATTGCG TCTAAAGATT

GTATCATCTC TCGATACAGG AGAAGTTGCT CTTGGGAGAT CGGAATAGCC CGGGTAAAGC

CAATGACCAG GATATTGTTG AAAATCGACA ACTCCTCTCT TACATGTTG AGTATGAGCT

GACAGCACA TTTGAATACTA CTCCCTAGTC CGAGGCAAGC GATGGGTTTA TAAAGCATA

AAGAGCTCTGC GACCCTTGAGC CCAAAATACT CTAATACTCTG AAAGTGGGAG CAGGCAAAT

CCACTGCCGC CCACCTTCTGA GTGCGCAGGG ACCCTTTTAA GATACAACAGC AGTCCAAAAT

TGTTGTAGAG GATGCTGTGAT AGCCCTCCCT CGCTCTCTCA CCCACTTACC TTCTTGAGAT

TCATGAAATGT CCGCGGCTTG AACTTGTGAT TGGGCAAGTG ACGCTCCTG TACCTGATAT

CAGCTCCAGC CCAATAGGT TTTCCATTTG CGGCCARACT GACCTTGGAG GACGCTTCAA

CATCAATGCA GRATGTGGGA AGATAAACCT GCCGACCCCAG CTGGGACAGG AACTAAGGGT

GTGGCCACAC ATCTCCATCA TTGGCTACTG GATCGAGGAAC CACAGTGAC TATGGGCGAT

GCCCTGTGCT ATTAAAGTGC TGGATGTCAA TCAGAAGGCG CCTGAATTGG CTTCGGAAAT

TGAGGGATT TTTATGTAAG AAGGAAAACC CGGCGAAGTA ATATCTCTCA TGGTGGTAAAT

ACGTGATTGG TTTGATACAA CTGCTGCTC CGCTCATTAC TTCTGATTT

TGCTTATGG TGGTATCAGA AGTCACACAG AGGAAAGTCC TCCGAGCGGT AACAGAAGGG

AAATTGCTTC TTCCCTAGAT GTTAACCTCA TTCTAACACTA GGAACCAATT GCGCTGAGAA

GTGTGATGAT CTCTCTCTCT CTCGCCCAG CCAAAATTTA GCTCAAACAT GTTCTAAATAC AGATCACATA

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GAATCAAGG AATAGCTCAT GGGAGCCATG CATTTTTGTG TTATGTTGAA AGAAAGATTA
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CTTAGTGCTG TACAGATATT TGCAAGTTTA GTAAACATGG TGTAGACATC AAATGTTAG 2580
ATATGCCCTT AAGGGATTTC AATATGTAGA GTGAAAGCTC GTAAGGCTACTA GAGGGGAGA 2640
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CAAAACAAAAA TCTACAGAAA CCACATATCC GCAAGTGCAC AATGCACACT AACCTCTGTA 2880
AAATCACCCA ACCACATCTG TAATAGATTT ATTTTAACGA GGTGCGGGG CTACATCTGT 2940
TTTAGAARCT TATCATTTT CACTTCTCA ATTTATTTCT GGATGGTGAC ATTTAATT 3000
AAATAAACAG CAGCTGACAT CATGAAAAAA AAAAAAAA AAA 3043

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 532 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Met Pro Glu Arg Leu Ala Glu Thr Leu Leu Asp Leu Trp Thr Pro Leu  
1  5
Ile Ile Leu Trp Ile Thr Leu Pro Ser Phe Val Tyr Met Ala Pro Met  
20 25
Asn Gln Ala His Val Leu Thr Thr Gly Ser Pro Leu Glu Leu Ser Ser Arg  
35 40 45
Gln Ser Glu Glu Met Arg Ile Leu Asn Arg Ser Lys Arg Gly Trp Val  
50 55 60
Trp Asn Gln Met Phe Val Leu Glu Glu Phe Ser Gly Pro Glu Pro Ile  
65 70 75 80
Leu Val Gly Arg Leu His Thr Asp Leu Asp Pro Gly Ser Lys Lys Ile  
85 90 95
Lys Tyr Ile Leu Ser Gly Asp Gly Ala Gly Thr Ile Phe Gln Ile Asn  
100 105 110
Asp Ile Thr Gly Asp Ile His Ala Ile Lys Arg Leu Asp Arg Glu Glu  
115 120 125
Lys Ala Glu Tyr Thr Leu Thr Ala Gln Ala Val Asp Trp Glu Thr Asn  
130 135 140
Lys Pro Leu Glu Pro Pro Ser Glu Phe Ile Lys Val Gln Asp Ile  
145 150 155 160
Asn Asp Asn Ala Pro Glu Phe Leu Asn Gly Pro Tyr His Ala Thr Val  
165 170 175
Pro Glu Met Ser Ile Leu Gly Thr Ser Val Thr Asn Val Thr Ala Thr  
180 185 190
(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2490 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(x) SEQUENCE DESCRIPTION: SEQ ID NO:45:

GGCACGAGGG CCAGTGGAGG CAGACCTACA ATTTGTGATC AAAATTCAAC ATATCAACGA
CAATGAGCCT ACATTCCCGAG AAGAATTAA TACAGCGCAG GTTCTCGAAA TGTCCTTGTT
AGGTACTTCT GTCTGTCAGG TCAAGAGCTC AGATGCGGAT GACCTTTCAT ATGGAAACAG
GGCAAGAGTC ATTTACAGCA TACTCTCAGGG CGACCTCCAT TTCTCTCTGG GACGAACAGG
AGGTACCATC AGAGACGCTG TACCAGGACAT GAACAGAGGA AAACAAGAAC AGTACGAGTT
GGTATTCAAA GGCAAGGACA TGCCGGTCGA GTAGGCGGTG ATGTCTTGAA CCACCAAGTT
GAACACACTCT CTCAGAAGTG TCAAGGACAA TGCCCTGATC TTCCCTCATA ACACCATCCA
CTCTGGAGTT CTGGATCTCT CTCCAGTGAG CAGACGGTGT GGAGATTTAA AAGGACCCGA
TGGCTGACCG GGGAAGATTG CGGAGATGGA TTACCGCATT ATTTGAGGAG AGTGGACAGA
TAGTGGACTG GATAGAGGCTC CAGTTTTCAG TGATCCTATC TATCTGTGTG AGTGTCACTG
GGGTATGGAG GTGGCGGCAAC TCCATCCATGC TCTCGATTTT AAGAATGGCA GACGAGGACT
TTCTGGGAAAG GGTGGACTTC ATATCATGAA GCCACCTTTG ATGTAGACTG TCTGCTGGCA
CAGCTTACCC GCTGATGCTG CGGAGATCAA TAATCCTAAA GAAACAACCT GTGTCTCTGT
TTTGTGGAGG ATTTGGAAG TTAAGGCAAA GCTCCACAAG TTTGCTGTGT TTAGATGACA
ATTGTGATGT AAAAAACGCA GACGAGGACA GTGATACAG ACAATAAGTG CAGGACGAGA
AGATGACCGC TTAGGGGAC AGAGATTCTT CTAGTGGTGG GTGCTGGTGA ATCTCAACTT
CACGGCGCAA GACAAAGAG ACAACACTGCG CAGAATTATA ACCGAAAAAG AGGGCTCTCAAA
CGCTCATGAA ATATGAGCCT ATCTACTGCC GGTAGTGATA TCTGATAATG ACTACCCCAT
TCAGACCCGC AGTGCCCACCC TGATGATCGG TGTGTGGGCC TGTGACAGCC AAGGCAACAT
GCCAGCTTCG AGTGGCGGAG CCGCTCTCCAT TCGCTGGGGG CTCAGACACTG GCCCCTTTGA
CGCATTCTCT CTCCTGCTCCG ATGTCTGCTG GGTATACTGA TCTCTTCTGG CAGGCGTGA
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Phe Ile Pro Arg Thr Pro Thr Ala Pro Asn Thr Asp Val Arg

Asp Phe Ile Asn Glu Arg Leu Lys Glu His Asp Leu Asp Pro Thr Ala

Pro Pro Tyr Asp Ser Leu Ala Thr Tyr Ala Tyr Glu Gly Asn Asp Ser

Val Ala Glu Ser Leu Ser Ser Leu Glu Ser Gly Thr Thr Glu Gly Asp

Gln Asn Tyr Asp Tyr Leu Arg Glu Trp Gly Pro Arg Phe Asn Lys Leu

Ala Glu Met Tyr Gly Gly Gly Gly Ser Asp Lys Asp Ala

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 3048 base pairs
   (B) TYPE: nucleic acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

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CTGAGATGGA TTACACGGCA TTAATCTCC AAAAAATTC TTAAAGGGGAA AAGCTACTTC
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AAGTCAAGTT CAGCAGCTGT GTGGGGACCA AGGGGACACA ATATAGGACC AACAGCATGG
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(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 916 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

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Leu Glu Gly Glu Lys Leu Leu Gln Val Lys Phe Ser Ser Cys Val Gly  50  55  60
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Ala Asp Gly Thr Val Phe Ala Thr Arg Glu Leu Gln Val Pro Ser Glu  85  90  95
Gln Val Ala Phe Thr Val Thr Ala Trp Asp Ser Gly Thr Ala Glu Lys 100 105 110
Trp Asp Ala Val Val Arg Leu Leu Val Ala Gln Thr Ser Ser Pro His 115 120 125
Ser Gly His Lys Lys Pro Gln Lys Gly Lys Lys Val Ala Leu Asp Pro 130 135 140
Ser Pro Pro Pro Lys Asp Thr Leu Leu Pro Trp Pro Gln His Gln Asn 145 150 155 160
Ala Asn Gly Leu Arg Arg Arg Lys Arg Asp Trp Val Ile Pro Pro Ile 165 170 175
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(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3164 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:49:

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GCCCAACGGG ACACCCACAG CCTGCGTCCC ACCGACCGGC GCGAAAAGAG AGATTTGAGT
TGGAAACCGGA TGCCGATGGA TGAAGAGAAA AACAACCTCA TTCCCCATCA TGTAAGCGAG
ATCAAGTCAA CGGGCGTCTG CCAGAATGGCC AGTACTCAGG TAAGGAGGAC ATACGTGGGC
AAGGCTCTCC GGGTGATGGC AGAGACAGGA AGCCTGCTCG CCAATGAGAG GTGTGAGCGG 420
GAGATAACCT CAGATTACCA CCTCAGCTGT GCTATTTAGG ACAAGGACAC TGGCGAAGAC
CTGGACACTG CTTCAGCATT AACATCCAAA TTCCATGAGC TGAACGCACA CTGCGCCGTG
TTCCACGTCC GTGGTGATCG CCTGAGCTTG GGCGCGTGGG GACCTCAGTC
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ATAACGAAAAC GCGTGGACCC AGAGAGACAC GCCGATATGG AGATCTTGCT GGAACGGGGA
GACGCCCGGG GCCTCCCCGGG GAGACTCGGG ACGGCCACGC TGCTGGTCAG TCTGCAAGAC
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TGGACTGTTGG GGGCAGGATT CTCTGCGACC CATTCCCGAG GAGAGCTGAC CATTGATCCC 2940
TCTCCTGGGA GCCCTACCCC TGCTCATACT CCACACTTGA CTCCGAGTGC CCGCCACTTC 3000
CCGACCCCTT CTCCAGGGCT GTCAAGAGGG AGGAGGCGGC CCCATGCGAC CGCTCTGACCT 3060
TGGGTCTCTGA AGTGACCTCA GTGCTCCCGT ATGCCAGTAA CTGCTGCTGA CTGACGACTG 3120
AACCCACATT AGGGAAATGG CTTATAAACC TTTGAGCCCA CTGT 3164

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 780 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
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   (B) TYPE: amino acid
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:52:

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Gly Glu Glu Asp Thr Gln Ala Phe Asp Ile Gly Thr Leu Arg Asn Pro
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Glu Ala Ile Glu Asp Asn Lys Leu Arg Arg Asp Ile Val Pro Glu Ala
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Leu Phe Leu Pro Arg Arg Thr Pro Thr Ala Arg Asp Thr Asp Val
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Arg Asp Phe Ile Asn Gln Arg Leu Lys Glu Asn Thr Asp Pro Thr
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Ala Pro Pro Tyr Asp Ser Leu Ala Thr Tyr Ala Tyr Glu Gly Thr Gly
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Ser Val Ala Asp Ser Leu Ser Ser Leu Glu Ser Val Thr Thr Ala
370 375 380

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(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 2550 base pairs
    (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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AATCAGAGAT TTGTCCTGGA AGAGTTCTTC GGAGCTGAAC CGATTCTTG TGAGGCGGTATA 240
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(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 793 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

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<tr>
<td>Ser Tyr Asp Ile Ile Asp Gly Gly Thr Ala Leu Phe Glu Ile Thr</td>
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<tr>
<td>Gly Ala Gly Thr Ile Phe Gln Ile Asn Asp Val Thr Gly Asp Ile His</td>
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<tr>
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Ser Asp Ala Gln Ala Gln Asp Gly Ile Ile Arg Leu Arg Lys Pro Leu
          325 330 335
Asp Phe Glu Thr Lys Ser Tyr Thr Leu Leu Asp Glu Ala Ala Asn
          340 345 350
Val His Ile Asp Pro Arg Phe Ser Gly Arg Gly Pro Phe Lys Asp Thr
          355 360 365
Ala Thr Val Lys Ile Val Val Glu Ala Asp Glu Pro Pro Val Phe
          370 375 380
Ser Ser Pro Thr Tyr Leu Leu Glu Val His Glu Asn Ala Ala Leu Asn
          385 390 395 400
Ser Val Ile Gly Gln Val Thr Ala Arg Asp Pro Asp Ile Thr Ser Ser
          405 410 415
Pro Ile Arg Phe Ser Ile Asp Arg His Thr Asp Leu Glu Arg Gln Phe
          420 425 430
Asn Ile Asn Ala Asp Gly Lys Ile Thr Leu Ala Thr Pro Leu Asp
          435 440 445
Arg Glu Leu Ser Val Trp His Asn Ile Thr Ile Ala Ala Thr Glu Ile
          450 455 460
Arg Asn His Ser Gln Ile Ser Arg Val Pro Val Ala Ile Lys Val Leu
          465 470 475 480
Asp Val Asn Asp Ala Pro Glu Phe Ala Ser Glu Tyr Glu Ala Phe
          485 490 495
Leu Cys Glu Asn Gly Lys Pro Gly Gln Val Ile Gln Thr Val Ser Ala
          500 505 510
Met Asp Lys Asp Asp Pro Lys Asp Gly His Tyr Phe Leu Tyr Ser Leu
          515 520 525
Leu Pro Glu Met Val Asn Pro Asn Phe Thr Ile Lys Asn Glu
          530 535 540
Asp Asn Ser Leu Ser Ile Leu Ala Lys His Asn Gly Phe Asn Arg Gln
          545 550 555 560
Lys Gln Glu Val Tyr Leu Leu Pro Ile Ile Ile Ser Asp Ser Gly Asn
          565 570 575
Pro Pro Leu Ser Thr Ser Thr Leu Thr Ile Arg Val Cys Gly Cys
          580 585 590
Ser Asn Asp Gly Val Val Gln Ser Cys Asn Val Glu Ala Tyr Val Leu
          595 600 605
Pro Ile Gly Leu Ser Met Gly Ala Leu Ile Ala Ile Leu Ala Cys Ile
          610 615 620
Ile Leu Leu Val Ile Val Val Phe Val Thr Leu Arg Arg His
          625 630 635 640
Gln Lys Asn Glu Pro Leu Ile Ile Lys Asp Asp Glu Asp Val Arg Glu
          645 650 655
Asn Ile Ile Arg Tyr Asp Glu Gly Gly Gly Glu Asp Thr Glu
          660 665 670
-75-

Ala Phe Asp Ile Ala Thr Leu Gln Asn Pro Asp Gly Ile Asn Gly Phe
675

Leu Pro Arg Lys Asp Ile Lys Pro Asp Leu Gln Phe Met Pro Arg Gln
690

Gly Leu Ala Pro Val Pro Asn Gly Val Asp Val Asp Glu Phe Ile Asn
705

Val Arg Leu His Glu Ala Asp Asn Pro Thr Ala Pro Pro Tyr Asp
725

Ser Ile Gln Ile Tyr Gly Tyr Glu Gly Arg Gly Ser Val Ala Gly Ser
740

Leu Ser Ser Leu Glu Ser Thr Thr Ser Ser Asp Ser Asp Gln Asn Phe Asp
755

Tyr Leu Ser Asp Trp Gly Pro Arg Phe Lys Arg Leu Gly Glu Leu Tyr
775

Ser Val Gly Glu Ser Asp Lys Glu Thr
790

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
A) LENGTH: 730 base pairs
B) TYPE: nucleic acid
C) STRANDEDNESS: single
D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
A) NAME/KEY: CDS
B) LOCATION: 2..730

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

G AAT TCG AGC TCG GTA CCC GGG GAT CCT CTA GAG TCG ACC TGC AGT
1 5 10 15

Asn Ser Ser Ser Val Pro Gly Asp Pro Leu Glu Ser Thr Cys Ser

GCT GAA GCC CTG CTC CTC CCT GCC GCC CTC ACC ACT GGG GCC TCG ATC
20

Ala Glu Ala Leu Leu Leu Pro Ala Gly Leu Ser Thr Gly Ala Leu Ile
25 30

GCC ATC CTC TCC TCC ATC ATC ATT CTA CGT GTA GTA GTA CGT TTT
35 40 45

Ala Ile Leu Leu Cys Ile Ile Leu Leu Val Ile Val Leu Phe

GCA GCT CGT AAA AGA CAG CGA AAA AAA GAG CCT CTG ATC TTG TCA AAA
50 55 60

Ala Ala Leu Lys Arg Gln Arg Lys Lys Glu Pro Leu Ile Leu Ser Lys

GAA GAT ATC AGA GAC AAC ATT GTG AGC TAT AAC GAT GAG GGT GGA
65 70 75

Glu Asp Ile Arg Asp Asn Val Ser Tyr Asn Asp Glu Gly Gly Gly

GAG GAG GAC ACC CAG GCC TTT GAT ATC GGC ACC CTG AGG AAT CCT GCA
80 85 90 95

Glu Glu Asp Thr Gln Ala Phe Asp Ile Gly Thr Leu Arg Asn Pro Ala

GCC ATT GAG GAA AAA AAG CTC CGG GCA GAT ATT ATT CCA GAA ACG TTA
Ala Ile Glu Glu Lys Lys Leu Arg Arg Asp Ile Ile Pro Glu Thr Leu
100 105 110

TTT ATT CCT CGG AGG ACT CCT ACA GCT CCA GAT AAC ACG GAC GTC CGG
Phe Ile Pro Arg Arg Thr Pro Thr Ala Pro Asn Thr Asp Val Arg
115 120 125

GAT TTC ATT AAT GAA AGG CTA AAA GAG CAT GAT CTT GAC CCC ACC GCA
Asp Phe Ile Asn Glu Arg Leu Lys Glu His Asp Leu Asp Pro Thr Ala
130 135 140

CCC CCC TAC GAC TCA CTT GCA ACC TAT GCC TAT GAA GGA AAT GAT TCC
Pro Pro Tyr Asp Ser Leu Ala Thr Tyr Ala Tyr Glu Gly Asn Asp Ser
145 150 155

ATT GCT GAA TCT CTG AGT TCA TTA GAA TCA GGT ACT ACT GAA GGA GAC
Ile Ala Glu Ser Leu Ser Leu Glu Ser Gly Thr Thr Gly Thr Gly Asp
160 165 170 175

CAA AAC TAC GAT TAC CTC CGA GAA TGG GGC CCT CGG TTT AAT AAG CTA
Gln Asn Tyr Asp Tyr Leu Arg Glu Trp Gly Pro Arg Phe Asn Lys Leu
180 185 190

GCA GAA ATG TAT GGT GCT GGG GAA AAT GAC AAA GAC TCT TAA CTT AGG
Ala Glu Met Tyr Gly Gly Gly Glu Ser Asp Asp Ser * Arg Arg
195 200 205

ATA TAT GCT CGT TCC AAA CAA GAG AAT GCT ACT ATA CCC ACG CTG TCT
Ile Tyr Val Leu Phe Lys Glu Lys Val Thr Leu Pro Met Leu Ser
210 215 220

CCA CTT CAC AAT ATT TGA TAT TCA GGA GCA TTT CCT GCA GTC AGC ACA
Pro Leu His Asn Ile * Tyr Ser Gly Ala Phe Pro Ala Val Ser Thr
225 230 235

ATT TTC TCA
Ile Phe Phe Ser
240

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 241 amino acids
    (B) TYPE: amino acid
    (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Asn Ser Ser Ser Val Pro Gly Asp Pro Leu Glu Ser Thr Cys Ser Ala
1  5 10 15

Glu Ala Leu Leu Leu Pro Ala Gly Leu Ser Thr Gly Ala Leu Ile Ala
20 25 30

Ile Leu Leu Cys Ile Ile Leu Leu Val Ile Val Val Leu Phe Ala
35 40 45

Ala Leu Lys Arg Gln Arg Lys Lys Glu Pro Leu Ile Leu Ser Lys Glu
50 55 60

Asp Ile Arg Asp Asn Ile Val Ser Tyr Asn Asp Glu Gly Gly Gly Glu
65 70 75 80
(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2625 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

CGGCGCCCT GACGTGATGA GCTCAACCAG CAGAGACATTT CCACTCCCAAG AGAGGCTCTGC  
60
GTGACGGCTC CGGGGGCCA CCCTCAAGAA GACACCCGTA CAGTTGGTGG AAGGGGTGAC  
120
AGCTGCATTCC TCTCTGGGCT ACCACGTAC CAAAATGAA GGAGAATATC TTTTACAG  
180
CGCCCTGGGT GTGCCCTGGGC ATGGCTGTCG GCACCGCATGC TTTGCCCCCA GAGCGGCGGG  
240
GGCCACTGGC GCCCTCCCTC CATGGGACCC ATGAGAAGGG CAGGGGCGGG CAGGTGCTAC  
300
AGCCTGCCC AGCCTGCTGGG CTGCGGAACCG AGTCTTGGGT GATAGAGGAG TACACCGGGG  
360
CTGACCGCCGG CAGTGTGGGC AGGCCTCATT CCACTTTGTA CTTCTGGATG GGGAAACATT  
420
AATACATCT CTGAGGGGAA GAGTGGTCA CCCATTTGGT GATGGATGAC AAATCAGGGG  
480
ACATTGAGTC CACCGGAGCC TGCGATGCGGA AAGAGAGACC CCGTACACCG TGGATGGCTC  
540
AGCGCGTGGCA CAGGGACACC AATCGGCCAAG TGGAGCCACC GTCGGAATTC ATGTCAAGG  
600
TGAGGAGTCT TAATGACACG CCTCCGGAGT TCCTGCAAGA GACCTATCAT GCCAACGTGC 660
CTGAGGAGTCT CAATGGCAGA AGTCACTGAA TCATCGTGAC AGCTTCGAGT GACGATGCC 720
CAGCTTGAGG CGAGATCGCC AAGAGGTGGTC AGAATGATCAC CCGAGCCAGC CAGCTTTTGC 780
CGGTGGAGG TGGCTAAGTGG ATCTACAGA CAGCCCTACC AACAGCAGCCAG AGGGAGCCCA 840
AGGGAGGTA CCACGCTTGGT ATCCAGCGCA CGGAGATGGT TCGAGAAATG GCCGGCATCT 900
CAGGGAGGCA CAAGTGGAGC ATGCACAGTCG CTGATGTGCA TGAACACCCCA CCAAGTTTGC 960
CGGAGGCAAT ATACCAGATG TCTGCTTCAG AAGCAGCCGT CCTGCGGGAG GAGTACGGAA 1020
GAGTGGAAGC TAAAGATCCA GACATGGGCT AAAATGGGCTT AGTCACATAC AATATTTGTTG 1080
ATGAGGATGG TAGGAATGCG TTTGAAATCA CAACGAGCTA TGAACACGAG GAGGGGGTGTA 1140
TAAAGCTGAAG AAGCCGGTGA GATTTTGCGA CGGAAAGAGGC CTAAGGCTCTG AGGGTAGAGG 1200
CAGCCAGAAG TGCAGTCGGA CGGAGTCTTA TGACACATGG CCTTTCAGAG GACACTGTA 1260
CGGTGACATG ACTCAGACTG AAAGTCAGTG ATGGCTAGTG AGGCCCCCTAT GTTCTTGGCC CCAAGTTTACA 1320
TCCAGAACGG TCAAGAAAAT CGCCGGCTCG CGACGGTGGT TGGGAGAGTG CATGGCAGAG 1380
ACCCGTAGTG TGGCAGACCC GGAGTAAAGT ATCCATGCA TCGTCACACT GACCTCGACA 1440
GATTTTCCAC TATTATACCA GAGAGTGTTT TATATTAAC TACAACACCT CTGGGATAGG 1500
AGAGAAACAGC CGGCTCAACC ATCACTGTCT TGGCACAGAG AATCCACATA CGGAGTCAGG 1560
 AACGGCACTG CCGGCTGGCC ATTAGGGTCC TTGGATGCTAA CGATAATGGCT CCAAGTTTGC 1620
CTGCCCTCTA TGAAGGGTTTC ATCTGTGGAG GTGATCGAGC CAGGCCAATCT TCCACCAGCC 1680
CAATTGGTTAC AAATAGTGCA GATGACAGAA ATGACACCCGC CAATGGGACCA AGATTTATCT 1740
TCCAGCTACC CCGTGAATTC ATTCACATTC CAAATTTCAC ATGCAGAGAC AACCCAGATA 1800
ACACGGCCGG CTGCTAGTCGC CGGCGGCGG GGTGATGTGC GCAGAAGCGA GACTTTGACC 1860
TTCTGCCCCTG ATGTCGACGG GATGCGCGCGA TCCGCGCCT GCAGTAGACC AACACCTCTCA 1920
CCATCAAAGTG CGCGGGGTGC GAGGCTAACG GGGCCACTGC CTCTGCGAAC GACAGGCGGT 1980
ACATTCTGAA CCGCGCCTGC AGACAGGGG CCGTGTACGC CATCTCAGCC TGCACTGGTC A 2040
TTCCTCTGGT CATTCTGCTG TAGTTTTGGC CTTCTGAGAG GCGAAGAGAA GCACACTCCT 2100
TTGTCTTTTG GGGAGAGAT GCGCGTGGAG AGATCATAC TTTATAGTAG GAAAGGGTGTA 2160
GGGAAAGAGA CACGGAAGCC TTTGATATGC CCACACCTCA AGATTCCATG GGATTCAATGT 2220
GATTAATGCC CGGCGAAGAC ATCAAACCTG AGATATCGTG ATGCGCTAGA CCTGGGGCTCC 2280
GGCCGCGGCC CAAGCCAGTT GATGGCTAGT ATCTGCTCAAG CACGAGAAAT CAGGGCAAG 2340
ACAACTGACC CACGGCTCCT CCTTATGAGC CACATTTCAT CTCAGGTTAT GAAAGCGGCG 2400
GCGAGTGGGC CGGGCTCTTG AGCTGCTTACG TCTCTCCAGG CACAGATCTT GACCTGGACT 2460
AGATTATCT ACAAGACTGC GGACATCGTTG TTAAGAAACT AGCAGATTTTG TATGTGTCCCA 2520
AAGAACATT TGAATGAGAT TCTTAAATAC AACGGATAAA ATTTTCGCTT AAGAAGCTTG 2580
TCTGCGGCTTC TCAAGAATCT AGAAGATGTC TAAAGGTAT TTTTTT 2625
(2) INFORMATION FOR SEQ ID NO:58:

    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 796 amino acids
        (B) TYPE: amino acid
        (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: protein

    (x) SEQUENCE DESCRIPTION: SEQ ID NO:58:

    Met  Lys  Glu  Asn  Tyr  Cys Leu  Gln  Ala  Ala  Leu  Val  Cys Leu  Gly  Met
    1      5       10      15
    Leu  Cys  His  Ser  His  Ala  Phe  Ala  Pro  Glu  Arg  Arg  Gly  His  Leu  Arg
    20     25       30      35
    Pro  Ser  Phe  His  Gly  His  His  Glu  Lys  Gly  Lys  Glu  Gln  Val  Leu
    35     40       45      50
    Gln  Arg  Ser  Lys  Arg  Gly  Trp  Val  Trp  Asn  Gln  Phe  Phe  Val  Ile  Glu
    55     60
    Glu  Tyr  Thr  Gly  Pro  Asp  Pro  Val  Leu  Val  Gly  Arg  Leu  His  Ser  Asp
    65     70       75      80
    Ile  Asp  Ser  Gly  Asp  Gly  Asn  Ile  Tyr  Ile  Leu  Ser  Gly  Glu  Gly
    85     90
    Ala  Gly  Thr  Ile  Phe  Val  Ile  Asp  Asp  Lys  Ser  Gly  Asn  Ile  His  Ala
    100    105      110
    Thr  Lys  Thr  Leu  Asp  Arg  Glu  Arg  Ala  Gln  Tyr  Thr  Leu  Met  Ala
    115    120      125
    Gln  Ala  Val  Asp  Arg  Asp  Thr  Asn  Arg  Pro  Leu  Glu  Pro  Pro  Ser  Glu
    130    135      140
    Phe  Ile  Val  Lys  Val  Gln  Asp  Ile  Asn  Asp  Asp  Pro  Glu  Phe  Leu
    145    150      155     160
    His  Glu  Thr  Tyr  His  Ala  Asn  Pro  Glu  Arg  Ser  Asn  Val  Gly  Thr
    165    170      175
    Ser  Val  Ile  Gln  Val  Thr  Ala  Ser  Asp  Ala  Asp  Asp  Pro  Thr  Tyr  Gly
    180    185      190
    Asn  Ser  Ala  Lys  Leu  Val  Tyr  Ser  Ile  Leu  Glu  Gly  Glu  Pro  Tyr  Phe
    195    200      205
    Ser  Val  Glu  Ala  Gln  Thr  Gly  Ile  Ile  Arg  Thr  Ala  Leu  Pro  Asn  Met
    210    215      220
    Asp  Arg  Glu  Ala  Lys  Glu  Tyr  His  Val  Ile  Gln  Ala  Lys  Asp
    225    230      235     240
    Met  Gly  Gly  His  Met  Gly  Gly  Leu  Ser  Gly  Thr  Thr  Lys  Val  Thr  Ile
    245    250      255
    Thr  Leu  Thr  Asp  Val  Asn  Asp  Asp  Pro  Pro  Lys  Phe  Pro  Glu  Arg  Leu
    260    265      270
    Tyr  Gln  Met  Ser  Val  Ser  Glu  Ala  Ala  Val  Pro  Gly  Glu  Glu  Val  Gly
    275    280      285
    Arg  Val  Lys  Ala  Lys  Asp  Pro  Asp  Ile  Gly  Glu  Asn  Gly  Leu  Val  Thr
    290    295      300
Tyr  Asn  Ile  Val  Asp  Gly  Asp  Gly  Met  Glu  Ser  Phe  Glu  Ile  Thr  Thr  
 305         310         315         320
Asp  Tyr  Glu  Thr  Gln  Glu  Gly  Val  Ile  Lys  Leu  Lys  Lys  Pro  Val  Asp  
 325         330         335
Phe  Glu  Thr  Glu  Arg  Ala  Tyr  Ser  Leu  Lys  Val  Glu  Ala  Ala  Asn  Val  
 340         345         350
His  Ile  Asp  Pro  Lys  Phe  Ile  Ser  Asn  Gly  Pro  Phe  Lys  Asp  Thr  Val  
 355         360         365
Thr  Val  Lys  Ile  Ser  Val  Glu  Asp  Ala  Asp  Glu  Pro  Pro  Met  Phe  Leu  
 370         375         380
Ala  Pro  Ser  Tyr  Ile  His  Glu  Val  Gln  Glu  Asn  Ala  Ala  Ala  Gly  Thr  
 385         390         395         400
Val  Val  Gly  Arg  Val  His  Ala  Lys  Asp  Pro  Asp  Ala  Asn  Ser  Pro  
 405         410         415
Ile  Arg  Tyr  Ser  Ile  Asp  Arg  His  Thr  Asp  Leu  Asp  Arg  Phe  Phe  Thr  
 420         425         430
Ile  Asn  Pro  Glu  Asp  Gly  Phe  Ile  Lys  Thr  Thr  Lys  Pro  Leu  Asp  Arg  
 435         440         445
Glu  Glu  Thr  Ala  Trp  Leu  Asn  Ile  Thr  Val  Phe  Ala  Ala  Glu  Ile  His  
 450         455         460
Asn  Arg  His  Gln  Glu  Ala  Gln  Val  Pro  Val  Ala  Ile  Arg  Val  Leu  Asp  
 465         470         475         480
Val  Asn  Asp  Ala  Pro  Lys  Phe  Ala  Ala  Pro  Tyr  Glu  Gly  Phe  Ile  
 485         490         495
Cys  Glu  Ser  Asp  Gln  Thr  Lys  Pro  Leu  Ser  Asn  Gln  Pro  Ile  Val  Thr  
 500         505         510
Ile  Ser  Ala  Asp  Lys  Asp  Thr  Ala  Asn  Gly  Pro  Arg  Phe  Ile  
 515         520         525
Phe  Ser  Leu  Pro  Pro  Glu  Ile  Ile  His  Pro  Asn  Phe  Thr  Val  Arg  
 530         535         540
Asp  Asn  Arg  Asp  Thr  Ala  Gly  Val  Tyr  Ala  Arg  Gly  Arg  Gly  Phe  
 545         550         555         560
Ser  Arg  Gln  Lys  Gln  Asp  Leu  Tyr  Leu  Pro  Ile  Val  Ile  Ser  Asp  
 565         570         575
Gly  Gly  Ile  Pro  Pro  Met  Ser  Ser  Thr  Asn  Thr  Leu  Thr  Ile  Lys  Val  
 580         585         590
Cys  Gly  Cys  Asp  Val  Asn  Gly  Ala  Leu  Leu  Ser  Cys  Asn  Ala  Glu  Ala  
 595         600         605
Tyr  Ile  Leu  Asn  Ala  Gly  Leu  Ser  Thr  Gly  Ala  Leu  Ile  Ala  Ile  Leu  
 610         615         620
 Ala  Cys  Ile  Val  Ile  Leu  Leu  Val  Ile  Val  Val  Leu  Phe  Val  Thr  Leu  
 625         630         635         640
Arg  Arg  Gln  Lys  Gly  Pro  Leu  Ile  Val  Phe  Glu  Glu  Glu  Asp  Val  
 645         650         655
Arg Glu Asn Ile Ile Thr Tyr Asp Asp Glu Gly Gly Gly Gly Gly Glu Asp
660 665 670
Thr Glu Ala Phe Asp Ile Ala Thr Leu Gln Asn Pro Asp Gly Ile Asn
675 680 685
Gly Phe Ile Pro Arg Lys Asp Ile Lys Pro Glu Tyr Gln Tyr Met Pro
690 695 700
Arg Pro Gly Leu Arg Pro Ala Pro Asn Ser Val Asp Val Asp Asp Phe
705 710 715 720
Ile Asn Thr Arg Ile Gln Glu Ala Asp Asn Pro Thr Ala Pro
725 730 735
Tyr Asp Ser Ile Gln Ile Tyr Gly Tyr Gly Arg Gly Ser Val Ala
740 745 750
Gly Ser Leu Ser Ser Leu Glu Ser Ala Thr Thr Asp Ser Asp Leu Asp
755 760 765
Tyr Asp Tyr Leu Gln Asn Trp Gly Pro Arg Phe Lys Lys Leu Ala Asp
770 775 780
Leu Tyr Gly Ser Lys Asp Thr Phe Asp Asp Asp Ser
785 790 795

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2521 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

CGGTGGAGGC CACAGACACC TCAAACCTGG ATCCACAAAT TCTACCTTTAA GTGTGGAGT
60
TTTTATTACT CTGTGTAGG AAGGCCTTGG CCAATGCTTA CAGGAACTG TGTACCCCTG
120
CTTCTCGGG TTTCTTTTGA TGGGAGCTTGC TAACACCCAC TACAACACAA GCCACAGCAG
180
ACTTTAGCCA CAGAGCCAGG AAGAAATGGT ATCCATCTGG CAGGACACGC GTCACATTTTC
240
CAAGGTGTTA AAGCTGCCGTC GTATGGGATT CAATTTTGTG TGTCTGGAGAG ATACGTGGG
300
TCGGACCTTC AGTATGTGGG AAGCTCCAT TCCGACTTAG ACGAGGGGAG GGGCAGCTTTG
360
AAATACACCC TCTCAGGAGA TGGGGCTTGG ACCGTTTTTA CAATTGATGA AACCCACAGG
420
GACATTCTAG CAATAAGGAG CCTAGATAGA CAAGAGAAAC TTTCTCATAC CTTTCTGCTCT
480
CAGGCTGTGG ACATAGAAAC CAGAAGGCCC CTGGAGCCTTG AATCAAGATT CATCATGAAA
540
GTGGAGGATA TTAATGATA TGAGCCCAAG TTTTTGGATG GACCTTATGT TGCTACTGTT
600
CCAGGAAATCT TCTCTGTGGG TTGATATGTA TCCAGGTCTA AGGCCACAGA TGCAAGATGAC
660
CCAGAATTATG GAAGAATGGC CAGAGCTGTT TCAAGCATTC TCCAGGGACA ACGTTATTTC
720
TCTATTGATG CCAAGACAGG TGTTATTAGA ACGCTTTGCA CAAACATGGA CAGAGAAGTC
780
WO 93/21302

PCT/US93/03681

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AAAGAAACAT ATCAAGTACT CATCCCAAGCC AAGGATATGG GAGGACAGCT TGGAGGATTA 840
GGCCGAACAA CAAATTGCTAA CATCCTCTCT ACCGAGTCTA ATGAGCAATCC ACGCTGATTC 900
CCCAAAGGCA TCTTCTACCT TAAAAGGCTT GAGTCTTCCC CTATTGGTAC AGCTATTGGA 960
AGAATAGAGG CTGTTGATCC TGATTTTTGA CAAAAATGAGG AAATTGAAAT ACAATTTGTT 1020
CCAGGAGATG GGCGGAATTT GTTTGACACT GTCACAGATG AGGATACACAG AGAGGGAGTC 1080
ATCAAGATGA AAAAAAGTTT AGATTGTGAA ACAGGAAAGG CATACACTTT CAAAGGTGAG 1140
GCTTCCAACC TTTACCTTGA CCACCCGGTTT CACTGCAGGG GCGCTTTTCA AGACACAGCT 1200
ACGGGTAGAGA TCAGCTTGCTG GGACGTAGAT GAGCCAGCCG TTTTCGACAA GCGGCCCTTC 1260
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GAAAGCCTGG CAGCAGTATAA TTTCTCTCAAA ATGTGCAAGTA AAGTTAGTAA CCCCTTATTG 1500
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CCTGAGGGCTG CTAACAAACC AAATTTTACAA GTTGTGACTC TCAAGAACAA CAGAGGGGG 1740
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GTAAATGAGG ACAGCAGCTA CCCCCTCCAG AGCAGCAGCA AAACAAATGAC TATTGGGATC 1860
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GTCAGACTTG CAGCAGGCGC GTTGTCATTAT ATGTGCAAGTA AATGAAATACCT TCCAGAATAA 1980
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CCTGATAAAG TCACCTTAAG GAGCTTGAGA GCGTAAATAA CAACCGAGAG GGGAGATTIT 2520

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(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
   (a) LENGTH: 794 amino acids
   (B) TYPE: amino acid
   (D) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Met Leu Thr Arg Asn Cys Leu Ser Leu Leu Leu Trp Val Leu Phe Asp 1 5 10 15
Gly Gly Leu Leu Thr Pro Leu Gln Pro Gln Pro Gln Thr Leu Ala 20 25 30
Thr Glu Pro Arg Glu Asn Val Ile His Leu Pro Gly Gln Arg Ser His 35 40 45
Phe Glu Arg Val Lys Arg Gly Trp Val Trp Asn Gln Phe Phe Val Leu 50 55 60
Glu Glu Tyr Val Gly Ser Glu Pro Gln Tyr Val Gly Lys Leu His Ser 65 70 75 80
Asp Leu Asp Lys Gly Glu Gly Thr Val Lys Tyr Thr Leu Ser Gly Asp 85 90 95
Gly Ala Gly Thr Val Phe Thr Ile Asp Glu Thr Thr Gly Asp Ile His 100 105 110
Ala Ile Arg Ser Leu Asp Arg Glu Lys Pro Phe Tyr Thr Leu Arg 115 120 125
Ala Glu Ala Val Asp Ile Glu Thr Arg Glu Pro Leu Glu Pro Glu Ser 130 135 140
Glu Phe Ile Lys Val Glu Asp Ile Asn Asp Asn Glu Pro Lys Phe 145 150 155 160
Leu Asp Gly Pro Tyr Val Ala Thr Val Pro Glu Met Ser Pro Val Gly 165 170 175
Ala Tyr Val Leu Glu Val Lys Ala Thr Asp Ala Asp Asp Pro Thr Tyr 180 185 190
Gly Asn Ser Ala Arg Val Val Tyr Ser Ile Leu Gln Gly Glu Pro Tyr 195 200 205
Phe Ser Ile Asp Pro Lys Thr Gly Val Ile Arg Thr Ala Leu Pro Asn 210 215 220
Met Asp Arg Glu Val Lys Glu Gln Tyr Glu Glu Val Leu Ile Gln Ala Lys 225 230 235 240
Asp Met Gly Gly Lys Glu Gly Leu Gly Leu Gly Ala Gly Thr Thr Ile Val Asn 245 250 255
Ile Thr Leu Thr Asp Val Asn Asp Pro Pro Arg Phe Pro Lys Ser 260 265 270
Ile Phe His Leu Lys Val Pro Glu Ser Ser Pro Ile Gly Ser Gly Ile 275 280 285
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(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2690 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

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(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 713 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

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Arg Tyr Glu Val Ser Ser Pro Tyr Phe Lys Val Asn Ser Asp Gly Gly
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675 680 685

Cys Asn Ala Ala Gly Ala Leu Arg Phe Ser Leu Pro Ser Val Ile Leu

690 695 700

Leu Ser Leu Phe Ser Leu Ala Cys Leu

705 710
INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page 6, line 12-21.

<table>
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<th>B. IDENTIFICATION OF DEPOSIT</th>
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<tr>
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<tr>
<td>Date of deposit</td>
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C. ADDITIONAL INDICATIONS (leave blank if not applicable)

"In respect of those designations in which a European patent is sought, a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 23(4) EPC)."

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)

EP

E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)

The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

For receiving Office use only

[ ] This sheet was received with the international application

Authorized officer

Helen Bell

For International Bureau use only

[ ] This sheet was received by the International Bureau on:

Authorized officer

Form PCT/RO/134 (July 1992)
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What is claimed is:

1. A purified and isolated polynucleotide encoding a cadherin selected from the group consisting of cadherin-6, cadherin-7, cadherin-9 and cadherin-10.

2. The polynucleotide of claim 1 which is a DNA sequence.

3. The polynucleotide of claim 2 which is a cDNA sequence or biological replica thereof.

4. The polynucleotide of claim 3 which is SEQ ID NO: 51.

5. The polynucleotide of claim 3 which is SEQ ID NO: 15.

6. The polynucleotide of claim 3 which is SEQ ID NO: 19 or SEQ ID NO: 33.

7. The polynucleotide of claim 3 which is SEQ ID NO: 55.

8. The polynucleotide of claim 2 which is a genomic DNA or a biological replica thereof.

9. The DNA of claim 2 which is a wholly or partially chemically synthesized DNA or a biological replica thereof.

10. A biologically functional DNA vector comprising a DNA according to claim 2.
11. The vector of claim 10 wherein said DNA is operatively linked to an expression control DNA sequence.

12. A host cell stably transformed or transfected with a DNA according to claim 2 in a manner allowing the expression in said host cell of the cadherin polypeptide encoded thereby.

13. A method for producing a cadherin polypeptide comprising the steps of growing a host cell according to claim 12 in a suitable nutrient medium and isolating the cadherin from said cell or from the medium of its growth.

14. A purified and isolated full length cadherin polypeptide selected from the group consisting of cadherin-6 polypeptide (SEQ ID NO: 52), cadherin-7 polypeptide (SEQ ID NO: 16), cadherin-9 polypeptide (SEQ ID NO: 20 or 34) and cadherin-10 polypeptide (SEQ ID NO: 56).

15. A hybridoma cell line producing a monoclonal antibody specific for a cadherin selected from the group consisting of cadherin-6, cadherin-7, cadherin-9 and cadherin-10.

16. A hybridoma cell line producing a monoclonal antibody specific for cadherin-5 selected from the group consisting of 30Q8A (ATCC HB11316), 30Q4H (ATCC HB11317), 45A5G (ATCC HB11318), 30S2F (ATCC HB11319), 45C6A (ATCC HB11320) and 30T11G (ATCC 11324).

17. A monoclonal antibody produced by the hybridoma cell line of claim 16.
18. An antibody substance specific for a cadherin selected from the group consisting of cadherin-6, cadherin-7, cadherin-9 and cadherin-10.

19. A method for modulating the binding capability of a cadherin selected from the group consisting of cadherin-6, cadherin-7, cadherin-9 and cadherin-10 comprising contacting the cadherin with an antibody substance specific for said cadherin according to claim 18.

20. A method for modulating the binding capability of a cadherin selected from the group consisting of cadherin-6, cadherin-7, cadherin-9 and cadherin-10 comprising contacting the cadherin with a polypeptide or peptide ligand of the cadherin.

21. A method for modulating the binding capability of a cadherin selected from the group consisting of cadherin-6, cadherin-7, cadherin-9 and cadherin-10 comprising contacting the cadherin with a peptide of said cadherin.
FIGURE 1
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

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

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

Medline, APS, Dialog, WPI

Search terms: neural cadherin, cloning, antibodies

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C. See patent family annex.

| Special categories of cited documents: |
|---|---|
| T | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| X | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| Y | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| G | document member of the same patent family |

**Date of the actual completion of the international search**

12 JULY 1993

**Date of mailing of the international search report**

21 JUL 1993

**Name and mailing address of the ISA/US Commissioner of Patents and Trademarks**

Box PCT
Washington, D.C. 20231

**Facsimile No.** NOT APPLICABLE

**Authorized officer**

SALLY P. TEN

**Telephone No.** (703) 308-0196
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<td>Journal of Cell Science, Volume 97, issued December 1990, B. Geiger et al., &quot;Broad Spectrum Pan-Cadherin Antibodies, Reactive with the C-Terminal 24 Amino Acid Residues of N-Cadherin&quot;, pages 607-614, see abstract</td>
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