



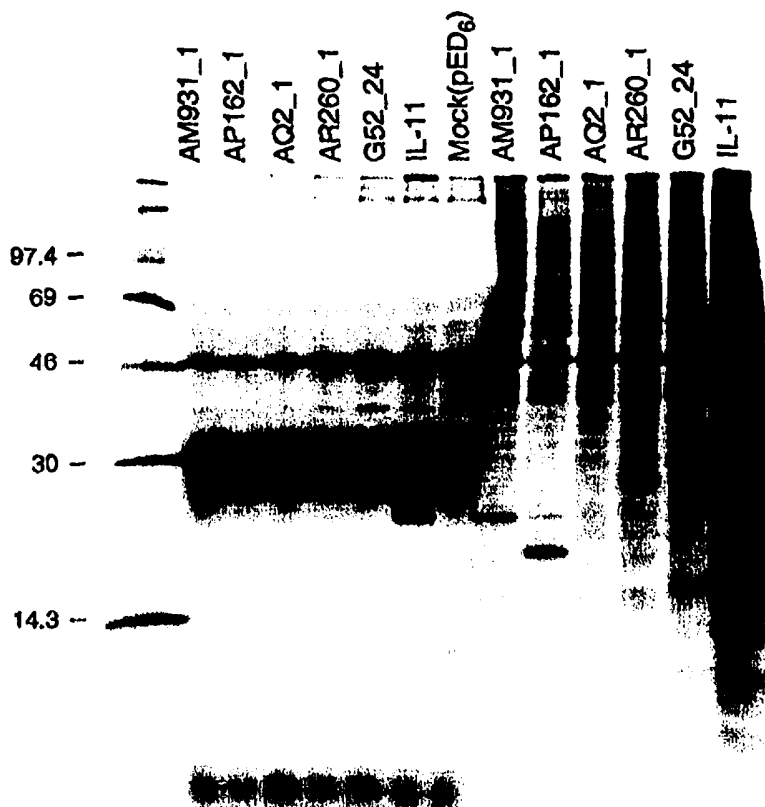
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(21) International Application Number: PCT/US97/06134 (22) International Filing Date: 14 April 1997 (14.04.97) (30) Priority Data: 08/635,311 19 April 1996 (19.04.96) US (71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 CambridgePark Drive, Cambridge, MA 02140 (US). (72) Inventors: JACOBS, Kenneth; 151 Beaumont Avenue, Newton, MA 02160 (US). MCCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). LAVALLIE, Edward, R.; 90 Green Meadow Drive, Tewksbury, MA 01876 (US). MERBERG, David; 2 Orchard Drive, Acton, MA 01720 (US). SPAULDING, Vikki; 11 Meadowbank Road, Billerica, MA 01821 (US). (74) Agent: BROWN, Scott, A.; Genetics Institute, Inc., 87 CambridgePark Drive, Cambridge, MA 02140 (US).	(81) Designated States: AU, CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>	

(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract

The invention provides 15 clones comprising cDNAs encoding secreted proteins, isolated from a human PBMC, from a human neural tissue and from a human dendritic cell cDNA library using methods of screening relective for secreted proteins. Polynucleotide and deduced amino acid sequences determination.



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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

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FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

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BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

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SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 348;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 201 to nucleotide 348;

- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone S185_2 deposited under accession number ATCC 98028;
- 5 (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone S185_2 deposited under accession number ATCC 98028;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone S185_2 deposited under accession number ATCC 98028;
- 10 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone S185_2 deposited under accession number ATCC 98028;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;
- 15 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions
- 20 to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 348; the nucleotide sequence of SEQ ID NO:1 from nucleotide 201 to nucleotide 348; the nucleotide sequence of the full length protein coding sequence of clone S185_2 deposited under accession number ATCC 98028; or the

25 nucleotide sequence of the mature protein coding sequence of clone S185_2 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone S185_2 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid

30 sequence of SEQ ID NO:2 from amino acid 1 to amino acid 42.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1 or SEQ ID NO:3 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:2;
- 5 (b) the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 42;
- (c) fragments of the amino acid sequence of SEQ ID NO:2; and
- (d) the amino acid sequence encoded by the cDNA insert of clone S185_2 deposited under accession number ATCC98028;
- 10 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 42.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 15 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 1014;
- (c) a polynucleotide comprising the nucleotide sequence of the full
- 20 length protein coding sequence of clone G52_24 deposited under accession number ATCC 98028;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC 98028;
- (e) a polynucleotide comprising the nucleotide sequence of the mature
- 25 protein coding sequence of clone G52_24 deposited under accession number ATCC 98028;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding a protein comprising the amino acid
- 30 sequence of SEQ ID NO:6;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

5 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 1014; the nucleotide sequence of the full length protein coding sequence of clone G52_24 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone G52_24 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide
10 encodes the full length or mature protein encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 201 to amino acid 221.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ
15 ID NO:5, SEQ ID NO:4 or SEQ ID NO:7 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:6;
- 20 (b) the amino acid sequence of SEQ ID NO:6 from amino acid 201 to amino acid 221;
- (c) fragments of the amino acid sequence of SEQ ID NO:6; and
- (d) the amino acid sequence encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC98028;
- 25 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 201 to amino acid 221.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 30 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 138 to nucleotide 375;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone J218_15 deposited under accession number ATCC 98028;

5 (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J218_15 deposited under accession number ATCC 98028;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J218_15 deposited under accession number ATCC 98028;

10 (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J218_15 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

15 (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

20 (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 138 to nucleotide 375; the nucleotide sequence of the full length protein coding sequence of clone J218_15 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone J218_15 deposited
25 under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone J218_15 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10 from amino acid 20 to amino acid 69.

30 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9, SEQ ID NO:8 or SEQ ID NO:11 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:10;
 - (b) the amino acid sequence of SEQ ID NO:10 from amino acid 20 to amino acid 69;
 - (c) fragments of the amino acid sequence of SEQ ID NO:10; and
 - 5 (d) the amino acid sequence encoded by the cDNA insert of clone J218_15 deposited under accession number ATCC98028;
- the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10 or the amino acid sequence of SEQ ID NO:10 from amino acid 20 to amino acid 69.
- 10 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID
 - 15 NO:12 from nucleotide 163 to nucleotide 345;
 - (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone M8_2 deposited under accession number ATCC 98028;
 - (d) a polynucleotide encoding the full length protein encoded by the
 - 20 cDNA insert of clone M8_2 deposited under accession number ATCC 98028;
 - (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone M8_2 deposited under accession number ATCC 98028;
 - (f) a polynucleotide encoding the mature protein encoded by the cDNA
 - 25 insert of clone M8_2 deposited under accession number ATCC 98028;
 - (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;
 - (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;
 - 30 (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;
 - (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:12 from nucleotide 163 to nucleotide 345; the nucleotide sequence of the full length protein coding sequence of clone M8_2 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone M8_2 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone M8_2 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13 from amino acid 13 to amino acid 62.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:12 or SEQ ID NO:14 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:13;
 - (b) the amino acid sequence of SEQ ID NO:13 from amino acid 13 to amino acid 62;
 - (c) fragments of the amino acid sequence of SEQ ID NO:13; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone M8_2 deposited under accession number ATCC98028;
- the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:13 or the amino acid sequence of SEQ ID NO:13 from amino acid 13 to amino acid 62.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 181 to nucleotide 325;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 274 to nucleotide 325;

- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone M97_2 deposited under accession number ATCC 98028;
- 5 (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC 98028;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone M97_2 deposited under accession number ATCC 98028;
- 10 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC 98028;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;
- 15 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 181 to nucleotide 325; the nucleotide sequence of SEQ ID NO:15 from nucleotide 274 to nucleotide 325; the nucleotide sequence of the full length protein coding sequence of clone M97_2 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone M97_2 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 48.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15 or SEQ ID NO:17 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 48;

(c) fragments of the amino acid sequence of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone
5 M97_2 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16 or the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 48.

In one embodiment, the present invention provides a composition comprising an
10 isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 221 to nucleotide 601;

(c) a polynucleotide comprising the nucleotide sequence of the full
15 length protein coding sequence of clone B219_2 deposited under accession number ATCC 98028;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone B219_2 deposited under accession number ATCC 98028;

(e) a polynucleotide comprising the nucleotide sequence of the mature
20 protein coding sequence of clone B219_2 deposited under accession number ATCC 98028;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone B219_2 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding a protein comprising the amino acid
25 sequence of SEQ ID NO:19;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of
30 (a)-(d) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:18 from nucleotide 221 to nucleotide 601; the nucleotide sequence of the full length

protein coding sequence of clone B219_2 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone B219_2 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone B219_2
5 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:19 from amino acid 1 to amino acid 79.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:18.

10 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:19;
- (b) the amino acid sequence of SEQ ID NO:19 from amino acid 1 to
15 amino acid 79;
- (c) fragments of the amino acid sequence of SEQ ID NO:19; and
- (d) the amino acid sequence encoded by the cDNA insert of clone B219_2 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins. Preferably such protein
20 comprises the amino acid sequence of SEQ ID NO:19 or the amino acid sequence of SEQ ID NO:19 from amino acid 1 to amino acid 79.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID
25 NO:20;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20 from nucleotide 36 to nucleotide 522;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20 from nucleotide 93 to nucleotide 522;
- (d) a polynucleotide comprising the nucleotide sequence of the full
30 length protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC 98028;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028;

5 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC 98028;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:21;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:21 having biological activity;

10 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID
15 NO:20 from nucleotide 36 to nucleotide 522; the nucleotide sequence of SEQ ID NO:20 from nucleotide 93 to nucleotide 522; the nucleotide sequence of the full length protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide
20 encodes the full length or mature protein encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:21 from amino acid 1 to amino acid 101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ
25 ID NO:20 or SEQ ID NO:22 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- 30 (a) the amino acid sequence of SEQ ID NO:21;
- (b) the amino acid sequence of SEQ ID NO:21 from amino acid 1 to amino acid 101;
- (c) fragments of the amino acid sequence of SEQ ID NO:21; and
- (d) the amino acid sequence encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:21 or the amino acid sequence of SEQ ID NO:21 from amino acid 1 to amino acid 101.

In one embodiment, the present invention provides a composition comprising an
5 isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 88 to nucleotide 499;
- 10 (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone J59_41 deposited under accession number ATCC 98028;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC 98028;
- 15 (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J59_41 deposited under accession number ATCC 98028;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC 98028;
- 20 (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:24 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of
25 (a)-(d) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

30 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:23 from nucleotide 88 to nucleotide 499; the nucleotide sequence of the full length protein coding sequence of clone J59_41 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone J59_41 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide

encodes the full length or mature protein encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24 from amino acid 45 to amino acid 113.

- 5 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:23 or SEQ ID NO:25 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- 10 (a) the amino acid sequence of SEQ ID NO:24;
(b) the amino acid sequence of SEQ ID NO:24 from amino acid 45 to amino acid 113;
(c) fragments of the amino acid sequence of SEQ ID NO:24; and
(d) the amino acid sequence encoded by the cDNA insert of clone

- 15 J59_41 deposited under accession number ATCC98028;
the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:24 or the amino acid sequence of SEQ ID NO:24 from amino acid 45 to amino acid 113.

- In one embodiment, the present invention provides a composition comprising an
20 isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26;
(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26 from nucleotide 23 to nucleotide 613;
25 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26 from nucleotide 137 to nucleotide 613;
(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone O238_1 deposited under accession number ATCC 98028;
30 (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone O238_1 deposited under accession number ATCC 98028;
(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone O238_1 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone O238_1 deposited under accession number ATCC 98028;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:27;

5 (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:27 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

10 (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:26 from nucleotide 23 to nucleotide 613; the nucleotide sequence of SEQ ID NO:26
15 from nucleotide 137 to nucleotide 613; the nucleotide sequence of the full length protein coding sequence of clone O238_1 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone O238_1 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone O238_1
20 deposited under accession number ATCC 98028.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:26.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group
25 consisting of:

(a) the amino acid sequence of SEQ ID NO:27;

(b) fragments of the amino acid sequence of SEQ ID NO:27; and

(c) the amino acid sequence encoded by the cDNA insert of clone O238_1 deposited under accession number ATCC98028;

30 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:27.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:28;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:28 from nucleotide 44 to nucleotide 472;
- 5 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:28 from nucleotide 440 to nucleotide 472;
- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone G86_2 deposited under accession number ATCC 98028;
- 10 (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone G86_2 deposited under accession number ATCC 98028;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone G86_2 deposited under accession number ATCC 98028;
- 15 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone G86_2 deposited under accession number ATCC 98028;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:29;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:29 having biological activity;
- 20 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- 25 (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:28 from nucleotide 44 to nucleotide 472; the nucleotide sequence of SEQ ID NO:28 from nucleotide 440 to nucleotide 472; the nucleotide sequence of the full length protein coding sequence of clone G86_2 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone G86_2 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone G86_2 deposited under accession number ATCC 98028.

30

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:28 or SEQ ID NO:30 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group
5 consisting of:

- (a) the amino acid sequence of SEQ ID NO:29;
- (b) fragments of the amino acid sequence of SEQ ID NO:29; and
- (c) the amino acid sequence encoded by the cDNA insert of clone
G86_2 deposited under accession number ATCC98028;

10 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:29.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID
15 NO:31;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:31 from nucleotide 26 to nucleotide 409;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:31 from nucleotide 176 to nucleotide 409;
- 20 (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H298_23 deposited under accession number ATCC 98028;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H298_23 deposited under accession number ATCC 98028;
- 25 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H298_23 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H298_23 deposited under accession number ATCC 98028;
- 30 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:32;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:32 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

5 (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:31 from nucleotide 26 to nucleotide 409; the nucleotide sequence of SEQ ID NO:31 from nucleotide 176 to nucleotide 409; the nucleotide sequence of the full length protein
10 coding sequence of clone H298_23 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone H298_23 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone H298_23 deposited under accession number ATCC 98028.

15 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:31 or SEQ ID NO:33 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

20 (a) the amino acid sequence of SEQ ID NO:32;
(b) fragments of the amino acid sequence of SEQ ID NO:32; and
(c) the amino acid sequence encoded by the cDNA insert of clone H298_23 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins. Preferably such protein
25 comprises the amino acid sequence of SEQ ID NO:32.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34;
30 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34 from nucleotide 138 to nucleotide 479;
(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H83_22 deposited under accession number ATCC 98028;

- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC 98028;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H83_22 deposited under accession number ATCC 98028;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:35;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:35 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:34 from nucleotide 138 to nucleotide 479; the nucleotide sequence of the full length protein coding sequence of clone H83_22 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone H83_22 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC 98028.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:34 or SEQ ID NO:36 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:35;
- (b) fragments of the amino acid sequence of SEQ ID NO:35; and
- (c) the amino acid sequence encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:35.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:37;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:37 from nucleotide 139 to nucleotide 463;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID
10 NO:37 from nucleotide 196 to nucleotide 463;
- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H849_24 deposited under accession number ATCC 98028;
- (e) a polynucleotide encoding the full length protein encoded by the
15 cDNA insert of clone H849_24 deposited under accession number ATCC 98028;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H849_24 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA
20 insert of clone H849_24 deposited under accession number ATCC 98028;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:38;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:38 having biological activity;
- 25 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions
30 to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:37 from nucleotide 139 to nucleotide 463; the nucleotide sequence of SEQ ID NO:37 from nucleotide 196 to nucleotide 463; the nucleotide sequence of the full length protein coding sequence of clone H849_24 deposited under accession number ATCC 98028; or the

nucleotide sequence of the mature protein coding sequence of clone H849_24 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone H849_24 deposited under accession number ATCC 98028.

- 5 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:37 or SEQ ID NO:39 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- 10 (a) the amino acid sequence of SEQ ID NO:38;
 (b) fragments of the amino acid sequence of SEQ ID NO:38; and
 (c) the amino acid sequence encoded by the cDNA insert of clone H849_24 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins. Preferably such protein
15 comprises the amino acid sequence of SEQ ID NO:38.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:40;
20 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:40 from nucleotide 149 to nucleotide 461;
 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:40 from nucleotide 212 to nucleotide 461;
 (d) a polynucleotide comprising the nucleotide sequence of the full
25 length protein coding sequence of clone J143_1 deposited under accession number ATCC 98028;
 (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC 98028;
 (f) a polynucleotide comprising the nucleotide sequence of the mature
30 protein coding sequence of clone J143_1 deposited under accession number ATCC 98028;
 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC 98028;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:41;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:41 having biological activity;

5 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID
10 NO:40 from nucleotide 149 to nucleotide 461; the nucleotide sequence of SEQ ID NO:40 from nucleotide 212 to nucleotide 461; the nucleotide sequence of the full length protein coding sequence of clone J143_1 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone J143_1 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide
15 encodes the full length or mature protein encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC 98028.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:40 or SEQ ID NO:42 .

In other embodiments, the present invention provides a composition comprising a
20 protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:41;

(b) fragments of the amino acid sequence of SEQ ID NO:41; and

(c) the amino acid sequence encoded by the cDNA insert of clone
25 J143_1 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:41.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

30 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:43;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:43 from nucleotide 144 to nucleotide 590;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H905_107 deposited under accession number ATCC 98028;

5 (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H905_107 deposited under accession number ATCC 98028;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H905_107 deposited under accession number ATCC 98028;

10 (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H905_107 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:44;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:44 having biological activity;

15 (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

20 (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:43 from nucleotide 144 to nucleotide 590; the nucleotide sequence of the full length protein coding sequence of clone H905_107 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone
25 H905_107 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone H905_107 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:44 from amino acid 1 to amino
30 acid 86.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:43.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:44;
- 5 (b) the amino acid sequence of SEQ ID NO:44 from amino acid 1 to amino acid 86;
- (c) fragments of the amino acid sequence of SEQ ID NO:44; and
- (d) the amino acid sequence encoded by the cDNA insert of clone H905_107 deposited under accession number ATCC98028;

10 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:44 or the amino acid sequence of SEQ ID NO:44 from amino acid 1 to amino acid 86.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial,
15 yeast, insect and mammalian cells, transformed with such polynucleotide compositions.

Processes are also provided for producing a protein, which comprise:

- (a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and
- (b) purifying the protein from the culture.

20 The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which
25 specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

30

BRIEF DESCRIPTION OF FIGURES

Fig. 1 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: G52_24.

Fig. 2 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: B219_2.

Fig. 3 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: H298_23, H83_22, H849_24, H905_107.

5

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences are reported below for each clone and protein disclosed in the present application. In some instances the sequences are preliminary and may include some incorrect or ambiguous bases or amino acids. The actual nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence.

For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Because of the partial ambiguity in reported sequence information, reported protein sequences include "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined nucleotide sequence where applicants believe one should not exist (if the nucleotide sequence were determined definitively).

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Clone "S185_2"

A polynucleotide of the present invention has been identified as clone "S185_2". S185_2 was isolated from a human neural tissue (glioblastoma line TG-1) cDNA library using methods which are selective for cDNAs encoding secreted proteins. S185_2 is a full-

length clone, including the entire coding sequence of a secreted protein (also referred to herein as "S185_2 protein").

The nucleotide sequence of the 5' portion of S185_2 as presently determined is reported in SEQ ID NO:1. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:2. The predicted acid sequence of the S185_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2.

Amino acids 1 to 46 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 47. Additional nucleotide sequence from the 3' portion of S185_2, including the polyA tail, is reported in SEQ ID NO:3.

The nucleotide sequence disclosed herein for S185_2 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "G52_24"

A polynucleotide of the present invention has been identified as clone "G52_24". G52_24 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. G52_24 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "G52_24 protein").

The nucleotide sequence of the 5' portion of G52_24 as presently determined is reported in SEQ ID NO:4. An additional internal nucleotide sequence from G52_24 as presently determined is reported in SEQ ID NO:5. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:6. Additional nucleotide sequence from the 3' portion of G52_24, including the polyA tail, is reported in SEQ ID NO:7.

The nucleotide sequence disclosed herein for G52_24 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. G52_24 demonstrated at least some homology with the early activation cell surface antigen CD69 (GenPept accession number Z22576). The search also found hits at GenBank accession numbers R12300 and X87344. Based upon homology, G52_24 proteins and each homologous protein or peptide may share at least some activity.

Clone "J218_15"

A polynucleotide of the present invention has been identified as clone "J218_15". J218_15 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. J218_15 is a full-length clone, including

the entire coding sequence of a secreted protein (also referred to herein as "J218_15 protein").

The nucleotide sequence of the 5' portion of J218_15 as presently determined is reported in SEQ ID NO:8. An additional internal nucleotide sequence from J218_15 as
5 presently determined is reported in SEQ ID NO:9. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:10. Additional nucleotide sequence from the 3' portion of J218_15, including the polyA tail, is reported in SEQ ID NO:11.

The nucleotide sequence disclosed herein for J218_15 was searched against the
10 GenBank database using BLASTA/BLASTX and FASTA search protocols. J218_15 demonstrated at least some homology with an oligopeptide transporter protein (Oryctolagus cuniculus) (GenBank accession number H65908). The search also found a hit at GenBank accession number R51893. Based upon homology, J218_15 proteins and each homologous protein or peptide may share at least some activity.

15 Clone "M8_2"

A polynucleotide of the present invention has been identified as clone "M8_2". M8_2 was isolated from a human neural tissue (glioblastoma cell line T98G) cDNA library using methods which are selective for cDNAs encoding secreted proteins. M8_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to
20 herein as "M8_2 protein").

The nucleotide sequence of the 5' portion of M8_2 as presently determined is reported in SEQ ID NO:12. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:13. The predicted acid sequence of the M8_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID
25 NO:13. Additional nucleotide sequence from the 3' portion of M8_2, including the polyA tail, is reported in SEQ ID NO:14.

The nucleotide sequence disclosed herein for M8_2 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. M8_2 demonstrated at least some homology with Rattus norvegicus plasma membrane Ca^{2+}
30 ATPase isoform 3 (PMCA3). The search also found a hit at GenBank accession number R97122. Based upon homology, M8_2 proteins and each homologous protein or peptide may share at least some activity.

Clone "M97_2"

A polynucleotide of the present invention has been identified as clone "M97_2". M97_2 was isolated from a human neural tissue (glioblastoma cell line T98G) cDNA library using methods which are selective for cDNAs encoding secreted proteins. M97_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to
5 herein as "M97_2 protein").

The nucleotide sequence of the 5' portion of M97_2 as presently determined is reported in SEQ ID NO:15. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:16. The predicted acid sequence of the M97_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID
10 NO:16. Amino acids 1 to 31 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 32. Additional nucleotide sequence from the 3' portion of M97_2, including the polyA tail, is reported in SEQ ID NO:17.

The nucleotide sequence disclosed herein for M97_2 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. M97_2
15 demonstrated at least some identity with an EST identified as "H. sapiens partial cDNA sequence; clone C6F07" (GenBank accession number Z25379). Based upon identity, M97_2 proteins and each identical protein or peptide may share at least some activity.

Clone "B219_2"

A polynucleotide of the present invention has been identified as clone "B219_2".
20 B219_2 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. B219_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "B219_2 protein").

The nucleotide sequence of B219_2 as presently determined is reported in SEQ ID NO:18. What applicants presently believe to be the proper reading frame and the predicted
25 amino acid sequence of the B219_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:19.

The nucleotide sequence disclosed herein for B219_2 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. B219_2 demonstrated at least some identity with two ESTs identified as "yg83a06.s1 Homo sapiens
30 cDNA clone 39817 3'" (GenBank accession number R53932) and "yg83a06.r1 Homo sapiens cDNA clone 39817 5'" (GenBank accession number R53326). The clone and EST sequences show some similarity to NADH-ubiquinone oxidoreductase ASH1 subunit precursor (GenBank accession number Q02372). Based upon identity, B219_2 proteins and each identical protein or peptide may share at least some activity.

Clone "H1075_1"

A polynucleotide of the present invention has been identified as clone "H1075_1". H1075_1 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. H1075_1 is a full-length clone, including
5 the entire coding sequence of a secreted protein (also referred to herein as "H1075_1 protein").

The nucleotide sequence of the 5' portion of H1075_1 as presently determined is reported in SEQ ID NO:20. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:21. The predicted acid sequence of the
10 H1075_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:21. Amino acids 1 to 19 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 20. Additional nucleotide sequence from the 3' portion of H1075_1, including the polyA tail, is reported in SEQ ID NO:22.

The nucleotide sequence disclosed herein for H1075_1 was searched against the
15 GenBank database using BLASTA/BLASTX and FASTA search protocols. H1075_1 demonstrated at least some identity with the sequence of a tissue specific secretory protein identified at GenBank accession number X67698 (GenPept A18921). Based upon identity, H1075_1 proteins and each identical protein or peptide may share at least some activity.

Clone "J59_41"

20 A polynucleotide of the present invention has been identified as clone "J59_41". J59_41 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. J59_41 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "J59_41 protein").

The nucleotide sequence of the 5' portion of J59_41 as presently determined is
25 reported in SEQ ID NO:23. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:24. The predicted acid sequence of the J59_41 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:24. Additional nucleotide sequence from the 3' portion of J59_41, including the polyA tail, is reported in SEQ ID NO:25.

30 The nucleotide sequence disclosed herein for J59_41 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. J59_41 demonstrated at least some homology with the cosmid F54E7.1 gene product (caenorhabditis elegans). The search found a hit at GenBank accession number R21739.

Based upon homology, J59_41 proteins and each homologous protein or peptide may share at least some activity.

Clone "O238_1"

A polynucleotide of the present invention has been identified as clone "O238_1".

- 5 O238_1 was isolated from a human dendritic cell cDNA library using methods which are selective for cDNAs encoding secreted proteins. O238_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "O238_1 protein").

- The nucleotide sequence of O238_1 as presently determined is reported in SEQ ID
10 NO:26 What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the O238_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:27. Amino acids 1 to 38 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 39.

- The nucleotide sequence disclosed herein for O238_1 was searched against the
15 GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "G86_2"

A polynucleotide of the present invention has been identified as clone "G86_2".

- G86_2 was isolated from a human PBMC cDNA library using methods which are selective
20 for cDNAs encoding secreted proteins. G86_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "G86_2 protein").

- The nucleotide sequence of the 5' portion of G86_2 as presently determined is reported in SEQ ID NO:28 What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:29. The predicted acid sequence of the
25 G86_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:29. Amino acids 1 to 132 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 133. Additional nucleotide sequence from the 3' portion of G86_2, including the polyA tail, is reported in SEQ ID NO:30.

- The nucleotide sequence disclosed herein for G86_2 was searched against the
30 GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "H298_23"

A polynucleotide of the present invention has been identified as clone "H298_23".

H298_23 was isolated from a human PBMC cDNA library using methods which are

selective for cDNAs encoding secreted proteins. H298_23 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "H298_23 protein").

5 The nucleotide sequence of the 5' portion of H298_23 as presently determined is reported in SEQ ID NO:31. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:32. The predicted acid sequence of the H298_23 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:32. Amino acids 1 to 50 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 51. Additional nucleotide sequence
10 from the 3' portion of H298_23, including the polyA tail, is reported in SEQ ID NO:33.

The nucleotide sequence disclosed herein for H298_23 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. H298_23 demonstrated at least some homology with the early activation antigen CD69. The search also found a hit at GenPept A10540. Based upon homology, H298_23 proteins and each
15 homologous protein or peptide may share at least some activity.

Clone "H83_22"

A polynucleotide of the present invention has been identified as clone "H83_22". H83_22 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. H83_22 is a full-length clone, including the entire
20 coding sequence of a secreted protein (also referred to herein as "H83_22 protein").

The nucleotide sequence of the 5' portion of H83_22 as presently determined is reported in SEQ ID NO:34. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:35. The predicted acid sequence of the H83_22 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID
25 NO:35. Additional nucleotide sequence from the 3' portion of H83_22, including the polyA tail, is reported in SEQ ID NO:36.

The nucleotide sequence disclosed herein for H83_22 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database. The amino acid sequence of H83_22 indicates that it may be a novel
30 serine protease.

Clone "H849_24"

A polynucleotide of the present invention has been identified as clone "H849_24". H849_24 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. H849_24 is a full-length clone, including

the entire coding sequence of a secreted protein (also referred to herein as "H849_24 protein").

The nucleotide sequence of the 5' portion of H849_24 as presently determined is reported in SEQ ID NO:37. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:38. The predicted acid sequence of the H849_24 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:38. Amino acids 1 to 19 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 20. Additional nucleotide sequence from the 3' portion of H849_24, including the polyA tail, is reported in SEQ ID NO:39.

The nucleotide sequence disclosed herein for H849_24 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "J143_1"

A polynucleotide of the present invention has been identified as clone "J143_1". J143_1 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. J143_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "J143_1 protein").

The nucleotide sequence of the 5' portion of J143_1 as presently determined is reported in SEQ ID NO:40. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:41. The predicted acid sequence of the J143_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:41. Amino acids 1 to 21 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 22. Additional nucleotide sequence from the 3' portion of J143_1, including the polyA tail, is reported in SEQ ID NO:42.

The nucleotide sequence disclosed herein for J143_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The clone showed at least some identity with an EST identified as "yh04a07.r1 H. sapiens cDNA clone 41951 5'".

Clone "H905_107"

A polynucleotide of the present invention has been identified as clone "H905_107". H905_107 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. H905_107 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "H905_107 protein").

The nucleotide sequence of H905_107 as presently determined is reported in SEQ ID NO:43. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the H905_107 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:44.

5 The nucleotide sequence disclosed herein for H905_107 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. H905_107 demonstrated at least some homology with human CD69 (GenPept L07555 and Z22576). Based upon homology, H905_107 proteins and each homologous protein or peptide may share at least some activity.

10

Figs. 1-3 are autoradiographs evidencing expression of clones of the present invention. All clones were expressed in COS cells.

Deposit of Clones

15 Clones S185_2, G52_24, J218_15, M8_2, M97_2, B219_2, H1075_1, J59_41, O238_1, G86_2, H298_23, H83_22, H849_24, J143_1 and H905_107 were deposited on April 19, 1996 with the American Type Culture Collection under accession number ATCC 98028, from which each clone comprising a particular polynucleotide is obtainable. Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit.

20 Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

25 An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

<u>Clone</u>	<u>Probe Sequence</u>
S185_2	SEQ ID NO:45
30 G52_24	SEQ ID NO:46
J218_15	SEQ ID NO:47
M8_2	SEQ ID NO:48
M97_2	SEQ ID NO:49
B219_2	SEQ ID NO:50

	H1075_1	SEQ ID NO:51
	J59_41	SEQ ID NO:52
	O238_1	SEQ ID NO:53
	G86_2	SEQ ID NO:54
5	H298_23	SEQ ID NO:55
	H83_22	SEQ ID NO:56
	H849_24	SEQ ID NO:57
	J143_1	SEQ ID NO:58
	H905_107	SEQ ID NO:59

10

The design of the oligonucleotide probe should preferably follow these parameters:

- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;
- 15 (b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-³²P ATP (specific activity 6000 Ci/mmol) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should
 20 preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmol.

The bacterial culture containing the pool of full-length clones should preferably be
 25 thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid
 30 bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at
5 a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The
10 filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization
15 analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein
20 may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding
25 sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

30 The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell.

The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials.

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster

Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

5 Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any
10 bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

15 The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art,
20 as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

 The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting
25 expressed protein may then be purified from such culture (*i.e.*, from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA
30 Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

 Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as

those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently
5 purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or
10 all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic
15 animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are
20 known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological
25 processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications
30 of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S.

Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify

polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bertagnolli et al., *J. Immunol.* 145:1706-1712, 1990; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Bertagnolli, et al., *J. Immunol.* 149:3778-3783, 1992; Bowman et al., *J. Immunol.* 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation. Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ , Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., *J. Exp. Med.* 173:1205-1211, 1991; Moreau et al., *Nature* 336:690-692, 1988; Greenberger et al., *Proc. Natl. Acad. Sci. U.S.A.* 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley

- and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 -
- 5 Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

- Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in:
- 10 *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun.
- 15 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

- A protein of the present invention may also exhibit immune stimulating or immune
- 20 suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may
- 25 be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, *Leishmania* spp., *malaria* spp. and various fungal infections such as candidiasis. Of course,
- 30 in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre

syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other
5 conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune
10 response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from
15 immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing
20 high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys
25 the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the
30 molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this manner prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-

blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

5 The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci
10 USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating
15 autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B
20 lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of
25 well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythematosus in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

30 Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral

infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient
5 by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-
pulsed APCs either expressing a peptide of the present invention or together with a
stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro*
activated T cells into the patient. Another method of enhancing anti-viral immune responses
would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding
10 a protein of the present invention as described herein such that the cells express all or a
portion of the protein on their surface, and reintroduce the transfected cells into the patient.
The infected cells would now be capable of delivering a costimulatory signal to, and thereby
activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably
15 B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor
cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma)
transfected with a nucleic acid encoding at least one peptide of the present invention can be
administered to a subject to overcome tumor-specific tolerance in the subject. If desired,
the tumor cell can be transfected to express a combination of peptides. For example,
20 tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector
directing the expression of a peptide having B7-2-like activity alone, or in conjunction with
a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells
are returned to the patient to result in expression of the peptides on the surface of the
transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell
25 for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B
lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation
signal to T cells to induce a T cell mediated immune response against the transfected tumor
cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or
30 which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can
be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain
truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an
MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC
class I or MHC class II proteins on the cell surface. Expression of the appropriate class I

or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected
5 with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured
10 by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-
15 3.19; Chapter 7, *Immunologic studies in Humans*); Herrmann et al., *Proc. Natl. Acad. Sci. USA* 78:2488-2492, 1981; Herrmann et al., *J. Immunol.* 128:1968-1974, 1982; Handa et al., *J. Immunol.* 135:1564-1572, 1985; Takai et al., *J. Immunol.* 137:3494-3500, 1986; Takai et al., *J. Immunol.* 140:508-512, 1988; Herrmann et al., *Proc. Natl. Acad. Sci. USA* 78:2488-2492, 1981; Herrmann et al., *J. Immunol.* 128:1968-1974, 1982; Handa
20 et al., *J. Immunol.* 135:1564-1572, 1985; Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bowman et al., *J. Virology* 61:1992-1998; Takai et al., *J. Immunol.* 140:508-512, 1988; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Brown et al., *J. Immunol.* 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching
25 (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, *J. Immunol.* 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

30 Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-

3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad. Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for

example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet
5 transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post
10 irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

15 Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al.,
20 Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic*
25 *Cells*. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994;
30 Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland,

H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

5 A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in
10 circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma
15 induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of
20 progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the
25 protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein
30 may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. *De novo* tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic

plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured
5 by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

10 Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

15 Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention,
20 alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- β group, may
25 be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

30 The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale

et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

5 A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide
10 particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

 A protein or peptide has chemotactic activity for a particular cell population if it can
15 stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

20 The activity of a protein of the invention may, among other means, be measured by the following methods:

 Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one
25 cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et
30 al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A
5 protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

10 Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

15 Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors
20 involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.
25 A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those
30 described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med.

169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

5 Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or
10 suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality,
15 arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

20 In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor
25 precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

30

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting

(suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

20 ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or complement its activity or use in treatment. Such additional factors and/or agents may be included in the

pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects
5 of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric
10 or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T
15 lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that
20 can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome
25 in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like.
30 Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or
5 amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a
10 therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or
15 other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic
20 factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous
25 administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an
30 adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain

physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μ g to about 100 mg (preferably about 0.1 μ g to about 10 mg, more preferably about 0.1 μ g to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending

physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may
5 be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10
10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic
15 cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the
20 composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair.
25 Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site
30 of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular

application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF- α and TGF- β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

5 The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of
10 matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

15 Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

20 Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully
25 set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: Jacobs, Kenneth
McCoy, John
LaVallie, Edward
Racie, Lisa
Merberg, David
Treacy, Maurice
Evans, Cheryl
- (ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES
ENCODING THEM
- (iii) NUMBER OF SEQUENCES: 59
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Genetics Institute, Inc.
 - (B) STREET: 87 CambridgePark Drive
 - (C) CITY: Cambridge
 - (D) STATE: MA
 - (E) COUNTRY: USA
 - (F) ZIP: 02140
- (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 #1.30
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER:
 - (B) FILING DATE:
 - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Brown, Scott A.
 - (B) REGISTRATION NUMBER: 32,724
- (ix) TELECOMMUNICATION INFORMATION:
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 - (B) TELEFAX: (617) 876-5851

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 348 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA

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

```

GAATTCGGCC AAAGANGCCT ATGACTGCTT CACTCTCTCA ATTCTTAAGC TTGAATTTGG      60
AAATGACTTT TGATGACCTA AAGATCCAGA CTGTGAAGGA CCAGCCTGAT GAGAAGTCAA      120
ATGGAAAAAA AGCTAAAGGT CTTCAAGTTTC TTTACTCTCC ATGGTGGTGC CTGGCTGCTG      180
CGACTCTAGG GGTCTTTTGC CTGGGATTAG TAGTGACCAT TATGGTGCTG GGCATGCAAT      240
TATCCCAGGT GTCTGACCTC CTAACACAAG AGCAAGCAAA CCTAACTCAC CAGAAAAAGA      300
AACTGGAGGG NCAGATACTC AGCCCGGCNA CNAGCAGNAG AANCTGTT                      348

```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 95 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

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

```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 94 base pairs
- (B) TYPE: nucleic acid

(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

ACTTGTTGAN GACATTNGGG TTGTTTTAGT TTTGGGATAT AACAAATAAA GCTGCTGTGA 60
ACATTTGTGT AAAAAAAAAA AAAAAAAAAA AAAA 94

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

GAATTCGGCC AAAGAGGCCT AGTGATATTA TAGTGTAGTT TTTTAGATGT TACCATTGGG 60
AGAAACTGAG TAAAGAAGAT GTGGGATCTT TCTTTAGTAT TTCTTAGAAC TGCATGTGAA 120
TCTACAATA GCTCAAAATA AAAAGTTTAA TTATAAATAA AA 162

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1014 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TTTGGGCTCA GTGAATTTGC TTCTTCAGGA GGGTAATTTT CTCTTCTTC TCTGCTAAGC 60

```

TGTTTAACAG TAGTTGCCCT GCCTAATGGG CTCATCCAT CCATTTCTCT CAGATTATTT 120
TCATGATGCA CTAGGATGAA GCACACCCTT TCTCCTAGTC TTGAGGAAAC GTCGATATTC 180
AGAATATTTA AACGCAGGCA CTGACCAATC AGAAGAGTTT CTGGCCAACG TTCCACACTT 240
GAGGGAAATG ACATTATCTG AGCCCTGAAG AAAAACGTTG TAGATATTCT CCAGATCAAA 300
GCATCGACAG GAAGATTTTA GATGTTGAAG TTCGTAATAT TTCCTAAAGC AGGTTGTGTG 360
CATTCAAARG AGMAKTCTAT TAAAGCTACC YTMNWTGGC GCTTATTTTT CTTAATCATG 420
TTTCTGACAA TCATAGTGTG TGGAGRKGST TGCTGCTTTA AGYGCAATAA GAGCTAWCTG 480
CCATCAAGAG CCATCAGTAT GTCTTCGAGC TGCATGCCCA GAAAGCTGGA TTGTTTTTCA 540
AACGAAAGTG TYTCTATTTT TCTGATGACR CCAAGAAACT GGACATCAAG TCAGAGGKKT 600
TGTGACTCAC AAGATGCTGA TCTTGCTCAG GTTGAAAGCT TCCAGGAACT GAATTCCTTG 660
TTGAGAKATA AAGGCCCATC TGATCACTGG ATTGGGCTGA GCANAGAACA NGGCCAACCA 720
TGGAAATGGA TAAATGGTAC TGAATGGACA ANACAGTTTC CTATCCTGGG AGCAGGANAN 780
TGTGCCTATT TGAATGACAA AGGTGCCAGT AGTGCCAGGC ACTACACAGA GAGGAANTGG 840
ATTTGTNCCA AATCANATNT NCTTNTCTAN ATGTTACAGC AAAGCCCCAA CTAATCTTTA 900
NAAGCATATT GGAAGTATA ACTCCATTTT AAAATGAGCA AANANTTTAT TTCTTATNCC 960
AACNGGTATA TGAAAATATG CTCNATNTCA CTAATAACTG GGAAAATAAC CNTT 1014

```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 338 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

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

```

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

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 177 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

```
ATATGCTCAA TATCACTAAT AACTGGGAAA TACAAATCAA AATCATAGTA AAATATTACC      60
TGTTTTTCATG GTGCTAATAT TACCTGTTCT CCCACTGCTA ATGACATACC CGAGACTGAG      120
TAATTTTATAA ATAAAAGAGA TTTAATTGAA AAAAAAAAAA AAAAAAAAAA AAAAAAA      177
```

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 176 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

```
GCGGCCGCGC GGCCTGGGGC GTTCGCGGGC CGGCGCGCGG CGTGCGGGGC CGTGCTGCTG      60
ACGGAGCTGC TGGAGCGCGC CGCTTTCTAC GGCATCACGT CCAACCTGGT GCTATTCCTG      120
AACGGGGCGC CGTTCTGCTG GGAGGGCGCG CAGGCCAGCG AGGCGCTGCT GCTCTT      176
```

(2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 375 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```

CTTGGCTTTG ATACCTTACT GGACAGTGTA TTTCCAAATG CAGACAACAT ATGTTTTTACA      60
GAGTCTTCAT TTGAGGATTC CAGAAATTTT AAATATTACA ACCACTCCTC ACACGCTCCC      120
TGCAACCNNN AATGACCATG TTTGATGCTG TGCTCATCCT CCTGCTCATC CCTCTGAAGG      180
ACAAACTGGT CGABCCCATT TTGAGAAGAC ATGGCCTGCT CCCATCCTCC CTGAAGAGGA      240
TCGCCGTGGG CATGTTCTTT GTCATGTGCT CAGCCTTTGC TGCAGGAATT TTGGAGAGTA      300
AAAGGCTGAA CCTTGTTAAA GAGAAAACCA TTAATCAGAC CATCGGCAAC GTCGTCTACC      360
ATGCTGCCGA TCTGT                                           375

```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 79 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```

Met Phe Asp Ala Val Leu Ile Leu Leu Ile Pro Leu Lys Asp Lys
1           5           10           15

Leu Val Xaa Pro Ile Leu Arg Arg His Gly Leu Leu Pro Ser Ser Leu
          20           25           30

Lys Arg Ile Ala Val Gly Met Phe Phe Val Met Cys Ser Ala Phe Ala
          35           40           45

Ala Gly Ile Leu Glu Ser Lys Arg Leu Asn Leu Val Lys Glu Lys Thr
50           55           60

Ile Asn Gln Thr Ile Gly Asn Val Val Tyr His Ala Ala Asp Leu
65           70           75

```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 161 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

AAATGTGAAC TTGAGCTGTT GACCAGTCAC ATTTTGTAT TGTTACTGTA CGTGTATCTG	60
GGGCTTCTCC GTTTGTTAAT ACTTTTCTG TATTGTTGC TGTATTTTG GCATAACTTT	120
ATTATAAAAA GCATMTCAWW TGCGAAAAA AAAAAAAAAA A	161

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 345 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

TTGCTGGTTG CCATTGAGGA CCCTGGAAT AGGGTTGGTG GCTTCATCAG AANTCAGGTT	60
NTTTAAAGAT ATTTNTNTTT NTCCAGCATT ACCGTTTAGT TCACCATAGC CNGTTTTNTT	120
TTTCGGCGTT TCCTGGTGCT GCTGGAGGN GTGTTTTTGC TCATGTTTCA GCGGCTTTGG	180
NTGGGCCTTG GGGNTGCCCT CGGCTCCATG CTGCAGGTAT TGGTGAGGCT GCTGGTGATG	240
ATGGTGGTGG TGGTGGTTGT GGCTGTGGTT GTAGAAATAA TAATGGTGGT GGTGGTGCGG	300
CTGCTGCTGC TGCTGCTGAG GGTGATGGTG CGGATGGTGG TGGCT	345

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 62 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

Met Phe Gln Arg Leu Trp Xaa Gly Leu Gly Xaa Ala Leu Gly Ser Met
 1 5 10 15
 Leu Gln Val Leu Val Arg Leu Leu Val Met Met Val Val Val Val Val
 20 25 30
 Val Ala Val Val Val Glu Ile Ile Met Val Val Val Val Arg Leu Leu
 35 40 45
 Leu Leu Leu Leu Arg Val Met Val Arg Met Val Val Ala Val
 50 55 60

(2) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 201 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

AAGGCCNAAA CCTTTGGGGA AGCNGGGATT TAAACCCAGG ATTTTATTTA GGAAACNGT 60
 NTGGANCAAA AGGATGGGGA GTTTTNTGGA AATNAATTTG GGGNGGATTA NAGANGNGGG 120
 ATATTTNTTA TAAATNAATA ATGGAAACCT TAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 180
 AAAAAAAAAA AAAGCGGCCG C 201

(2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 325 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TCTTTCTTTT TTCTCCCTT TACTCTTTGG GTGGTGTTC TTTTCCTTTC CTTTCCCTT 60
 TGARATTTTT TTGTTGTTGT TTCCTTTTTG TATTTACTG ATATCACCAG NATAGTTTAC 120
 TCTCCTTCTA GCTTTCTGCT TACCGCACAC TGGATAACAC ACACATACAC ACCCACAAAA 180

ATGCTCATGA ACCCAATCCG GAGAAGGTTT CAGCAGGTCC CCCACCCTCC CCTCCTCCTC 240
 CTACTTCTCC TCTTGACAGC GAGGACAGGA GGGGGACAAG GGGACACCTG GGCAGACCCG 300
 CCGGCTCTCC CCCCACCCCA CCCC 325

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

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

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 101 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

TATGTTTTGA TTTTAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 60
 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA A 101

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 730 base pairs
- (B) TYPE: nucleic acid

(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

```

NAANAATGTG AANATGGCGG TGGCCAGGGC CGGGGTCTTG GGANTCCAGT GGCTGCAAAG      60
GGCATCCCGG AACGTGATGC CGCTGGGCGC ACGGACAGCC TCCCACATGA CCAAGGACAT      120
GTTCCCGGGG CCCTATCCTA GGACCCCANANA ANAACGGGCC SCCSCCSCCA AGAAGWATAA      180
TATRCGTGTG GAAGACWCCG AACCTTACCC GGATGATGGC ATGGGGTATG GCGACTACCC      240
GAAGCTCCCT GACCGCTCAC AGCATGAGAG AGATCCATGG TATAGCTGGG ACCANCCGGG      300
CCTGAGGNTG AACTGGGGTG AACCGATRCA CTGGCACCTA GACATGTACA ACAGGAACCG      360
TGTGGATACA TCCCCACAC CTGTTTCTTG GCATGTCATG TGTATGCAGC TCTTCGGTTT      420
CCTGGCTTTC ATGATATTCA TGTNCTGGGT GGGGGACGTG TACCCTGTTT ACCAGCCTGT      480
GGGACCAAAG CAGTATCCTT ACAATAATTT GTACCTGGGA GGGGGNGGNN ATCCCTCCCA      540
GGGACCAGGG NGGGTGGTTC ACTATGANAT TTGGGGGGGN TTTGNGGGNT TTTGGGTCNT      600
TTAAATAGGA NTCCCTCATT CCTNGAAATT TAACCTTAAT GAAATCCCTA ATAAAANTCN      660
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA      720
AAAAAAAAAA                                         730

```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 127 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

Met Gly Tyr Gly Asp Tyr Pro Lys Leu Pro Asp Arg Ser Gln His Glu
1           5           10           15
Arg Asp Pro Trp Tyr Ser Trp Asp Xaa Pro Gly Leu Arg Xaa Asn Trp

```

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

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 522 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

GAATTCGGCA AAGAGCTANG AATTCGTTAT CCGCGATGCG TTTCCTGGCA GCTACATTCC	60
TGCTCCTGGC GCTCAGCACC GCTGCCCAGG CCGAACCGGT GCAGTTCAAG GACTGCGGTT	120
CTGTGGATGG AGTTATAAAG GAAGTGAATG TGAGCCCATG CCCCACCCAA CCCTGCCAGC	180
TGAGCAAAGG ACAGTCTTAC AGCGTCAATG TCACCTTCAC CAGCAATATT CAGTCTAAAA	240
GCAGCAAGGC CGTGGTGCAT GGCATCCTGA TGGGCGTCCC AGTTCCCTTT CCCATTCTCTG	300
AGCCTGATGG TTGTAAGAGT GGAATTAAC T GCCCTATCCA AAAAGACAAG ACCTATAGCT	360
ACCTGAATAA ACTACCAGTG AAAAGCGAAT ATCCCTCTAT AAAACTGGTG GTGGAGTGGC	420
AACTTCAGGA TGACAAAAAC CAAATCTCTT CTGCTGGGAA ATCCCAGTNC AGATCGTTTC	480
TCATCTCTAA GTGCCTCATT GAGTTCGGTG CATCTGGGCC AA	522

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 162 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

Met Arg Phe Leu Ala Ala Thr Phe Leu Leu Leu Ala Leu Ser Thr Ala
1           5           10           15

Ala Gln Ala Glu Pro Val Gln Phe Lys Asp Cys Gly Ser Val Asp Gly
          20           25           30

Val Ile Lys Glu Val Asn Val Ser Pro Cys Pro Thr Gln Pro Cys Gln
          35           40           45

Leu Ser Lys Gly Gln Ser Tyr Ser Val Asn Val Thr Phe Thr Ser Asn
          50           55           60

Ile Gln Ser Lys Ser Ser Lys Ala Val Val His Gly Ile Leu Met Gly
65           70           75           80

Val Pro Val Pro Phe Pro Ile Pro Glu Pro Asp Gly Cys Lys Ser Gly
          85           90           95

Ile Asn Cys Pro Ile Gln Lys Asp Lys Thr Tyr Ser Tyr Leu Asn Lys
          100          105          110

Leu Pro Val Lys Ser Glu Tyr Pro Ser Ile Lys Leu Val Val Glu Trp
          115          120          125

Gln Leu Gln Asp Asp Lys Asn Gln Ile Ser Ser Ala Gly Lys Ser Gln
          130          135          140

Xaa Arg Ser Phe Leu Ile Ser Lys Cys Leu Ile Glu Phe Gly Ala Ser
145          150          155          160

Gly Pro

```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 259 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```

TTTGTAGCAG AAAATGNGCT CCGGGNGGNT GGTttTCAGG GGGTGTNTCA AGTTTNTTTT    60
TCTGTTTTAG GGGGNTTCAT TAAANGCAGC ANTTGGTTAG CAGANGTTTA ATTTTTTTTT    120
TAACAANATT AAATTGNGGC CTCTTTTNAC ANCTGGNAAT TNANTTTTGN ATAAATAAAA    180
AATNGTTTGT TTTGTCCAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA    240
AAAAAAAAAA AAAAAAAG                                         259

```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 499 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```

AGCAANAAAC CAGTCAACTC ATGCACNCGA GCGGTNCANG AAACCAACAA AAATAACTCT    60
GAGAGCATAG AATGCAGAAA AATAACAATG GATCTCAATT TCAACCANTC CAGAAAAANAT    120
ATCTCTATCA CTGTNCCATC CAAAACCCAA ACAATGTCAC CACACATCAA GTCAGTTGAC    180
GACGTTGTGG TACTTGGCAT GAATCTCAGC AAGTTTAACA AACTTACTCA GTTTTTTCATA    240
TGTGTTGCTG GAGTTTTTGT ATTTTACCTA ATTTATGGGT ATTTACAGGA ATTAATATTT    300
TCAGTGGAGG GTTTTAAGTC CTGTGGCTGG TACCTTACCT TAGTGCAGTT TGCCTTTTAC    360
TCCATATTTG GCCTAATAGA ACTTCAGCTT ATTCAGGACA AAAGGAGGAG AATACCAGGA    420
AAAAACCTAC ATGATAATAG CTTTCTAAC TGTGGGTACT ATGGGGNNGG CAAACACTTC    480
CTTGGGCTAC CTGAATTAC                                         499

```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 137 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```

Met Asp Leu Asn Phe Asn Xaa Ser Arg Lys Xaa Ile Ser Ile Thr Val
1           5           10           15

Pro Ser Lys Thr Gln Thr Met Ser Pro His Ile Lys Ser Val Asp Asp
          20           25           30

Val Val Val Leu Gly Met Asn Leu Ser Lys Phe Asn Lys Leu Thr Gln
          35           40           45

Phe Phe Ile Cys Val Ala Gly Val Phe Val Phe Tyr Leu Ile Tyr Gly
50           55           60

Tyr Leu Gln Glu Leu Ile Phe Ser Val Glu Gly Phe Lys Ser Cys Gly
65           70           75           80

Trp Tyr Leu Thr Leu Val Gln Phe Ala Phe Tyr Ser Ile Phe Gly Leu
          85           90           95

Ile Glu Leu Gln Leu Ile Gln Asp Lys Arg Arg Arg Ile Pro Gly Lys
          100          105          110

Asn Leu His Asp Asn Ser Phe Ser Asn Cys Gly Tyr Tyr Gly Xaa Gly
          115          120          125

Lys His Phe Leu Gly Leu Pro Glu Leu
          130          135

```

(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 438 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```

ACTTTCCTCAA GGGATGATAA AACCAAAGAA TTGGAGGCAT TGTATCCCAT TTGTGGACAG      60
ATTTCATATG AAGTTGTTTT GCGGTGTCAG CCTTTTTTTC AGAGCATTTG TTTGACTGAC      120
TTCCAAAGCA ATCAAGAGAG CCACGTCTAG CAGACTTTAC AATAAAATGT CAATATGAAG      180

```

GACTGTAATT CCTAGCAGTT TATTGAGAAT TTCACTGGAA ATGGACCATG TGTTGCAAGA	240
CTAATTGGCT ATAATTATAT CCTATCAAAG AAATCGATAC GTAATAGCAG ATTGTTTTAT	300
ATTCATTCCA TTTTGATGGT GTTATTTAAA TTGTTCTCTG TTATAAGAGT AACTGATGA	360
GTTGAAGTCT GGAGAGAATA ACATTCATTA TAAATAAAAT TATTCTGTGT CTTTTTCAA	420
AAAAAAAAAA AAAAAAAAAA	438

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 664 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GCCAAAGAGG CTAGAGATCT GGATGGCATC TACTTCGTAT GACTATTGCA GAGTGCCCAT	60
GGAAGACGGG GATAAGCGCT GTAAGCTTCT GCTGGGGATA GGAATTCTGG TGCTCCTGAT	120
CATCGTGATT CTGGGGGTGC CCTTGATTAT CTTACCATC AAGGCCAACA GCGAGGCCTG	180
CCGGGACCGG CTTGGGCAG TGATGGAGTG TCGCAATGTC ACCCATCTCC TGCAACAAGA	240
GCTGACCGAG GCCCAGAAGG GCTTTCAGGA TGTGGAGGCC CAGGCGCACT GCAACCACAC	300
TGTGATGGCC CTAATGGCTT CCCTGGATGC AGAGAAGGCC CAAGGACAAA AGAAAGTGGA	360
GGAGCTTGAG GGAGAGATCA CTACATTAAG CCATAAGCTT CAGGACGCGT CTGCAGAGGT	420
GGAGCGACTG AGAAGAGAAA ACCAGGTCTT AAGCGTGAGA ATCGCGGACA AGAAGTACTA	480
CCCCAGCTCC CAGGACTCCA GCTCCGCTGC GCGCCCCAG CTGCTGATTG TGCTGCTGGG	540
CCTCAGCTCT GCTGCAGTGA GATCCCAGGA AGCTGGCACA TCTTGGAAGG TCCGTCCTGC	600
TCGGCTTTTC GCTTGAACAT TCCCTTGATC TCATCAGTTC TGAGCGGGTC ATGGGGCAAC	660
ACGG	664

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 197 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

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

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 472 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```

CCGTCGACGC GAGTGGAGAC CTGTGGTAGA GAAGCTCCTT TTGATGTCCT ACAGGCTTTC      60
CACTGTGGTG TCTCCAGTCA TTCAGAGCTC ATCCCCTGAA GGCCTCATCC CAATGGACAC      120
TGATTCAGAG TCAGCAAGCC GCTTACAGAT GATTCTGAAT GAGATTCATC CTCGAGATAC      180
TAATGATTAT TTTAACCAAG CCAAAATATT GAAAAGAACAT GATAGCTTTG ATATGAAGGA      240
CTTGAATGCT AGTGTGGTGA ATATTGATAC TTCTACAGAA ATCAAAGGTA AAGAAGTAAA      300
AACATGTGAT GTAAGTGGC AGATGGTGCT GGTATGTTGT TGGAGAAGTA TGAAGGAAGT      360
TGCTTTACTT TTAGGCATGT TGTGCCAGCT TCTGCCCATG CAGCCTGTGC CAGAATCTTC      420
TGATGGATTA TTGACGGTGG AGCAGGTAAA AGAAATAGGA GATTACTTTA AA              472

```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 143 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```

Met Ser Tyr Arg Leu Ser Thr Val Val Ser Pro Val Ile Gln Ser Ser
1           5           10           15

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

Arg Leu Gln Met Ile Leu Asn Glu Ile His Pro Arg Asp Thr Asn Asp
          35           40           45

Tyr Phe Asn Gln Ala Lys Ile Leu Lys Glu His Asp Ser Phe Asp Met
          50           55           60

Lys Asp Leu Asn Ala Ser Val Val Asn Ile Asp Thr Ser Thr Glu Ile
65           70           75           80

Lys Gly Lys Glu Val Lys Thr Cys Asp Val Thr Ala Gln Met Val Leu
          85           90           95

```

Val Cys Cys Trp Arg Ser Met Lys Glu Val Ala Leu Leu Leu Gly Met
 100 105 110

Leu Cys Gln Leu Leu Pro Met Gln Pro Val Pro Glu Ser Ser Asp Gly
 115 120 125

Leu Leu Thr Val Glu Gln Val Lys Glu Ile Gly Asp Tyr Phe Lys
 130 135 140

(2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 433 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

TCTTCTGTCT CCTCTCAAAG TCCGGGTGGC GTCCCCCAAG CCCTGAGATG NTTTGTCCAC	60
TTCAAAGGAT GGTGTCAGAG CAGTGCCACC TCCTGTTTCA GTTTTTCAGA GAGCTTCCAC	120
CAGCTGCTGA GTTTGTGAAG ACAGTGGAGT TNACAAGANT ANGCATTCAA GAGGAAAGGA	180
NTTTGGCTTG NTTGAGGCTG CTGGCCTTTT TGGAAGGAAA GGAAGGGGAA GACACCCTAG	240
TTTTCAGTGT TTGGGANTTT TATGCAGAAT NGAGGCAGTT AANTTTTCCA AGAACAGAAG	300
CGGCATGTTG AAGAAAATTT GGGGGATTGG GATGGGGGTA TGTGTGGATT TTTCTCCAC	360
TAAATTTGCA GGAAANATGT TGAANATAAA TTCAAAAATT TTATCCCCAA AAAAAAAAAA	420
AAAAAAAAAA AAA	433

(2) INFORMATION FOR SEQ ID NO:31:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 409 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```

GAATTCGGCC AAAGAGCTAN GCAAAATGCA TGACAGTAAC AATGTGGAGA AAGACATTAC      60
ACCATCTGAA TTGCCTGCAA AGCCAGGTTG TCTGCATTCA AAAGAGCATT CTATTAAAGC      120
TACCTTAATT TGGCGCTTAT TTTTCTTAAT CATGTTTCTG ACAATCATAG TGTGTGGAAT      180
GGTTGCTGCT TTAAGTGCAA TAAGAGCTAA CTGCCATCAA GAGCCATCAG TATGTCTTCA      240
AGCTGCATGC CCAGAAAGCT GGATTGGTTT TCAAAGAAAAG TGTTTCTATT TTTCTGATGA      300
CACCAAGAAC TGGACATCAA GTCAGAGGTT TTGTGACTCA CAAGATGCTG ATCTTGCTCA      360
GGTTGAAAGC TTCCAGGAAC TGAATTTCTCT GTTGAGATAT AAAGGCCCC      409

```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 128 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```

Met His Asp Ser Asn Asn Val Glu Lys Asp Ile Thr Pro Ser Glu Leu
1           5           10           15

Pro Ala Lys Pro Gly Cys Leu His Ser Lys Glu His Ser Ile Lys Ala
          20           25           30

Thr Leu Ile Trp Arg Leu Phe Phe Leu Ile Met Phe Leu Thr Ile Ile
          35           40           45

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

Gln Glu Pro Ser Val Cys Leu Gln Ala Ala Cys Pro Glu Ser Trp Ile
65           70           75           80

Gly Phe Gln Arg Lys Cys Phe Tyr Phe Ser Asp Asp Thr Lys Asn Trp
          85           90           95

Thr Ser Ser Gln Arg Phe Cys Asp Ser Gln Asp Ala Asp Leu Ala Gln
          100          105          110

Val Glu Ser Phe Gln Glu Leu Asn Phe Leu Leu Arg Tyr Lys Gly Pro
          115          120          125

```

(2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 108 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```

GTTTGNTAAA NGTTGTTTCNG GTTTTNTTGC CCAAAAAAAAAA AAAAAAAAAA AAAAAAAAAA      60
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAACAAAAAA AAANAAAAA                      108

```

(2) INFORMATION FOR SEQ ID NO:34:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 479 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

```

GTGGGATTTA ATTAAGAATT NGGCCCAAAG AGGCCTAACA GGATCAACAC ATTCATCTG      60
GGCTTCTTAA ATCTAAATCT TTAAAATGAC TAAGTTTCTC TCCTTTTCTC TGTTTTTCCT      120
AATAGTTGGG GCTTAATATG ACTCATGTGT GTTTCAATAT GGAAATTATT GGAGGGAAAG      180
AAGTGTCACC TCATTCCAGG CCANTTATGG CCTCCATCCA GTATGGCGGA CATCACGTTT      240
GTGGAGGTGT TCTGATTGAT CCACAGTGGG TGCTGACAGC AGCCCACTGC CAATATCGGT      300
TTACCAAAGG CCAGTCTCCC ACTGTGGTTT TAGGCGCACA CTCTCTCTCA AAGAATGAGG      360
CCTCCAAACA AACACTGGAG ATCAAAAAAT TTATACCATT CTCAAGAGTT ACATCAGATC      420
CTCAATCCAA TGATATCATG CTGGTTAAGC NTCAAACAGC CGCCAAACTC AATAAACAT      479

```

(2) INFORMATION FOR SEQ ID NO:35:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 114 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

Met Thr His Val Cys Phe Asn Met Glu Ile Ile Gly Gly Lys Glu Val
1           5           10           15

Ser Pro His Ser Arg Pro Xaa Met Ala Ser Ile Gln Tyr Gly Gly His
          20           25           30

His Val Cys Gly Gly Val Leu Ile Asp Pro Gln Trp Val Leu Thr Ala
      35           40           45

Ala His Cys Gln Tyr Arg Phe Thr Lys Gly Gln Ser Pro Thr Val Val
      50           55           60

Leu Gly Ala His Ser Leu Ser Lys Asn Glu Ala Ser Lys Gln Thr Leu
65           70           75           80

Glu Ile Lys Lys Phe Ile Pro Phe Ser Arg Val Thr Ser Asp Pro Gln
          85           90           95

Ser Asn Asp Ile Met Leu Val Lys Xaa Gln Thr Ala Ala Lys Leu Asn
      100           105           110

Lys His

```

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 173 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

```

GCAGGTTAGA GTTGGTGTAG TAAAGCAGAG CACATATGGG TCCATTTTGC ACTTGTAAGT      60
CATTTTATTA AGGAATCAAG TTCTTTTTCa CTTGTATCAC TGATGTATTT CTACCATGCT      120
GGTTTTATTC TAAATAAAAT TTAGAAGACT CTCAAAAAAA AAAAAAAAAA AAA              173

```

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 463 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

```

GAATTCGGCC AAAGAGGCCT ACGTTATACT ATTAGATCCT TTCATTATCA ATCCCTTTTA      60
AAGGCAAGGA AACAGGTTCA GCAAGATCAG CTGACTTCTC TGTGTAAGTG GGACCTGAGA      120
TTTGAAAGTT GAGAGCAGCA TGTTTTGCCC ACTGAAACTC ATCCTGCTGC CAGTGTTACT      180
GGATTATTCC TTGGGCCTGA ATGACTTGAA TGTTTCCCCG CCTGAGCTAA CAGTCCATGT      240
GGGTGATTCA GCTCTGATGG GATGTGTTTT CCAGAGCACA GAAGACAAAT GTATATTCAA      300
GATAGACTGG ACTCTGTCAC CAGGAGAGCA CGCCAAGGAC GAATATGTGC TATACTATTA      360
CTCCAATCTC AGTGTGCCTA TTGGGCGCTT CCAGAACCGC GTACACTTGA TGGGGGACAA      420
CTTATGCAAT GATGGCTCTC TCCTGCTCCA AGATGTGCAA GAT                          463

```

(2) INFORMATION FOR SEQ ID NO:38:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 110 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

Met Phe Cys Pro Leu Lys Leu Ile Leu Leu Pro Val Leu Leu Asp Tyr
1           5           10           15
Ser Leu Gly Leu Asn Asp Leu Asn Val Ser Pro Pro Glu Leu Thr Val
          20           25           30
His Val Gly Asp Ser Ala Leu Met Gly Cys Val Phe Gln Ser Thr Glu
          35           40           45
Asp Lys Cys Ile Phe Lys Ile Asp Trp Thr Leu Ser Pro Gly Glu His
          50           55           60

```

Ala Lys Asp Glu Tyr Val Leu Tyr Tyr Tyr Ser Asn Leu Ser Val Pro
65 70 75 80

Ile Gly Arg Phe Gln Asn Arg Val His Leu Met Gly Asp Asn Leu Cys
85 90 95

Asn Asp Gly Ser Leu Leu Leu Gln Asp Val Gln Asp Val Glu
100 105 110

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 131 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

TTCCTTCTTT CTCCCTTTTC CTTGATAGA GTCCATGGGA GAATGAGGGA GATGATTTTT	60
GTGCCCAGCC AAGAAAGCAA TGGGCTAGAC ATTAAAGTGT TACACTTTTA TTCTTAAAAA	120
AAAAAAAAAA A	131

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 461 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

CGATAATCTT CTTCCATTG NGGGGAAATT TATTGCATCC TTCTTTAAAC CGGGGTTTGA	60
GAAGTATNAT AACTTGGATC TNTNTCGGNA TCTCTTAAAT ATTCCAGGAC CAATTGACAN	120
NCCATCTCGA ATTCGGCCAA AGAGGCCTAG ATGATGATAT GTTTAACCAC CAAGTTCCTT	180
ATTTGTGGCT GATTTACTGC CTTTGTGATC CTCTTCAATC AAGTATTAAA GAAACAGTGG	240
AGGCATATGA GGCAGCATTG GGGGTGGCTA TGAGATGTGA TATAGTACAG AAGATATGGA	300

TGGATTATCT TGTCTTTGCA AATAATAGAG CTGCTGGATC CAGAAACAAA GTTCAAGAAT 360
 TCAAATTTTT TACTGATTTA GTGAATAGAT GTTTGGTTAC AGTCCCTGCC CGATACCCCA 420
 TTCCTTTT TAG CAGTGCTGAT TACTGGTCCA ACTATGAATT T 461

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 101 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

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

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 318 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

TTTTTTGAGA TTCTTCATTT CGGGATTTTA AAACNATAGC AGNCCATCTT AAGGAAAGTG	60
TANCTNCCAT GGCCACAAGT CTGCTAGTTG CACTTGAATG CTCTATCNGG GTTGTATTATT	120
ACCCTTTCNA CGTTCTGGAC TCCTTTCCGA GACTGTTTAA CTTGNAGATT AAAGAAACTA	180
TTCCAAATGC CAGTGCATCA GNACCTAAGA GTGGGCAAAT ATTATGTGCA ATTTTTTTGT	240
AAAGAAATTT TAATTTATAA TAAAGTTTAA CAGTTTAAAG GNCCCCAAAA AAAAAAAAAA	300
AAAAAAAAAA AAAAAAAAAA	318

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 742 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

CTAGTTTGGA GCTGTGCTGT AAAACAAGA GTAACATTTT TATATTAAAG TTAAATAAAG	60
TTACAACCTT GAAGAGAGTT TCTGCAAGAC ATGACACAAA GCTGCTAGCA GAAAATCAAA	120
ACGCTGATTA AAAGAAGCAC GGTATGATGA CCAAACATAA AAAGTGTTTT ATAATTGTTG	180
GTGTTTTAAT AACAACTAAT ATTATTACTC TGATAGTTAA ACTAACTCGA GATTCTCAGA	240
GTTTATGCCC CTATGATTGG ATTGGTTTCC AAAACAAATG CTATTATTTT TCTAAAGAAG	300
AAGGAGATTG GAATTCAAGT AAATACAAC TTTCCACTCA ACATGCCGAC CTAACATAA	360
TTGACAACAT AGAAGAAATG AATTTTCTTA GGCGGTATAA ATGCAGTTCT GATCACTGGA	420
TTGGACTGAA GATGNCAAAA AATCGAACAG GACAATGGGT AGATGGAGCT ACATTTACCA	480
AATCGTTTGB CATGAGAGGG AGTGAAGGAT GTGCCTACCT CAGCGATGAT GGTGCAGCAA	540
CAGCTAGATG TTACACCGNA AGAAAATGGA TTTGCAGGAA AAGAATACAC TAAGTTAATG	600
TCTAAGATAA TGGGGAAAAT AGAAAATAAC ATTATTAAGT GTAAAACCAG CAAAGTACTT	660
TTTTAATTAA ACAAGTTTCG AGTTTTGTAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA	720
AAAAAAAAAA ANAAAAAAAA AA	742

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 149 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

Met Met Thr Lys His Lys Lys Cys Phe Ile Ile Val Gly Val Leu Ile
1           5           10           15

Thr Thr Asn Ile Ile Thr Leu Ile Val Lys Leu Thr Arg Asp Ser Gln
          20           25           30

Ser Leu Cys Pro Tyr Asp Trp Ile Gly Phe Gln Asn Lys Cys Tyr Tyr
          35           40           45

Phe Ser Lys Glu Glu Gly Asp Trp Asn Ser Ser Lys Tyr Asn Cys Ser
          50           55           60

Thr Gln His Ala Asp Leu Thr Ile Ile Asp Asn Ile Glu Glu Met Asn
65           70           75           80

Phe Leu Arg Arg Tyr Lys Cys Ser Ser Asp His Trp Ile Gly Leu Lys
          85           90           95

Met Xaa Lys Asn Arg Thr Gly Gln Trp Val Asp Gly Ala Thr Phe Thr
          100          105          110

Lys Ser Phe Xaa Met Arg Gly Ser Glu Gly Cys Ala Tyr Leu Ser Asp
          115          120          125

Asp Gly Ala Ala Thr Ala Arg Cys Tyr Thr Xaa Arg Lys Trp Ile Cys
          130          135          140

Arg Lys Arg Ile His
          145

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(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

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

GGAAATGACT TTTGATGACC TAAAGATCCA

30

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CCATCAGTAT GTCTTCGAGC TGCATGC

27

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

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

TTGATGCTGT GCTCATCCTC CTGCTCA

27

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

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

GAAATAATAA TGGTGGTGGT GGTGCGG

27

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

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

ATGCTCATGA ACCCAATCCG GAGAAGG

27

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 25 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GGGCCTGAGG TTGAACTGGG GTGAA

25

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

GCTCAGGAAT GGGAAAGGGA ACTGGGA

27

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

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

CATGATAATA GCTTTTCTAA CTGTGGGTAC

30

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TTGATTATCT TCACCATCAA GGCCAACAG

29

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 45 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

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

CACAGTGGAA AGCCTGTAGG ACATCAAAAG GAGCTTCTCT ACCAC

45

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

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

CATGTTTCTG ACAATCATAG TGTGTGGAA

29

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

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

GTGGTTTTAG GCGCACACTC TCTCTCA

27

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

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

TTCCTGGGC CTGAATGACT TGAATGTTT

29

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 45 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

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

AAAGGCAGTA AATCAGCCAC AAATAAGGAA CTTGGTGGTT AAACA

45

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "oligonucleotide"

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

TTATGCCCCCT ATGATTGGAT TGGTTTCC

28

What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:
 - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 63 to nucleotide 348;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 201 to nucleotide 348;
 - (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone S185_2 deposited under accession number ATCC 98028;
 - (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone S185_2 deposited under accession number ATCC 98028;
 - (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone S185_2 deposited under accession number ATCC 98028;
 - (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone S185_2 deposited under accession number ATCC 98028;
 - (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
 - (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;
 - (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
 - (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
 - (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).
2. A composition of claim 1 wherein said polynucleotide is operably linked to an expression control sequence.
3. A host cell transformed with a composition of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.
5. A process for producing a protein, which comprises:
 - (a) growing a culture of the host cell of claim 3 in a suitable culture medium; and
 - (b) purifying the protein from the culture
6. A protein produced according to the process of claim 5.
7. The protein of claim 6 comprising a mature protein.
8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:
 - (a) the amino acid sequence of SEQ ID NO:2;
 - (b) the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 42;
 - (c) fragments of the amino acid sequence of SEQ ID NO:2; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone S185_2 deposited under accession number ATCC98028;the protein being substantially free from other mammalian proteins.
9. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.
10. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 42.
11. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.
12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.

13. The gene corresponding to the cDNA sequence of SEQ ID NO:1 or SEQ ID NO:3.
14. A composition comprising an isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 1014;
 - (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone G52_24 deposited under accession number ATCC 98028;
 - (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC 98028;
 - (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone G52_24 deposited under accession number ATCC 98028;
 - (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC 98028;
 - (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;
 - (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;
 - (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
 - (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
 - (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).
15. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:6;
 - (b) the amino acid sequence of SEQ ID NO:6 from amino acid 201 to amino acid 221;

- (c) fragments of the amino acid sequence of SEQ ID NO:6; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC98028;
- the protein being substantially free from other mammalian proteins.

16. The gene corresponding to the cDNA sequence of SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:7.

17. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 138 to nucleotide 375;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone J218_15 deposited under accession number ATCC 98028;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J218_15 deposited under accession number ATCC 98028;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J218_15 deposited under accession number ATCC 98028;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J218_15 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

18. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:10;
- (b) the amino acid sequence of SEQ ID NO:10 from amino acid 20 to amino acid 69;
- (c) fragments of the amino acid sequence of SEQ ID NO:10; and
- (d) the amino acid sequence encoded by the cDNA insert of clone J218_15 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins.

19. The gene corresponding to the cDNA sequence of SEQ ID NO:8, SEQ ID NO:9 or SEQ ID NO:11.

20. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 163 to nucleotide 345;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone M8_2 deposited under accession number ATCC 98028;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone M8_2 deposited under accession number ATCC 98028;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone M8_2 deposited under accession number ATCC 98028;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone M8_2 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

21. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:13;
- (b) the amino acid sequence of SEQ ID NO:13 from amino acid 13 to amino acid 62;
- (c) fragments of the amino acid sequence of SEQ ID NO:13; and
- (d) the amino acid sequence encoded by the cDNA insert of clone M8_2 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins.

22. The gene corresponding to the cDNA sequence of SEQ ID NO:12 or SEQ ID NO:14.

23. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 181 to nucleotide 325;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 274 to nucleotide 325;
- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone M97_2 deposited under accession number ATCC 98028;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC 98028;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone M97_2 deposited under accession number ATCC 98028;

- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC 98028;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above .

24. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:16;
- (b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 48;
- (c) fragments of the amino acid sequence of SEQ ID NO:16; and
- (d) the amino acid sequence encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins.

25. The gene corresponding to the cDNA sequence of SEQ ID NO:15 or SEQ ID NO:17.

26. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 221 to nucleotide 601;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone B219_2 deposited under accession number ATCC 98028;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone B219_2 deposited under accession number ATCC 98028;

- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone B219_2 deposited under accession number ATCC 98028;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone B219_2 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:19;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above .

27. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:19;
- (b) the amino acid sequence of SEQ ID NO:19 from amino acid 1 to amino acid 79;
- (c) fragments of the amino acid sequence of SEQ ID NO:19; and
- (d) the amino acid sequence encoded by the cDNA insert of clone B219_2 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins.

28. The gene corresponding to the cDNA sequence of SEQ ID NO:18.

29. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20 from nucleotide 36 to nucleotide 522;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:20 from nucleotide 93 to nucleotide 522;

- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC 98028;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC 98028;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:21;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:21 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above .

30. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:21;
- (b) the amino acid sequence of SEQ ID NO:21 from amino acid 1 to amino acid 101;
- (c) fragments of the amino acid sequence of SEQ ID NO:21; and
- (d) the amino acid sequence encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins.

31. The gene corresponding to the cDNA sequence of SEQ ID NO:20 or SEQ ID NO:22.

32. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 88 to nucleotide 499;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone J59_41 deposited under accession number ATCC 98028;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC 98028;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J59_41 deposited under accession number ATCC 98028;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:24 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

33. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:24;
- (b) the amino acid sequence of SEQ ID NO:24 from amino acid 45 to amino acid 113;
- (c) fragments of the amino acid sequence of SEQ ID NO:24; and
- (d) the amino acid sequence encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins.

34. The gene corresponding to the cDNA sequence of SEQ ID NO:23 or SEQ ID NO:25.
35. A composition comprising an isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26 from nucleotide 23 to nucleotide 613;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26 from nucleotide 137 to nucleotide 613;
 - (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone O238_1 deposited under accession number ATCC 98028;
 - (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone O238_1 deposited under accession number ATCC 98028;
 - (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone O238_1 deposited under accession number ATCC 98028;
 - (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone O238_1 deposited under accession number ATCC 98028;
 - (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:27;
 - (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:27 having biological activity;
 - (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
 - (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
 - (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).
36. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:27;

- (b) fragments of the amino acid sequence of SEQ ID NO:27; and
 - (c) the amino acid sequence encoded by the cDNA insert of clone O238_1 deposited under accession number ATCC98028;
- the protein being substantially free from other mammalian proteins.

37. The gene corresponding to the cDNA sequence of SEQ ID NO:26.

38. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:28;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:28 from nucleotide 44 to nucleotide 472;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:28 from nucleotide 440 to nucleotide 472;
- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone G86_2 deposited under accession number ATCC 98028;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone G86_2 deposited under accession number ATCC 98028;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone G86_2 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone G86_2 deposited under accession number ATCC 98028;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:29;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:29 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

39. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:29;
- (b) fragments of the amino acid sequence of SEQ ID NO:29; and
- (c) the amino acid sequence encoded by the cDNA insert of clone G86_2 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins.

40. The gene corresponding to the cDNA sequence of SEQ ID NO:28 or SEQ ID NO:30.

41. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:31;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:31 from nucleotide 26 to nucleotide 409;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:31 from nucleotide 176 to nucleotide 409;
- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H298_23 deposited under accession number ATCC 98028;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H298_23 deposited under accession number ATCC 98028;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H298_23 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H298_23 deposited under accession number ATCC 98028;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:32;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:32 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

42. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:32;

(b) fragments of the amino acid sequence of SEQ ID NO:32; and

(c) the amino acid sequence encoded by the cDNA insert of clone H298_23 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins.

43. The gene corresponding to the cDNA sequence of SEQ ID NO:31 or SEQ ID NO:33.

44. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34 from nucleotide 138 to nucleotide 479;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H83_22 deposited under accession number ATCC 98028;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC 98028;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H83_22 deposited under accession number ATCC 98028;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:35;

- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:35 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

45. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:35;
- (b) fragments of the amino acid sequence of SEQ ID NO:35; and
- (c) the amino acid sequence encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins.

46. The gene corresponding to the cDNA sequence of SEQ ID NO:34 or SEQ ID NO:36.

47. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:37;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:37 from nucleotide 139 to nucleotide 463;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:37 from nucleotide 196 to nucleotide 463;
- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H849_24 deposited under accession number ATCC 98028;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H849_24 deposited under accession number ATCC 98028;

- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H849_24 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H849_24 deposited under accession number ATCC 98028;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:38;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:38 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

48. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:38;
- (b) fragments of the amino acid sequence of SEQ ID NO:38; and
- (c) the amino acid sequence encoded by the cDNA insert of clone H849_24 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins.

49. The gene corresponding to the cDNA sequence of SEQ ID NO:37 or SEQ ID NO:39.

50. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:40;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:40 from nucleotide 149 to nucleotide 461;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:40 from nucleotide 212 to nucleotide 461;

- (d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone J143_1 deposited under accession number ATCC 98028;
- (e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC 98028;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J143_1 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC 98028;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:41;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:41 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above .

51. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:41;
- (b) fragments of the amino acid sequence of SEQ ID NO:41; and
- (c) the amino acid sequence encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC98028;

the protein being substantially free from other mammalian proteins.

52. The gene corresponding to the cDNA sequence of SEQ ID NO:40 or SEQ ID NO:42.

53. A composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:43;

- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:43 from nucleotide 144 to nucleotide 590;
- (c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H905_107 deposited under accession number ATCC 98028;
- (d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H905_107 deposited under accession number ATCC 98028;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H905_107 deposited under accession number ATCC 98028;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H905_107 deposited under accession number ATCC 98028;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:44;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:44 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

54. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:44;
 - (b) the amino acid sequence of SEQ ID NO:44 from amino acid 1 to amino acid 86;
 - (c) fragments of the amino acid sequence of SEQ ID NO:44; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone H905_107 deposited under accession number ATCC98028;
- the protein being substantially free from other mammalian proteins.

55. The gene corresponding to the cDNA sequence of SEQ ID NO:43.

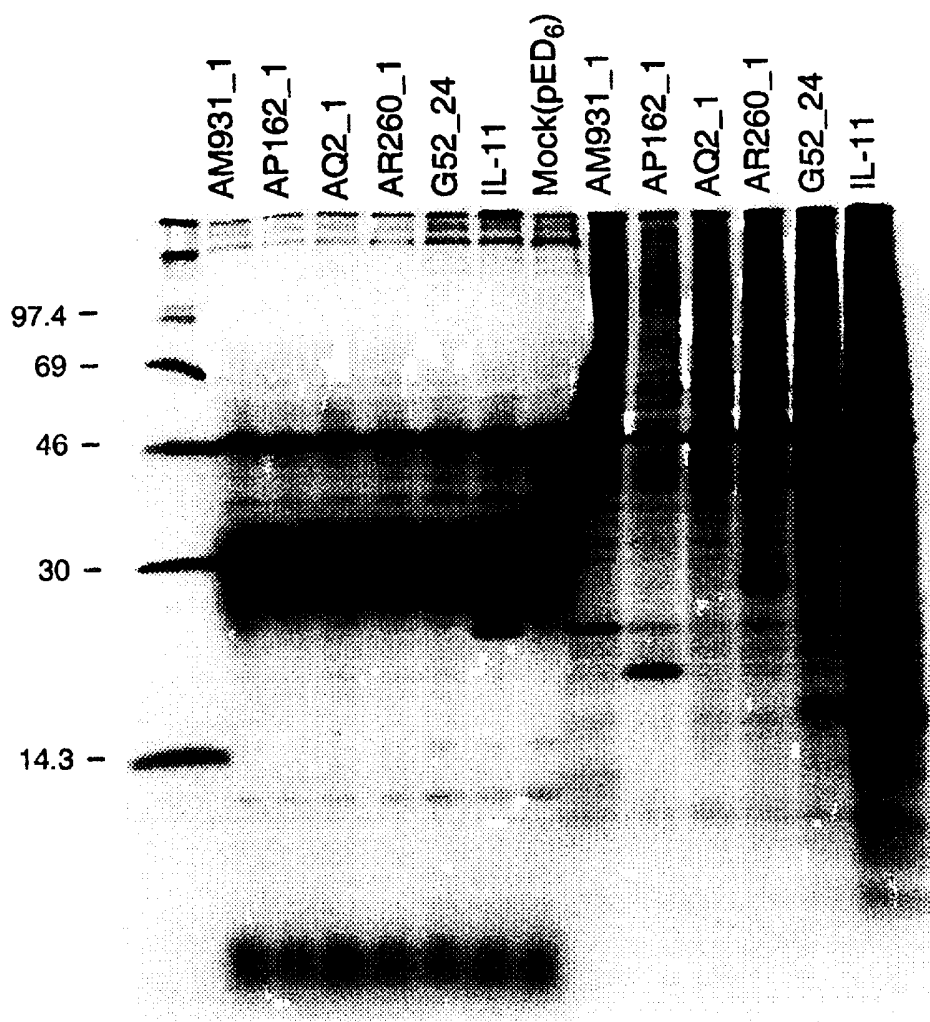


Fig. 1
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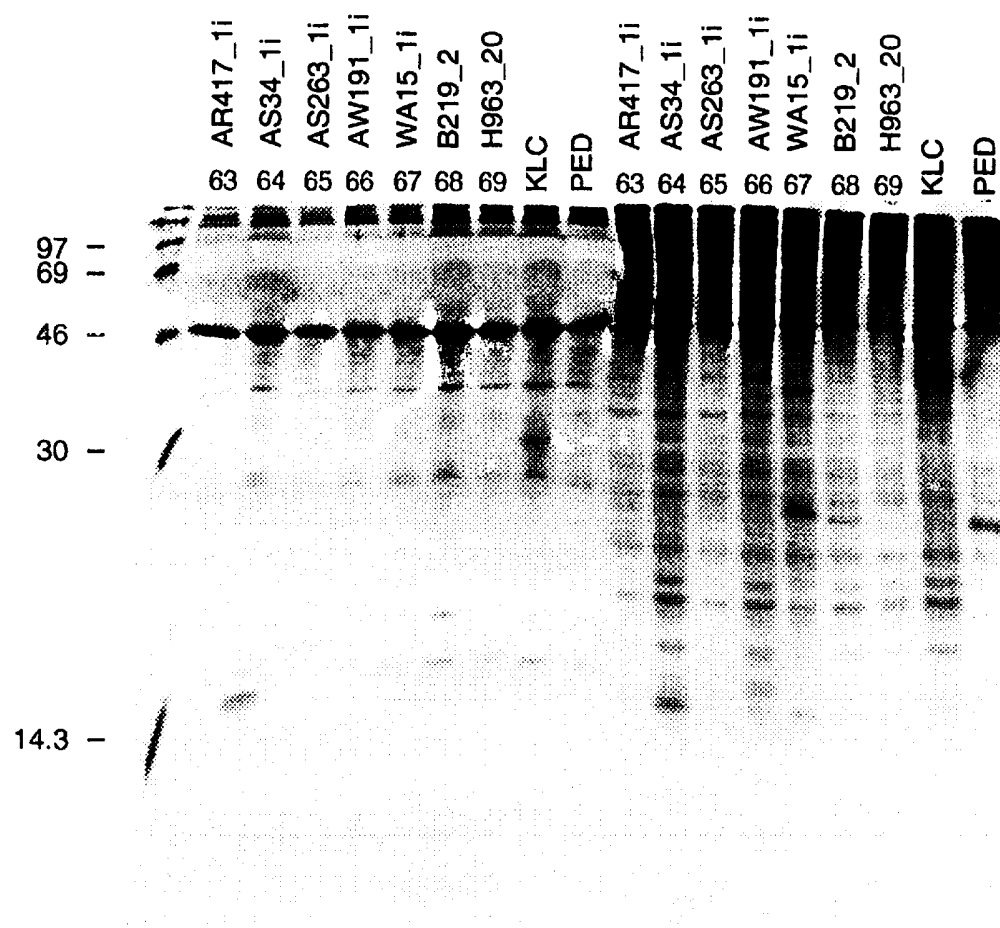


Fig. 2
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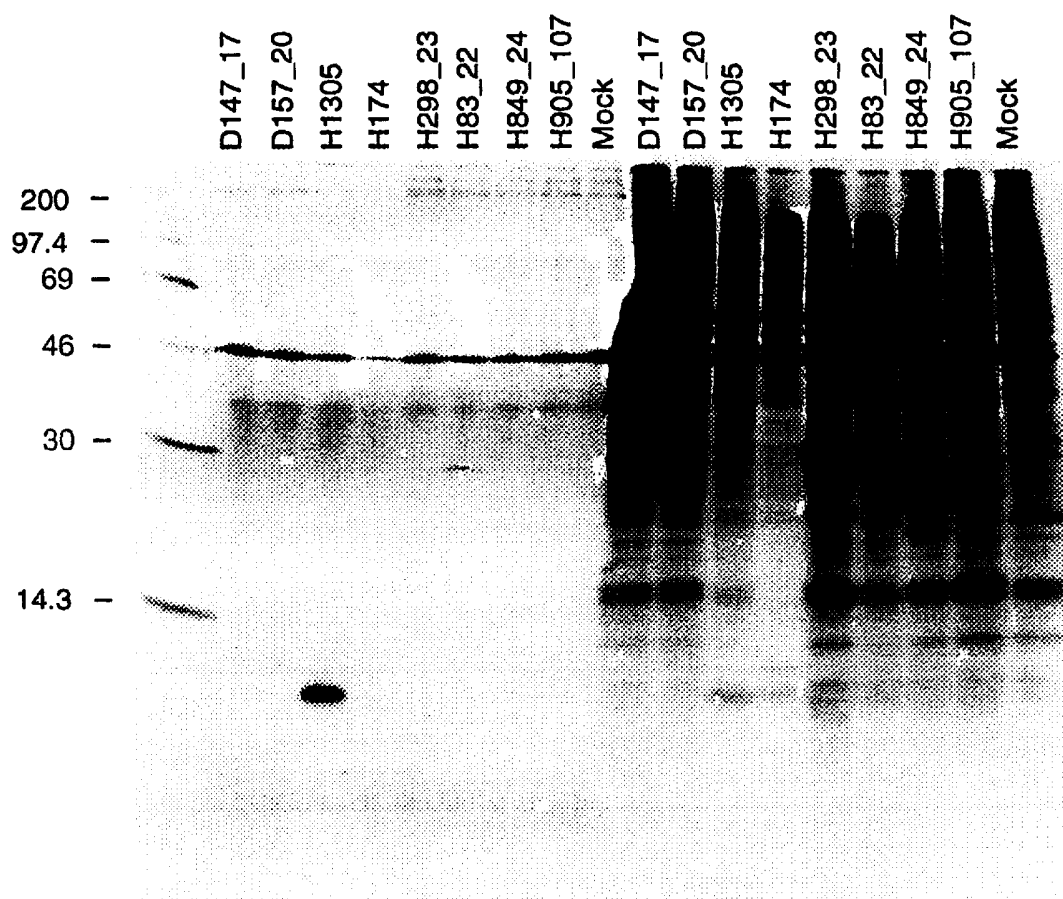


Fig. 3
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