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(54) **PROTEINES SECRETEES ET POLYNUCLEOTIDES LES
CODANT**
(54) **SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING
THEM**

(57) La présente invention concerne de nouveaux
polynucléotides et les protéines codées par ceux-ci.

(57) Novel polynucleotides and the proteins encoded
thereby are disclosed.



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(57) Abstract Novel polynucleotides and the proteins encoded thereby are disclosed.		

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of the following applications: Ser. No. 08/677,231, filed July 9, 1996; Ser. No. 08/701,819, filed August 23, 1996; Ser. No. 08/721,488, filed September 27, 1996; and Ser. No. 08/739,066, filed October 28, 1996.

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FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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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.

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;
- 5 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 113 to nucleotide 742;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 179 to nucleotide 742;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 568;
- 10 (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;
- 15 (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;
- 20 (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;
- 25 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).
- 30 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 113 to nucleotide 742; the nucleotide sequence of SEQ ID NO:1

from nucleotide 179 to nucleotide 742; the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 568; the nucleotide sequence of the full-length protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129.

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

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;
- (b) the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129;
- (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 AC41_1 deposited under accession number ATCC 98101;

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 53 to amino acid 129.

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:3;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 161 to nucleotide 1126;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:3 from nucleotide 218 to nucleotide 1126;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 553;

5 (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

10 (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 15 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

20 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

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

(m) a polynucleotide capable of hybridizing under stringent 25 conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 161 to nucleotide 1126; the nucleotide sequence of SEQ ID NO:3 from nucleotide 218 to nucleotide 1126; the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 553; the nucleotide sequence of the full-length protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101; or the 30 nucleotide sequence of the mature protein coding sequence of clone AC222_1 deposited

under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131.

Other embodiments provide the gene corresponding to the cDNA sequence of 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:4;
- (b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131;
- (c) fragments of the amino acid sequence of SEQ ID NO:4; and
- (d) the amino acid sequence encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131.

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:5;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 827 to nucleotide 994;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 869 to nucleotide 994;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;

- 5 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;
- 10 (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 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
- 15 (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:5 from nucleotide 827 to nucleotide 994; the nucleotide sequence of SEQ ID NO:5 from nucleotide 869 to nucleotide 994; the nucleotide sequence of the full-length protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101. 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 1 to amino acid 20.

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

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;
- (b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20;
- (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 AJ143_1 deposited under accession number ATCC 98101;

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 1 to amino acid 20.

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:7;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 91 to nucleotide 204;
- (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;
- (d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 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

5 (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:7 from nucleotide 91 to nucleotide 204; the nucleotide sequence of the full-length protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101. In other preferred
10 embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of
15 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:8;
- 20 (b) fragments of the amino acid sequence of SEQ ID NO:8; and
- (c) the amino acid sequence encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8.

25 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:9;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID
30 NO:9 from nucleotide 60 to nucleotide 230;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:9 from nucleotide 1 to nucleotide 323;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;

5 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

10 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

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

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

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

20 (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).

25 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 60 to nucleotide 230; the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 323; the nucleotide sequence of the full-length protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101. In other preferred embodiments, the
30 polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

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) fragments of the amino acid sequence of SEQ ID NO:10; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

AK684_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO: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:11;

- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 812 to nucleotide 2731;

- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 944 to nucleotide 2731;

- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 855 to nucleotide 1186;

- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;

- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;

- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;

5 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

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

10 (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 812 to nucleotide 2731; the nucleotide sequence of SEQ ID NO:11 from nucleotide 944 to nucleotide 2731; the nucleotide sequence of SEQ ID NO:11 from nucleotide 855 to nucleotide 1186; the nucleotide sequence of the full-length protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101.

15 In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11.

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:

- 30 (a) the amino acid sequence of SEQ ID NO:12;
- (b) the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125;
- (c) fragments of the amino acid sequence of SEQ ID NO:12; and

(d) the amino acid sequence encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101; the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12 or the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125.

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:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 2196 to nucleotide 2708;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 489 to nucleotide 890;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX56_28 deposited under accession number ATCC 98180;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX56_28 deposited under accession number ATCC 98180;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 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).

5 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 2196 to nucleotide 2708; the nucleotide sequence of SEQ ID NO:13 from nucleotide 489 to nucleotide 890; the nucleotide sequence of the full-length protein coding sequence of clone AX56_28 deposited under accession number ATCC 98180; or the nucleotide sequence of the mature protein coding sequence of clone
10 AX56_28 deposited under accession number ATCC 98180. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180.

15 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

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:14;
(b) fragments of the amino acid sequence of SEQ ID NO:14; and
(c) the amino acid sequence encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;
the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14.

25 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
30 NO:15 from nucleotide 51 to nucleotide 1319;
(c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:15 from nucleotide 126 to nucleotide 1319;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 409 to nucleotide 495;

5 (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

10 (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

15 (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

20 (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

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

25 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 51 to nucleotide 1319; the nucleotide sequence of SEQ ID NO:15 from nucleotide 126 to nucleotide 1319; the nucleotide sequence of SEQ ID NO:15 from nucleotide 409 to nucleotide 495; the nucleotide sequence of the full-length protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone
30 AX92_3 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by

the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101.

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

5 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) fragments of the amino acid sequence of SEQ ID NO:16; and
 - (c) the amino acid sequence encoded by the cDNA insert of clone
- 10 AX92_3 deposited under accession number ATCC 98101;
- the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16.

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:18;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 210 to nucleotide 350;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID
- 20 NO:18 from nucleotide 300 to nucleotide 350;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101;
 - (e) a polynucleotide encoding the full-length protein encoded by the
- 25 cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101;
 - (g) a polynucleotide encoding the mature protein encoded by the
- 30 cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid

sequence of SEQ ID NO:19;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 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).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:18 from nucleotide 210 to nucleotide 350; the nucleotide sequence of SEQ ID NO:18 from nucleotide 300 to nucleotide 350; the nucleotide sequence of the full-length protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:18, SEQ ID NO:17 or SEQ ID NO:20.

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) fragments of the amino acid sequence of SEQ ID NO:19; and

(c) the amino acid sequence encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

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

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:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 322 to nucleotide 774;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 149 to nucleotide 477;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 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).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:21 from nucleotide 322 to nucleotide 774; the nucleotide sequence of SEQ ID NO:21 from nucleotide 149 to nucleotide 477; the nucleotide sequence of the full-length protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101. In other preferred

embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:21.

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:22;
- (b) the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121;
- (c) fragments of the amino acid sequence of SEQ ID NO:22; and
- (d) the amino acid sequence encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:22 or the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121.

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:23;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 80 to nucleotide 1801;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 1 to nucleotide 421;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152;
- (e) a polynucleotide encoding the full-length protein encoded by the

cDNA insert of clone BM46_10 deposited under accession number ATCC 98152;

5 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BM46_10 deposited under accession number ATCC 98152;

10 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:24 having biological activity;

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

15 (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).

20 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:23 from nucleotide 80 to nucleotide 1801; the nucleotide sequence of SEQ ID NO:23 from nucleotide 1 to nucleotide 421; the nucleotide sequence of the full-length protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152; or the nucleotide sequence of the mature protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152. In other preferred
25 embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BM46_10 deposited under accession number ATCC 98152. 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 1 to amino acid 112.

30 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:23.

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:24;
- 5 (b) the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112;
- (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 BM46_10 deposited under accession number ATCC 98152;
- 10 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 1 to amino acid 112.

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:25;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 719 to nucleotide 886;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 812 to nucleotide 886;
- 20 (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 1 to nucleotide 853;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;
- 25 (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;
- 30 (h) a polynucleotide encoding the mature protein encoded by the

cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:26;

5 (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:26 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

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

10 (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:25 from nucleotide 719 to nucleotide 886; the nucleotide sequence of SEQ ID NO:25 from nucleotide 812 to nucleotide 886; the nucleotide sequence of SEQ ID NO:25 from nucleotide 1 to nucleotide 853; the nucleotide sequence of the full-length protein coding sequence of clone J317_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone J317_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of 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:

(a) the amino acid sequence of SEQ ID NO:26;

(b) fragments of the amino acid sequence of SEQ ID NO:26; and

(c) the amino acid sequence encoded by the cDNA insert of clone

J317_1 deposited under accession number ATCC 98101;

30 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:26.

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:27;
- 5 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 442 to nucleotide 609;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 1 to nucleotide 483;
- 10 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone O289_1 deposited under accession number ATCC 98101;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;
- 15 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone O289_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;
- 20 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:28;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:28 having biological activity;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- 25 (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:27 from nucleotide 442 to nucleotide 609; the nucleotide sequence of SEQ ID NO:27 from nucleotide 1 to nucleotide 483; the nucleotide sequence of the full-length

protein coding sequence of clone O289_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone O289_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:27.

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:28;
- (b) fragments of the amino acid sequence of SEQ ID NO:28; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

O289_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:28.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, 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.

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 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.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1A and Fig. 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

Fig. 2 is an autoradiograph evidencing the expression of the following clone disclosed herein, BG33_7.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The 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.

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 "AC41_1"

A polynucleotide of the present invention has been identified as clone "AC41_1".

AC41_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AC41_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AC41_1 protein").

The nucleotide sequence of AC41_1 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AC41_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2. Amino acids 10 to 22 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 23, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AC41_1 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for AC41_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AC41_1 demonstrated at least some homology with sequences identified as L20319 (Rattus norvegicus developmentally regulated protein mRNA, complete cds), U46493 (Cloning vector pFlp recombinase gene, complete cds), and Z22650 (H.sapiens insertion polymorphism DNA). The predicted amino acid sequence disclosed herein for AC41_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AC41_1 protein demonstrated at least some identity with sequences identified as L20319 (developmentally regulated protein [Rattus norvegicus]) and X12544 (3 HLA-DR B protein precursor (AA -29 to 267) [Homo sapiens]). Based upon homology, AC41_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "AC222_1"

A polynucleotide of the present invention has been identified as clone "AC222_1". AC222_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No.

5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AC222_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AC222_1 protein").

5 The nucleotide sequence of AC222_1 as presently determined is reported in SEQ ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AC222_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4. Amino acids 7 to 19 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at
10 amino acid 20, or are a transmembrane domain.

 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AC222_1 should be approximately 1400 bp.

 The nucleotide sequence disclosed herein for AC222_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and
15 FASTA search protocols. AC222_1 demonstrated at least some homology with sequences identified as D10485 (Chicken mRNA for proteoglycan (PG-Lb) core protein, complete cds), D78274 (Mouse mRNA for proteoglycan, complete cds), N22463 (yw34c10.s1 Homo sapiens cDNA clone 254130 3'), U59111 (Human dermatan sulfate proteoglycan 3 (DSPG3) mRNA, complete cds), U77127 (Bos taurus epiphykan mRNA, complete cds), and Z32693 (E.coli pT7hGH_pl DNA, 6160bp). The predicted amino acid
20 sequence disclosed herein for AC222_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AC222_1 protein demonstrated at least some identity with sequences identified as D10485 (proteoglycan core protein [Gallus gallus]), D78274 (proteoglycan [Mus musculus]), U77127 (epiphykan [Bos taurus]), and U59111 (dermatan sulfate proteoglycan 3 [Homo sapiens]). Based upon homology, AC222_1 proteins and each homologous
25 protein or peptide may share at least some activity.

Clone "AJ143_1"

30 A polynucleotide of the present invention has been identified as clone "AJ143_1". AJ143_1 was isolated from a human adult testes cDNA library using

methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AJ143_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ143_1 protein").

The nucleotide sequence of AJ143_1 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AJ143_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Amino acids 2 to 14 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 15, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AJ143_1 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for AJ143_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AJ143_1 demonstrated at least some homology with sequences identified as T19431 (d08002s Homo sapiens cDNA clone d08002 5' end) and Z41997 (H. sapiens partial cDNA sequence; clone c-05c07); it may also show some similarity to phosphoenolpyruvate phosphomutase. Based upon homology, AJ143_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "AJ168_4"

A polynucleotide of the present invention has been identified as clone "AJ168_4". AJ168_4 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AJ168_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ168_4 protein").

The nucleotide sequence of AJ168_4 as presently determined is reported in SEQ ID NO:7. What applicants presently believe to be the proper reading frame and the

predicted amino acid sequence of the AJ168_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AJ168_4 should be approximately 700 bp.

5 The nucleotide sequence disclosed herein for AJ168_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AJ168_4 demonstrated at least some homology with sequences identified as T65223 (yc79c02.s1 Homo sapiens cDNA clone 22106 3'). Based upon homology, AJ168_4 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the AJ168_4 protein sequence (SEQ ID NO:8).

Clone "AK684_1"

15 A polynucleotide of the present invention has been identified as clone "AK684_1". AK684_1 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AK684_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AK684_1 protein").

20 The nucleotide sequence of AK684_1 as presently determined is reported in SEQ ID NO:9. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AK684_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10.

25 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AK684_1 should be approximately 1000 bp.

30 The nucleotide sequence disclosed herein for AK684_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AK684_1 demonstrated at least some homology with sequences identified as AA226405 (nc20c05.r1 NCI CGAP Pr1 Homo sapiens cDNA clone 2817), G15531 (human STS SHGC-17023), and T68858 (yc30d08.s1 Homo sapiens

cDNA clone 82191 3' similar to contains MSR1 repetitive element). Based upon homology, AK684_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the AK684_1 protein sequence centered around amino acid 20 of SEQ ID NO:10.

Clone "AS209_1"

A polynucleotide of the present invention has been identified as clone "AS209_1". AS209_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AS209_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AS209_1 protein").

The nucleotide sequence of AS209_1 as presently determined is reported in SEQ ID NO:11. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AS209_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12. Amino acids 32 to 44 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 45, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AS209_1 should be approximately 2882 bp.

The nucleotide sequence disclosed herein for AS209_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AS209_1 demonstrated at least some homology with sequences identified as AA055217 (zf17h02.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 377235 3') and H29533 (ym60h11.r1 Homo sapiens cDNA clone 52955 5' similar to SP:A60164 S34329; PLATELET MEMBRANE GLYCOPROTEIN V PRECURSOR). The predicted amino acid sequence disclosed herein for AS209_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AS209_1 protein demonstrated at least some

identity with sequences identified as D63875 (ORF [Homo sapiens]) and X53959 (slit protein [Drosophila melanogaster]). Based upon homology, AS209_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts four potential transmembrane domains within the AS209_1 protein sequence, centered around amino acids 32, 387, 449, and 538 of SEQ ID NO:12.

Clone "AX56_28"

A polynucleotide of the present invention has been identified as clone "AX56_28". AX56_28 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AX56_28 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AX56_28 protein").

The nucleotide sequence of AX56_28 as presently determined is reported in SEQ ID NO:13. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AX56_28 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AX56_28 should be approximately 4500 bp.

The nucleotide sequence disclosed herein for AX56_28 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AX56_28 demonstrated at least some homology with sequences identified as M20816 (Chicken cytotactin mRNA, partial cds, clone pEC803 [Gallus gallus]), N67571 (yz42a06.s1 Homo sapiens cDNA clone 285682 3'), and T19080 (e05023t Testis 1 Homo sapiens cDNA clone e05023 5' end). The predicted amino acid sequence disclosed herein for AX56_28 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AX56_28 protein demonstrated at least some identity with sequences identified as L12018 (putative protein [Caenorhabditis elegans]). Based upon homology, AX56_28 proteins and each homologous protein or peptide may share at least some activity. The

TopPredII computer program predicts a potential transmembrane domain within the AX56_28 protein sequence (SEQ ID NO:14).

Clone "AX92_3"

5 A polynucleotide of the present invention has been identified as clone "AX92_3". AX92_3 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AX92_3 is a full-length
10 clone, including the entire coding sequence of a secreted protein (also referred to herein as "AX92_3 protein").

The nucleotide sequence of AX92_3 as presently determined is reported in SEQ ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AX92_3 protein corresponding to the foregoing
15 nucleotide sequence is reported in SEQ ID NO:16. Amino acids 13 to 25 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 26, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AX92_3 should be approximately 1800 bp.

20 The nucleotide sequence disclosed herein for AX92_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AX92_3 demonstrated at least some homology with sequences identified as AA003356 (mg49g01.r1 Soares mouse embryo NbME13.5 14.5 Mus musculus cDNA clone 427152 5'), AA036247 (mi74a03.r1 Soares mouse p3NMF19.5 Mus musculus cDNA clone 472300 5'), F19608 (H.sapiens mitochondrial
25 EST sequence (009-X4-35) from skeletal muscle), M10546 (Human mitochondrial DNA, fragment M1, encoding transfer RNAs, cytochrome oxidase I, and 2 URFs [Mitochondrion Homo sapiens]), and U46493 (Cloning vector pFlp recombinase gene, complete cds). Based upon homology, AX92_3 proteins and each homologous protein or peptide may
30 share at least some activity. The TopPredII computer program predicts four potential transmembrane domains within the AX92_3 protein sequence, centered around amino

acids 20, 183, 269, and 295 of SEQ ID NO:16.

Clone "BF245_1"

5 A polynucleotide of the present invention has been identified as clone "BF245_1". BF245_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BF245_1 is a full-length clone, including the entire coding sequence of a secreted protein (also
10 referred to herein as "BF245_1 protein").

The nucleotide sequence of the 5' portion of BF245_1 as presently determined is reported in SEQ ID NO:17. An additional internal nucleotide sequence from BF245_1 as presently determined is reported in SEQ ID NO:18. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by
15 such internal sequence is reported in SEQ ID NO:19. Amino acids 18 to 30 of SEQ ID NO:19 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 31, or are a transmembrane domain. Additional nucleotide sequence from the 3' portion of BF245_1, including the polyA tail, is reported in SEQ ID NO:20.

20 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BF245_1 should be approximately 2300 bp.

The nucleotide sequence disclosed herein for BF245_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BF245_1 demonstrated at least some homology with
25 sequences identified as AA001743 (zh86h02.s1 Soares fetal liver spleen 1NFLS S1 Homo sapiens cDNA clone 428211 3' similar to SW YY02_HUMAN P42285 HYPOTHETICAL MYELOID CELL LINE PROTEIN 2), D29641 (Human mRNA for KIAA0052 gene, partial cds), Q92779 (Human thymopoietin continuous gene fragment), and R39256 (yc91h04.s1 Homo sapiens cDNA clone 23509 3'). The predicted amino acid sequence
30 disclosed herein for BF245_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted BF245_1 protein

demonstrated at least some identity with sequences identified as Z70271 (W08D2.7 [Caenorhabditis elegans]). Based upon homology, BF245_1 proteins and each homologous protein or peptide may share at least some activity.

5 Clone "BG33_7"

A polynucleotide of the present invention has been identified as clone "BG33_7". BG33_7 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BG33_7 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BG33_7 protein").

The nucleotide sequence of BG33_7 as presently determined is reported in SEQ ID NO:21. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BG33_7 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:22.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BG33_7 should be approximately 900 bp.

The nucleotide sequence disclosed herein for BG33_7 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BG33_7 demonstrated at least some homology with sequences identified as AA033818 (zf02c08.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 375758 3') and AA462657 (vg68e04.r1 Soares mouse NbMH Mus musculus cDNA clone 871134 5'). Based upon homology, BG33_7 proteins and each homologous protein or peptide may share at least some activity.

Fig. 2 is an autoradiograph evidencing expression in COS cells of clone BG33_7 of the present invention.

30 Clone "BM46_10"

A polynucleotide of the present invention has been identified as clone "BM46_10". BM46_10 was isolated from a human adult muscle cDNA library using

methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BM46_10 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BM46_10 protein").

The nucleotide sequence of BM46_10 as presently determined is reported in SEQ ID NO:23. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BM46_10 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:24.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BM46_10 should be approximately 3600 bp.

The nucleotide sequence disclosed herein for BM46_10 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BM46_10 demonstrated at least some homology with sequences identified as F19321 (H.sapiens EST sequence 008-X (391 nt)), N79027 (zb43c09.s1 Homo sapiens cDNA clone 306352 3'), U46493 (Cloning vector pFlp recombinase gene, complete cds), and W74198 (zd74d05.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 346377 3'). Based upon homology, BM46_10 proteins and each homologous protein or peptide may share at least some activity.

Clone "J317_1"

A polynucleotide of the present invention has been identified as clone "J317_1". J317_1 was isolated from a human peripheral blood mononuclear cells (treated with phytohemagglutinin and phorbol myristate acetate and mixed lymphocyte reaction) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. J317_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "J317_1 protein").

The nucleotide sequence of J317_1 as presently determined is reported in SEQ ID NO:25. What applicants presently believe to be the proper reading frame and the

predicted amino acid sequence of the J317_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:26. Amino acids 19 to 31 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 32, or are a transmembrane domain.

5 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone J317_1 should be approximately 1300 bp.

10 The nucleotide sequence disclosed herein for J317_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. J317_1 demonstrated at least some homology with sequences identified as N21491 (yx58f09.s1 Homo sapiens cDNA clone 265961 3'), R39024 (yd08h03.s1 Homo sapiens cDNA clone 25214 3'), T93953 (ye06h06.r1 Homo sapiens cDNA clone 116987 5' similar to contains HGR repetitive element), and Z25379 (H. sapiens partial cDNA sequence; clone C6F07; version 1; strand(+), single read). Based upon homology, J317_1 proteins and each homologous protein or peptide may share
15 at least some activity.

Clone "O289_1"

20 A polynucleotide of the present invention has been identified as clone "O289_1". O289_1 was isolated from a human adult blood (dendritic cells) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. O289_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "O289_1 protein").

25 The nucleotide sequence of O289_1 as presently determined is reported in SEQ ID NO:27. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the O289_1 protein, corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:28.

30 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone O289_1 should be approximately 700 bp.

 The nucleotide sequence disclosed herein for O289_1 was searched against the

GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. O289_1 demonstrated at least some homology with sequences identified as H59298 (yr04c07.r1 Homo sapiens cDNA clone 204300 5' similar to contains MER22 repetitive element). Based upon homology, O289_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts a large potential transmembrane domain within the O289_1 protein sequence, centered around amino acid 35 of SEQ ID NO:28. The nucleotide/amino acid sequence of O289_1 indicates that it may contain MER transposon repetitive elements.

Deposit of Clones

Clones AC41_1, AC222_1, AJ143_1, AJ168_4, AK684_1, AS209_1, AX92_3, BF245_1, BG33_7, J317_1 and O289_1, along with AX56_8 and BM46_3 (additional isolates of clones AX56_28 and BM46_10, respectively), were deposited on July 9, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the accession number ATCC 98101, from which each clone comprising a particular polynucleotide is obtainable. AX56_28 was deposited on September 26, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and was given the accession number ATCC 98180; BM46_10 was deposited on August 23, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and was given the accession number ATCC 98152. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b).

Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Fig. 1A or Fig. 1B, respectively. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* 19: 4485-4490); the pNOTs vector was derived from

pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* 9: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still
 5 be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

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

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
 15 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>
	AC41_1	SEQ ID NO:29
20	AC222_1	SEQ ID NO:30
	AJ143_1	SEQ ID NO:31
	AJ168_4	SEQ ID NO:32
	AK684_1	SEQ ID NO:33
	AS209_1	SEQ ID NO:34
25	AX56_28	SEQ ID NO:35
	AX92_3	SEQ ID NO:36
	BF245_1	SEQ ID NO:37
	BG33_7	SEQ ID NO:38
	BM46_10	SEQ ID NO:39
30	J317_1	SEQ ID NO:40
	O289_1	SEQ ID NO:41

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite) (Glen Research, cat. no. 10-1953)).

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;
- (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 $\gamma\text{-}^{32}\text{P}$ 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 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 4×10^6 dpm/pmol.

The bacterial culture containing the pool of full-length clones should preferably be thawed and $100\ \mu\text{l}$ of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at $100\ \mu\text{g/ml}$. 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 bacteriological media containing L-broth containing ampicillin at $100\ \mu\text{g/ml}$ 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 μ g/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 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 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 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 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 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.

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.

5 The present invention also provides genes corresponding to the cDNA sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which the cDNA sequences are derived and any contiguous regions of the genome necessary for the regulated expression of such genes, including but not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. 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
10 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
15 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.

20 Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by
25 comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any
30 of the disclosed proteins.

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.

5 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 .

10 The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

 The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent
15 conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

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Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) [‡]	Hybridization Temperature and Buffer [†]	Wash Temperature and Buffer [†]
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	< 50	T _B *; 1xSSC	T _B *; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	< 50	T _D *; 1xSSC	T _D *; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	< 50	T _F *; 1xSSC	T _F *; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	< 50	T _H *; 4xSSC	T _H *; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	< 50	T _J *; 4xSSC	T _J *; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	< 50	T _L *; 2xSSC	T _L *; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	< 50	T _N *; 6xSSC	T _N *; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	< 50	T _P *; 6xSSC	T _P *; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	< 50	T _R *; 4xSSC	T _R *; 4xSSC

[‡]: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

[†]: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6(log₁₀[Na⁺]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na⁺] is the concentration of sodium ions in the hybridization buffer ([Na⁺] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

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.

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 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.

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, 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 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 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 purified by using a specific antibody directed to such epitope.

5 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 all of the foregoing purification steps, in various combinations, can

10 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 animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which

15 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 known to those skilled in the art. The synthetically-constructed protein sequences, by

20 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 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 of interest in the protein sequences may include the alteration,

25 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

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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.

5 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.

10 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 - 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.

25 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: 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. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai

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et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

5 A protein of the present invention may also exhibit immune stimulating or immune 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
10 deficiencies may 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
15 such as candidiasis. Of course, 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
20 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
25 respiratory problems. Other 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 modulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking
30 an immune response already in progress or may involve preventing the induction of an immune 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 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 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 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 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.

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 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 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 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 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).

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.

5 Alternatively, anti-viral immune responses may be enhanced in an infected patient 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 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*.

15 In another application, up regulation or enhancement of antigen function (preferably 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, 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 for transfection *in vivo*.

25 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 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

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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 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 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 3.1-3.19; 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 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 (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.

5 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.

15 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., 20 *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, 25 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.

30 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

5 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
10 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
15 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 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
20 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 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
25 or genetically manipulated for gene therapy.

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

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

30 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., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

5 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 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, 10 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; 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 15 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.

20 Tissue Growth Activity

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.

25 A protein of the present invention, which induces cartilage and/or bone growth in 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. 30 *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma 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 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 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 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 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).

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).

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, 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 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.

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

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 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 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.

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 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 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 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:

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.

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 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. 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 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

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 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, 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.

Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

5 The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

10 E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

20 Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

30 Additionally, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to generate

antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

Tumor Inhibition Activity

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 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.

Other Activities

A protein of the invention may also exhibit one or more of the following

5 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
10 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
15 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
20 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.

ADMINISTRATION AND DOSING

25 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
30 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 compliment 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 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 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 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 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 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
5 limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. 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.

10 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 amelioration of such conditions. When applied to an individual
15 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
20 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,
25 lymphokines or 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
30 cytokine(s), lymphokine(s), other hematopoietic 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.

5 Intravenous 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
10 such as a gelatin or an 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
15 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.

20 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
25 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
30 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 μg to about 100 mg (preferably about 0.1 ng to about 10 mg, more preferably about 0.1 μg 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 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 (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 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 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. 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 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.

5 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.

10 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
15 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
20 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
25 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.

30 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
5 may vary with the type of 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
10 determinations and tetracycline labeling.

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,
15 without limitation, in the form of viral vectors or naked DNA).

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.

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

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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Spaulding, Vikki
Bowman, Michael
Agostino, Michael J.

(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES
ENCODING THEM

(iii) NUMBER OF SEQUENCES: 41

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(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Sprunger, Suzanne A.
(B) REGISTRATION NUMBER: 41,323

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(A) TELEPHONE: (617) 498-8284
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1032 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

WO 99/20644

PCT/US98/22034

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

CTTCGTTCAA GTGTGAGCTG CGGCTGAGCC CAGCGCTCGA GGCGCGAGGC AGCCAGGAGG	60
GCCCGTGCGG CGCGGGGAGC CAGCGAGCGC GCCTTCGGCA TTGGCCGCCG CGATGTCAGC	120
TCAGTGCTGT GCGGGCCACC TGGCCTGCTG CTGTGGGTCT GCAGGCTGCT CTCTCTGCTG	180
TGATTGCTGC CCCAGGATTC GGCAGTCCCT CAGCACCCGC TTCATGTACG CCCTCTACTT	240
CATTCTGGTC GTCGTCCTCT GCTGCATCAT GATGTCAACA ACCGTGGCTC ACAAGATGAA	300
AGAGCACATT CCTTTTTTTG AAGATATGTG TAAAGGCATT AAAGCTGGTG ACACCTGTGA	360
GAAGCTGGTG GGATATTCTG CCGTGTATAG AGTCTGTTTT GGAATGGCTT GTTTCTTCTT	420
TATCTTCTGT CTA CTGACCT TGAAAATCAA CAACAGCAAA AGTTGTAGAG CTCATATTCA	480
CAATGGCTTT TGGTTCTTTA AACTTCTGCT GTTGGGGGCC ATGTGCTCAG GAGCTTTCTT	540
CATTCCAGAT CAGGACACCT TTCTGAACGC CTGGCGCTAT GTGGGAGCCG TCGGAGGCTT	600
CCTCTTCATT GGCATCCAGT CCTCCTGCTC GTGGAGTTTG CACATAAGTG GAACAAGAAC	660
TGGTGTGTGC CTTTATGGAA AGCTTCCCAT TGA CTACAG AACTGCCCA GTTTTGACCA	720
AGGCTGTACT CAACTGCATT GCTAGGGATT TGCAGTTTTG TTTCCCTTTA TACCTGCTTT	780
TTTGTACCTC TTCATATACT CCTCTCCTTC ATTCACTTCT CACTTTTTGA CCCCCTGCCC	840
CTACTCCCTT GCTTGGGCTC TGAGTCAACC AGTGGTGTGA ATTAGCCACA CTCAATCCCC	900
TGCTCGTACG GGTCTCGATC TCCTGACCTC GTGATCCGCC CACCTCGGCC TCCCAAAGTG	960
CTGGGATTAC AGGCTCGAGC CACCGCACCT GGCCTGATGD TTCTGCAAAA AAAAAAAAAA	1020
AAAAAAAAAA AA	1032

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 210 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

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

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1626 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

AGGGCCAGGT TTTCCGGGCC NTCACATTGC CAAAAGACGG CAATATGGTG GGAAATAACA	60
TATAGACAAA CGCACACCGG CCTTATTCCA AGCGGNTTCG GCCAGTAACG TTAGAATTGC	120
GGCCGCAGGT YTAGGTCAGA GCCAAAGGAA AGCTTGAAAA ATGAAGACAT TAGCAGGACT	180
TGTTCTGGGA CTTGTCATCT TTGATGCTGC TGTGACTGCC CCAACTCTAG AGTCCATCAA	240
CTATGACTCA GAAACCTATG ATGCCACCTT AGAAGACCTG GATAATTTGT ACAACTATGA	300
AAACATACCT GTTGATAAAG TTGAGATTGA AATAGCCACA GTGATGCCTT CAGGGAACAG	360
AGAGCTCCTC ACTCCACCCC CACAGCCTGA GAAGGCCCAG GAAGAGGAAG AGGAGGAGGA	420
ATCTACTCCC AGGCTGATTG ATGGCTCTTC TCCCCAGGAG CCTGAATTCA CAGGGGTTCT	480
GGGGCCACAC ACAAATGAAG ACTTTCCAAC CTGTCTTTTG TGTACTTGTA TAAGTACCAC	540
CGTGTACTGT GATGACCATG AACTTGATGC TATTCCTCCG CTGCCAAAGA ACACCGCTTA	600
TTTCTATTCC CGCTTTAACA GAATTAAAAA GATCAACAAA AATGACTTTG CAAGCCTAAG	660
TGATTTAAAA AGGATTGATC TGACATCAAA TTTAATATCT GAGATTGATG AAGATGCATT	720
CCGAAAACTG CCTCAACTTC GAGAGCTTGT CCTGCGTGAC AACAAAATAA GGCAGCTCCC	780
AGAATTGCCA ACCACTTTGA CATTTATTGA TATTAGCAAC AATAGACTTG GAAGGAAAGG	840
GATAAAGCAA GAAGCATTTA AAGACATGTA TGATCTCCAT CATCTGTACC TCACTGATAA	900
CAACTTGGAC CACATCCCTC TGCCACTCCC AGAAAATCTA CGAGCCCTTC ACCTCCAGAA	960
TAACAACATT CTGGAAATGC ACGAAGATAC GTTCTGCAAT GTTAAAAATT TGACTTATAT	1020
TCGTAAGGCA CTAGAGGACA TTCGATTGGA TGGAAACCCT ATTAATCTCA GCAAAACTCC	1080
TCAAGCATAc ATGTGTCTAC CTCGTCTGCC TGTGAGGAGC CTTGTCTAAT TTCAGATAAT	1140
GGTTAGCATT ACGATGGCTA CTATAAATAA ACCATTCTTA CTGCTCTCTT CCAAAACAAA	1200
ACTCAGCATG ATACTTTGAG ATTGTGTTCT GAGAGATGAT ATGACTACAT AAAATACAAT	1260
TAAAAATGTT ATAATATAAT GAAAATGTAG TAATTTAAGA AAACACCAGA TGAGTTAGGA	1320
ATAAACCTAT AACATTTACA AAAAGAGCAA AAYTAAGTGA TAGAAAATAT TTCACACATG	1380
TTCTTATAGA TCATGTATCA CTTGCAAGTT TTAGGAGTTC ATATCCTATA TCATTTCAA	1440
TTAAGTACAT AATAAAGTAA AATTTTGAAA TGAACACTTT AGGTATTTTT GCCAAGATTT	1500

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AGATGTTTTT AATTAACTT TTYTCTTCCT TTTTTTTTCA CTAAAGCATG TTTATTCCCC 1560
 TAATCCATTA AAGAGCATGA AAAAAAGAAT AAATGTATTT GAAAATTAAA AAAAAAAAAA 1620
 AAAAAA 1626

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 322 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

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

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ACCCCAGCYT TCCGGCCACC ACAACAAAGA GCCGCWCCGA CCGGCGAGGA TWAACAGCGG      420
CGGAGGGCGA KAGGGCGGCG GGGCGAGCGC CTCCACGCAG CAACTCCGGA GTCCCCCGCT      480
TGCCCGAGCG CAGTTTCTCC GCTGCTGTTT CCACCGGCTT TGTAACACTG GGAATTTACA      540
TCCTCACCCG CACCCCTCAC GCCCGAGGAT TTTAAACTCA CCTTTACTCT CGAACTGAGA      600
GTTGCGGTAG ATGGGATTTT TGCCTTTTCC CCAGATGGTT GAAGGTTAAG ATTTTGGAA      660
ACCCCMCCAC CTCCTTATTT CTATTATTAT TTCTGCAAGA AAAGTATAAA GAGAGTTGTA      720
GTGGAGGTGA GATTTGTGAT CGGGAAAGCC TTCGACTCCC TCCTTCTCCG TCTTCCGCTT      780
CTCTCTCTCT GATTAGTTCC TATCCAGCAG CAGATTGAAG CAGGAGATGA TTCTTCTCAA      840
GGTTTGTTC A GCAGCTTCAC TTCTAGGCGA AGGCTTCATG AACCAAGTGA CGTCAACCAA      900
CAAGGCTTCT CTCTCTCTCC TCTCTCTAAC AATGAAAGTT GCTGTTAACA AGGGAAAAAA      960
AGAGAGAGAA TTGTTTATAC CATTTAGTT CCAATAATAA AKGACCTATC AGYTCCTAAA     1020
GGAGCCAAAA AANANAAANA AAAAAAAAAA AANAAGANAA GNNNNNAAAA AAANAAAAAA     1080
AAA                                                                 1083

```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 56 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

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

```

(2) INFORMATION FOR SEQ ID NO:7:

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(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 643 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

```

GAAAGAGGAG CTGGGCGGGG TGGGGGGAAG GCGGAGGCAG TYTAGTAATG TAAAGCTCCG      60
CTGAGAGGGA GAGTGCCGCC CTAAACACTC ATGCTGCCAG TCCCCAAAAG ACTTCATTCA      120
TTCAACATAT ATGTGACCGC CTGCTACGTG CCAGGCGTGG GCCAGGTCCT AGGGACAAAG      180
GAGAGGCCTC CGCACCCAC CCCATGACCC ATACCTCCTC TTCCCCACCT CCCTGGGCCA      240
GCCTGCCTTC CTTCTCCCTC CTCCTCCTTC CTGGGGGAAG GAAGCCCCAC CTTCTGTGCG      300
CAGTCAGCTC CTAAGCACGC TCCCGCTTCC CCTGGCCTCC CCATTTAAAA AGGGAGGCAA      360
AGGATGTCAC CACTGTCACT AACTCATGG CTTTGCTCTG GGAAGTCCTG CAAATAAAAT      420
GAAAGTTCTC CAACCCCTCC MTACCCAYTC GGGCCACAAA GGCGAGGGGA GGCAGGTYTG      480
AGGCAGAGGA GCCAGGGCAG GTGCGGCGCT TCCGCTCTG GTCCCAAAGC AAAGAKTCCC      540
CCTGTGACTG ACAGCCCGTG TTATGTTAAA TACATTTTGT TGGTTTGTA TCAAAATCCC      600
ATAAAGCAGG AGGTAGAGAG CCAAAAAAAAA AAAAAAAAAA AAA                        643

```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

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

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Pro Pro His Pro Thr Pro
35

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1047 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

```

AGGCGATGCC CCATAAAAGG GCTCCTGAAG CTCTTTGTGA AGGGGTCTGA AAAGGGCAGA      60
TGAGGGTGTC CTTTGGGGCG GATGTGGGGT TTGGGACAAT TGCATGTGAT TGTCATTCTT      120
TAGCTGTCTG CATCCACAG AAACTTTTTT CTGAGTCTTC CAGCTGGCCC AAGTCCTGGG      180
TCTCTTTTAC TGTTCCTGTA GCTGACTACA GTAGGCAGAT GAGGAACTCT TAGTCAATCT      240
GGGAAACTC GACTGACTAT AAACAATCCT AAATTGAAAG AAGTGTATGG CATTGGGGGG      300
TGGGTGTGAT AGTACAGAGT GGAGCCTGCA AGTTCACGCA CCGGGAACCA AACCCACCT      360
AACTTGACT GGACGTCCTC TTCCAGGGAA TCCAGCCAGG GCCAATTAGA AATGTGTCTT      420
AAATTGGTGT CAGGTCACCA AAAACAAAAA CAGGATCCAT GGGGGCCTGT GAAACTTCGA      480
GTGCCATTCA TGCTCGGTTC AGTCATCTGA CTCGTCAGGA TGACCAGCAG TGCTCCCTGT      540
AACTCGCCAT TATCTGACCA ATTACTGGAG CTACTTTATA ATGAGGCTTC TGGAGCTACT      600
TTATAATGAG GCTTCTGTTT GCTGTCATGG TGGGGAGTTT GGAATTGTGG CTTCTTGCTT      660
AACACCAATG AGAGGACTTT GGGACAAACC CCCAGAGCCA GGAGTGTTTT GAGGCCTAGT      720
GGGGTTGGGA ACAAAGGGTC AAGTGTCGAG GGAGTGGGGA AATTATGGGT TGGGGACAGG      780
TGTGAACAGT GGGCTTGGGG GTGGCCCAAG AGTACTAGAC CAGAGAGGTC CAGTGCCACC      840
CGCAGCCTGC AGTGATACTA GACAGGGGGC GGCTGTGTGG AACCACAGAT GACATCCCTT      900
CTCCTCTTGA TGGAAGTGGA GGCTGCATCT GAGAGCTTCC CAGCCTAGAT TCTGGTGGCT      960
GCATCTGAGA GCTTCCCAGC CTAGATTCTG GTGGGATTGG ATCTGGGAGG GGAAGACCC     1020
CAAAAAGCAA AAAAAAAAAA AAAAAAA                                1047

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(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

Met Arg Val Ser Phe Gly Ala Asp Val Gly Phe Gly Thr Ile Ala Cys
1              5              10              15

Asp Cys His Ser Leu Ala Val Cys Ile Pro Gln Lys Leu Phe Ser Glu
                20              25              30

Ser Ser Ser Trp Pro Lys Ser Trp Val Ser Phe Thr Val Leu Val Ala
          35              40              45

Asp Tyr Ser Arg Gln Met Arg Asn Ser
      50              55

```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2851 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

```

ATTTCGTACA GTAGGAGATT TCAACAACGT GACAATATTC TCTAGGCACT TGGGCTCACT      60
GTCTGTAGCC CCCACCCCCC GCCTTTCGCC ACCTCCTTGC TTCCCTACTC CCCCTTCTGC      120
TTTTCGCTTT GATGAGTTTT TGGCTTACTT TTTGGCGGAG TCTCTTGGAC ACGTTTTTGC      180
TGGTGCTGGA AGATCAGATA CATGGAACCT TTGAAACTG ATTATTTTTC TCCGATATGA      240
CTTAAAAAAA AATAAAAAGA AGAAAAGAAA ATAGAGTAGT GCACGGCAAG CTAGAGGATT      300
GTAAATTTTC CTTGGTGAAC TTTGAGGATC CATAAAGAAG AAATGGTTCT CTTTACTGCG      360
AGGCTGCAAG GTCACCCAAT GAGAGAGGGG CCAAATAAGC TGGAACATCA TCTAATACAC      420
TGAATGTAGC CACTCTGTGT CTTTGTATTG GAGAGTTTAG TCCATTTACA TTCAATGCTA      480

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TAATTGGAGT TACTGGAAAA GCAAGAATAA CTTATGCGGA TTAACAATAT GGAAACATCC	540
TGAGACTACT TTGGAATCGC CATAAATTAA GTGGGTTCCA GTTTTGCAAA CAGAGAAACG	600
GTCCATGAAC AATTTGCTAC AGGTATAAAG AAGTATCTGC AGAAATCCAG AGCACTTATT	660
AAACTTCTTT GAGTTTTCTC AGGAAGATCA ATACAAGATG GAGAAATTTT ATTAAGATTG	720
GCAAACGCAC TGCCTACTTA CAGCATAGAG ACCCCCAGTG GAGAGCTAGA CTGTTTGAAT	780
TCCAGAAGGA CCAACACCAG ATAAATTATG AATGTTGAAC AAGATGACCT TACATCCACA	840
GCAGATAATG ATAGGTCCTA GGTTTAACAG GGCCCTATTT GACCCCCTGC TTGTGGTGCT	900
GCTGGCTCTT CAACTTCTTG TGGTGGCTGG TCTGGTGCGG GCTCAGACCT GCCCTTCTGT	960
GTGCTCCTGC AGCAACCAGT TCAGCAAGGT GATTGTGTGTT CGGAAAAACC TCGGTGAGGT	1020
TCCGGATGGC ATCTCCACCA ACACACGGCT GCTGAACCTC CATGAGAACC AAATCCAGAT	1080
CATCAAAGTG AACAGCTTCA AGCACTTGAG ACACTTGGA ATCCTACAGT TGAGTAGGAA	1140
CCATATCAGA ACCATTGAAA TTGGGGCTTT CAATGGTCTG GCGAACCTCA ACACTCTGGA	1200
ACTCTTTGAC AATCGTCTTA CTACCATCCC GAATGGAGCT TTTGTATACT TGTCTAAACT	1260
GAAGGAGCTC TGGTTGCGAA ACAACCCCAT TGAAAGCATC CCTTCTTATG CTTTTAACAG	1320
AATTCCTTCT TTGCGCCGAC TAGACTTAGG GGAATTGAAA AGACTTTCAT ACATCTCAGA	1380
AGGTGCCTTT GAAGGTCTGT CCAACTTGAG GTATTTGAAC CTTGCCATGT GCAACCTTCG	1440
GGAAATCCCT AACCTCACAC CGCTCATAAA ACTAGATGAG CTGGATCTTT CTGGGAATCA	1500
TTTATCTGCC ATCAGGCCTG GCTCTTTCCA GGGTTTGATG CACCTTCAAA AACTGTGGAT	1560
GATACAGTCC CAGATTCAAG TGATTGAACG GAATGCCTTT GACAACCTTC AGTCACTAGT	1620
GGAGATCAAC CTGGCACACA ATAATCTAAC ATTACTGCCT CATGACCTCT TCACTCCCTT	1680
GCATCATCTA GAGCGGATAC ATTTACATCA CAACCCTTGG AACTGTAACT GTGACATACT	1740
GTGGCTCAGC TGGTGGATAA AAGACATGGC CCCCTCGAAC ACAGCTTGTT GTGCCCGGTG	1800
TAACACTCCT CCCAATCTAA AGGGGAGGTA CATTGGAGAG CTCGACCAGA ATTACTTCAC	1860
ATGCTATGCT CCGGTGATTG TGGAGCCCCC TGCAGACCTC AATGTCACTG AAGGCATGGC	1920
AGCTGAGCTG AAATGTCGGG CCTCCACATC CCTGACATCT GTATCTTGGA TTA CTCCAAA	1980
TGGAACAGTC ATGACACATG GGGCGTACAA AGTGCGGATA GCTGTGCTCA GTGATGGTAC	2040
GTTAAATTTT ACAAATGTAA CTGTGCAAGA TACAGGCATG TACACATGTA TGGTGAGTAA	2100
TTCCGTTGGG AATACTACTG CTTAGCCAC CCTGAATGTT ACTGCAGCAA CCACTACTCC	2160

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TTTCTCTTAC TTTTCAACCG TCACAGTAGA GACTATGGAA CCGTCTCAGG ATGAGGCACG      2220
GACCACAGAT AACAATGTGG GTCCCACTCC AGTGGTCGAC TGGGAGACCA CCAATGTGAC      2280
CACCTCTCTC ACACCACAGA GCACAAGGTC GACAGAGAAA ACCTTCACCA TCCCAGTGAC      2340
TGATATAAAC AGTGGGATCC CAGGAATTGA TGAGGTCATG AAGACTACCA AAATCATCAT      2400
TGGGTGTTTT GTGGCCATCA CACTCATGGC TGCAGTGATG CTGGTCATTT TCTACAAGAT      2460
GAGGAAGCAG CACCATCGGC AAAACCATCA CGCCCCAACA AGGACTGTTG AAATTATTAA      2520
TGTGGATGAT GAGATTACGG GAGACACACC CATGGAAAGC CACCTGCCCCA TGCCTGCTAT      2580
CGAGCATGAG CACCTAAATC ACTATAACTC ATACAAATCT CCCTTCAACC ACACAACAAC      2640
AGTTAACACA ATAAATTCAA TACACAGTTC AGTGCATGAA CCGTTATTGA TCCGAATGAA      2700
CTCTAAAGAC AATGTACAAG AGACTCAAAT CTAAAACATT TACAGAGTTA CAAAAACAA      2760
ACAATCAAAA AAAAAGACAG TTTATTAAAA ATGACACAAA TGACTGGGCT AAATCTACTG      2820
TTTCAAAAAA GTGTCTTTAC AAAAAAAAAA A                                  2851

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(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 640 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

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

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

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Ser	Trp	Ile	Thr	Pro	Asn	Gly	Thr	Val	Met	Thr	His	Gly	Ala	Tyr	Lys	385	390	395	400
Val	Arg	Ile	Ala	Val	Leu	Ser	Asp	Gly	Thr	Leu	Asn	Phe	Thr	Asn	Val	405	410	415	
Thr	Val	Gln	Asp	Thr	Gly	Met	Tyr	Thr	Cys	Met	Val	Ser	Asn	Ser	Val	420	425	430	
Gly	Asn	Thr	Thr	Ala	Ser	Ala	Thr	Leu	Asn	Val	Thr	Ala	Ala	Thr	Thr	435	440	445	
Thr	Pro	Phe	Ser	Tyr	Phe	Ser	Thr	Val	Thr	Val	Glu	Thr	Met	Glu	Pro	450	455	460	
Ser	Gln	Asp	Glu	Ala	Arg	Thr	Thr	Asp	Asn	Asn	Val	Gly	Pro	Thr	Pro	465	470	475	480
Val	Val	Asp	Trp	Glu	Thr	Thr	Asn	Val	Thr	Thr	Ser	Leu	Thr	Pro	Gln	485	490	495	
Ser	Thr	Arg	Ser	Thr	Glu	Lys	Thr	Phe	Thr	Ile	Pro	Val	Thr	Asp	Ile	500	505	510	
Asn	Ser	Gly	Ile	Pro	Gly	Ile	Asp	Glu	Val	Met	Lys	Thr	Thr	Lys	Ile	515	520	525	
Ile	Ile	Gly	Cys	Phe	Val	Ala	Ile	Thr	Leu	Met	Ala	Ala	Val	Met	Leu	530	535	540	
Val	Ile	Phe	Tyr	Lys	Met	Arg	Lys	Gln	His	His	Arg	Gln	Asn	His	His	545	550	555	560
Ala	Pro	Thr	Arg	Thr	Val	Glu	Ile	Ile	Asn	Val	Asp	Asp	Glu	Ile	Thr	565	570	575	
Gly	Asp	Thr	Pro	Met	Glu	Ser	His	Leu	Pro	Met	Pro	Ala	Ile	Glu	His	580	585	590	
Glu	His	Leu	Asn	His	Tyr	Asn	Ser	Tyr	Lys	Ser	Pro	Phe	Asn	His	Thr	595	600	605	
Thr	Thr	Val	Asn	Thr	Ile	Asn	Ser	Ile	His	Ser	Ser	Val	His	Glu	Pro	610	615	620	
Leu	Leu	Ile	Arg	Met	Asn	Ser	Lys	Asp	Asn	Val	Gln	Glu	Thr	Gln	Ile	625	630	635	640

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4531 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

TTGCTCTTCA ACTTTCTTTT GAGGCTTTAA ATTAGGCAAA TATATTTTTC TTAGAATTTT	60
TGAAAACTCC TTTTCACTGG AGCTTATTTT AATTATATGG ATGCATTATC CTCTTAAACT	120
TCTGTGAAAA CAATAATTGG AGTTTTCAAT TGCATTGGCT GTTTCATGAG AGGTCAAGCT	180
TTTTGCTTAT TTATTTTGAT GTTTCCTTTT CATGATATCT GTGTCTTGGG ATTTGGTTGT	240
ATATTCACAT TTTTAATTAG CTACTTGATT TAAATAAAGT ATCAGTAGTT ACTTTCAGGG	300
TTCTTGGTGA TTATAATAAT TACTCACCTA CCAGGCTTCT TCCTTGCATG CAGCTCACTA	360
CAGGAATCTG TTGTGCCTAG AAGATTTCTG GACAAGTGGA GAAACCCAC TCCGTAACT	420
GCATACACAG GGAAGGAGCT ATGAGGGAGA CAGAATAATT TGGTCTCTAC TATTACCTTA	480
AGAGACCTTC CCCTGTCTTC GATTTAAAAA AAAACTACTG CATACAAAGG GTAGGAGCTA	540
CAAGGGACAT AGAATAATTT GGACTCCATT ACTACCTTAA GAGACCTTCC CCTGACTTCT	600
CTTTTAAAAA ACCTATGAGT CTCTGTACCC CTGAACTTAC TTTCCACACC TATTTCTCTC	660
TTCACCCCCA AAATCCATAT TAGAATGCCC CTGCAGGCTA TAAAGCCTTT CATAAAAGTA	720
AAATACCCAG TCTTTTCAAG AGACAATAA AATAGGCAGT CTCCTACCTC TTGTCTTACT	780
CTAATATAAA CTCCATGAAG ATAAGTATTG TATCCATACT GTTCATGCTG CACAGCAGTT	840
GCCCTTATCT GCAGGGCGAC GCATCCCAAG ACCCCCAGTG GATGCTTGAA ACTGCAGAGA	900
GTAACACACG TGATTGCCAC CATCGGAACA CATTTCTGTT CACGTCTTCC ACCCACAGAT	960
TTAATGCCTT TTCCATCTTA ACTAAGCACT CATCATGGAC TGTGGCCATA ACTTTTGCAG	1020
TTTTAGATGC AACAGCAAAA CTAACATTAA TTTTTTCTTC TTCTTCACAA TTTCATGGGT	1080
AGATTTGTTT TTACCGTAGA TCTTAGCAAC CTCAGCATAT GATGTTTTTT CTTTGTAGAA	1140
CTTTCACCTT TTCTCTTAAA GAAATCACTT TACAGCTTCT CTTTGGCATA TCTCAACTGC	1200
CAGCATCACT GCTCTTGAAC TTTGGGGCCA TTATTAAGTC AAAAGAGGGT TACTTCAAAA	1260
CAAGCACTGA GATACCACCA GAGTCCATCT GATAACTAAG ATGGTAACTA CATGACTAAC	1320
AGGCCGGTGA CGTATAAAGC ATGGATATGC TGGACAAAGG GGTGAGTCAT ATCCCAGGTA	1380

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GGATGAAGCA GGGTGACTTG AGATTTCACT ATTCAGTATG GTGCACAATT TAAAACTTAG	1440
GAATTGTTTA TTTCTTGGA CTTTTCGTTT AATGTTTTTG GACTGCAGTT AGCCACAGGT	1500
AACTGAAACT GTGGAAAGTG AGGATTGGAG GATAAGCAGA GACTGTGGTA TTCATTTCAT	1560
TGCACAGTGC CTAAAATACA GTAGGTGTAC TATAAATATT TTGTAAAGGG ACAACTTTTC	1620
TGAAACTAAA AATATTTATG TTTTACCCAA TAATTTTTCT TCTGGAAATT TATGCTAAGG	1680
AAATATTCAG AGATGCTTAC AAAGTTTTAT GCATGAGTGT CCATGTTATT TGTAATTGTG	1740
AAAAATGAAA ATAAC TCAA AGTTTAACAG TGGTCATCTA AAGTATTGTA TACACTGTAT	1800
ATATAGGTTG AATAGAAGGT CATCCTATTC ATTTATTAAT GAGAGGTACA ATCTCTAGGG	1860
ATCTGTAAAA TCTATTTTGT CTTAACCCAA GAACAAATTT TTGACATATC TTGAATAGGA	1920
TGACTATAAA TTATGACTTT TAAATTGTTG TAATTTTTGT ACTATTATCT GATATTTTTA	1980
TTTTTATGTA TTTTCGTAAG TAGTTTAGAG ATAGTCACAT TTAAAAATC TAAGATCAAG	2040
CAAATGAAGC TTATTTTTAT GTATTCATAG TATAAAGAC CTTCAGTAAA TAGGTAATAT	2100
TTTTGTTTTA TTCTAGAAAA CAGCTCCTTG AACACAGTGA GCTGGCTTTT CACACATTGC	2160
AGTTGTTAGT GTTTACTGCC CTTGCCATTT TAATTATGAG GCTAAAGATG TTTTGTACAC	2220
CGCACATGTG TGTATGGCT TCCTTGATAT GCTCTCGACA GCTCTTTGGC TGGCTTTTTC	2280
GCAGAGTTCG TTTTGAGAAG GTTATCTTTG GCATTTTAAC AGTGATGTCA ATACAAGGTT	2340
ATGCAAACCT CCGTAATCAA TGGAGCATAA TAGGAGAATT TAATAATTG CCTCAGGAAG	2400
AACTTTTACA GTGGATCAAA TACAGTACCA CATCAGATGC TGTCTTTGCA GGTGCCATGC	2460
CTACAATGGC AAGCATCAAG CTGTCTACAC TTCATCCCAT TGTGAATCAT CCACATTACG	2520
AAGATGCAGA CTTGAGGGCT CGGACAAAAA TAGTTTATTC TACATATAGT CGAAAATCTG	2580
CCAAAGAAGT AAGAGATAAA TTGTTGGAGT TACATGTGAA TTATTATGTT TTAGAAGAGG	2640
CATGGTGTGT TGTGAGAACT AAGTTTATAC TTCAAGATGG ACAAGAAGTT CTATCAGCTG	2700
CTGAGAAATG ATGCCAGATG GTAAC TCAGA TATACAAGAA ATACTCAAAT GCGCTGGAAA	2760
TGGCCTGGTT GCAGTATGCT TGAAATCTGG GATGTGGAAG ACCCTTCCAA TGCAGCTAAC	2820
CCTCCCTTAT GTAGCGTCCT GCTCGAAGAC GCCAGGCCTT ACTTCACCAC AGTATTTTCA	2880
AATAGTGTGT ACAGAGTATT GAAGGTTAAC TGAGAAGGAT ACTACCCATT TTACTATGGC	2940
ACAATGCCGT GTGTCAAAAA CAATCACCCCT TTGGCTTATT CACATTAATA AAAATCACAA	3000
GCTTTAATAA CAGACACTTA AAAATAAGAT AAAAATGGAT TGGAAATTTT TCTGATTACT	3060

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AAAAGGTAAA TTACTTTTCT GTTCATTGAA TGTCAGCCTT ATTAAGCTTG TCATATAAGT 3120
TATTAAATCA TTCATGTCAT ACTGCATAAA CAAATGTTCA TTTCAGAATT TTAAAGAGAA 3180
ATGTATATAA AAGAACAATG AATTTTAATA AATCAGGGGT ATGTAAGTCC TTTTTCATCC 3240
AACTAGGTGA ATTGCTTCAG ATTTTCTCTA GTACCAGAGG GTACCTCCTC AAACCTCTTG 3300
AACCACCTTA GGCAGAAGAA TGCAAGCTCT GAAATGACAT CCTTAAAATG CTGATACTGG 3360
TCACAGCCTC TTTACCTCTG TGAGGAAATT GTAACAGTGT GTCTTTTAAG GTGTTTTTAT 3420
TTTACCAGCC CTTAAGAAAG ATCTTTAATA CCTTTTAATA CTTTTTTTAA ATAATTTCAA 3480
GTTGAAGTGT TTTTAAAAAC ACTTTGTTTT GTAATGTTTT GAATCTCTTG AGATGTGTTT 3540
ACCCCACTAG ATACATATTT GCCACTGGTT AGTTCTCCAT CTAAGCTCAA GAGGTTATTC 3600
ATCTCTCTTT AGATTCCAGT GGTTTTTCTT TTAACATCCA GGTAAGATAG AAACCTGCTAT 3660
GGTATACAAC CAAGTTTTGG GGTAAACAT AATCAGAAAA GAAATCCAG TTAAATTTAT 3720
GAAGTGAGAT TTTCAGATCC TAGATCTTGA ATAAAGGAAA GGTCTTTTCA TCTTGATGGC 3780
CCCAAAGCTT GTTGATCATG GTCTTTATTT CTGGCCACTA TCTTCTTAAA TAATATATTT 3840
TTAAGCCCTC ATTTATTTTT GGTTTTGGGT GAGGAAAGTC ATGTTTTCTA AGTCCTCTCC 3900
CCTAATAAAA CCTACCCAAC AATAGTGCTT TGAAAAGTGG TAGTTATCTT GAAGATACTC 3960
TTGCCAAATG CAAAGATAAA CATTCTTTTT GTCTGCTTTA TAAATATGAA ATATGCCAGA 4020
TCTGTAGTAT TTTAATGTGC ATCTACTTTA AATGAGTCAT CTTGGGGTTT TTATAATTCC 4080
CTTATGTTCT CGCCCCTCTA CACTTGAAAT AACAAAATGC CTTAATTTTA TGGATTAGTT 4140
CTCTTATAGT AGACAGGCAG CTATATGCAG CAAAACCAAT AAAGTTATTT TTCAACTTTC 4200
ATAGTTGTAA AATATTTTAT AACAGAATAC AAAACAGCTA AGAAAACATG CCACATTTTA 4260
TTTTAGCATT TTCAAATAAT TTGTTTTTGG TGTAAGCACA GGATAAAAAA GGAGAGCGTC 4320
AAAGAAAAGA GACATAACAC CTAACATTCA TAAAAATTAA CAAAGTATAT TTTGGATGAT 4380
GTTTTTACAG GAAATATTTT AAATAAGTTG GTAGAACTTT TAAATGGTA CTGTATTAGC 4440
TAATAAAATA TTCAGTACAA ATATATGTTT GGATTTATGC ATTAAAAAAC TAATAAAATT 4500
ATTTCCAAC TTAACAAAAA AAAAAAAAAA A 4531

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(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 171 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

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

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1502 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

GTCGACGGGA ACGTAGAACT CTCCAACAAT AAATACATTT GATAAGAAAG ATGGCTTTAA	60
AAGTGCTACT AGAACAAGAG AAAACGTTTT TCACTCTTTT AGTATTACTA GGCTATTTGT	120
CATGTAAAGT GACTTGTGAA ACAGGAGACT GTAGACAGCA AGAATTCAGG GATCGGTCTG	180
GAAACTGTGT TCCCTGCAAC CAGTGTGGGC CAGGCATGGA GTTGTCTAAG GAATGTGGCT	240
TCGGCTATGG GGAGGATGCA CAGTGTGTGA CGTGCCGGCT GCACAGGTTC AAGGAGGACT	300
GGGGCTTCCA GAAATGCAAG CCCTGTCTGG ACTGCGCAGT GGTGAACCGC TTTCAGAAGG	360
CAAATTGTTC AGCCACCAGT GATGCCATCT GCGGGGACTG CTTGCCAGGA TTTTATAGGA	420
AGACGAAACT TGTCGGCTTT CAAGACATGG AGTGTGTGCC TTGTGGAGAC CCTCCTCCTC	480
CTTACGAACC GCACTGTGCC AGCAAGGTCA ACCTCGTGAA GATCGCGTCC ACGGCCTCCA	540
GCCCACGGGA CACGGCGCTG GCTGCCGTTA TCTGCAGCGC TCTGGCCACC GTCCTGCTGG	600
CCCTGCTCAT CCTCTGTGTC ATCTATTGTA AGAGACAGTT TATGGAGAAG AAACCCAGCT	660
GGTCTCTGCG GTCACAGGAC ATTCAGTACA ACGGCTCTGA GCTGTCTGTG CTTGACAGAC	720
CTCAGCTCCA CGAATATGCC CACAGAGCCT GCTGCCAGTG CCGCCGTGAC TCAGTGCAGA	780
CCTGCGGGCC GGTGCGCTTG CTCCCATCCA TGTGCTGTGA GGAGGCCTGC AGCCCCAACC	840
CGGCGACTCT TGGTTGTGGG GTGCATTCTG CAGCCAGTCT TCAGGCAAGA AACGCAGGCC	900
CAGCCGGGGA GATGGTGCCG ACTTTCTTCG GATCCCTCAC GCAGTCCATC TGTGGCGAGT	960
TTTCAGATGC CTGGCCTCTG ATGCAGAATC CCATGGGTGG TGACAACATC TCTTTTTGTG	1020
ACTCTTATCC TGAATCGCT GGAGAAGACA TTCATTCTCT CAATCCAGAA CTTGAAAGCT	1080
CAACGTCTTT GGATTCAAAT AGCAGTCAAG ATTTGGTTGG TGGGGCTGTT CCAGTCCAGT	1140
CTCATTCTGA AAACCTTACA GCAGCTACTG ATTTATCTAG ATATAACAAC AACTGGTAG	1200
AATCAGCATC AACTCAGGAT GCACTAACTA TGAGAAGCCA GCTAGATCAG GAGAGTGGCG	1260
CTATCATCCA CCCAGCCACT CAGACGTCCC TCCAGGTAAG GCAGCGACTG GGTTCCTGT	1320
GAACACAGCA CTGACTTACA GTAGATCAGA ACTCTGTTCC CAGCATAAGA TTTGGGGGAA	1380
CCTGATGAGT TTTTTTTTGG CATCTTTAAT AATTTCTTGT ATGTTGTAGA GTATGTTTTA	1440
AAATAAATTT CAAGTATTTT TTTTAAAAC TAAAAA AAAA AAAA AAAA	1500
AA	1502

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 423 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

Met Ala Leu Lys Val Leu Leu Glu Gln Glu Lys Thr Phe Phe Thr Leu
1              5              10              15

Leu Val Leu Leu Gly Tyr Leu Ser Cys Lys Val Thr Cys Glu Thr Gly
              20              25              30

Asp Cys Arg Gln Gln Glu Phe Arg Asp Arg Ser Gly Asn Cys Val Pro
              35              40              45

Cys Asn Gln Cys Gly Pro Gly Met Glu Leu Ser Lys Glu Cys Gly Phe
              50              55              60

Gly Tyr Gly Glu Asp Ala Gln Cys Val Thr Cys Arg Leu His Arg Phe
65              70              75              80

Lys Glu Asp Trp Gly Phe Gln Lys Cys Lys Pro Cys Leu Asp Cys Ala
              85              90              95

Val Val Asn Arg Phe Gln Lys Ala Asn Cys Ser Ala Thr Ser Asp Ala
              100              105              110

Ile Cys Gly Asp Cys Leu Pro Gly Phe Tyr Arg Lys Thr Lys Leu Val
              115              120              125

Gly Phe Gln Asp Met Glu Cys Val Pro Cys Gly Asp Pro Pro Pro Pro
              130              135              140

Tyr Glu Pro His Cys Ala Ser Lys Val Asn Leu Val Lys Ile Ala Ser
145              150              155              160

Thr Ala Ser Ser Pro Arg Asp Thr Ala Leu Ala Ala Val Ile Cys Ser
              165              170              175

Ala Leu Ala Thr Val Leu Leu Ala Leu Leu Ile Leu Cys Val Ile Tyr
              180              185              190

Cys Lys Arg Gln Phe Met Glu Lys Lys Pro Ser Trp Ser Leu Arg Ser
              195              200              205

Gln Asp Ile Gln Tyr Asn Gly Ser Glu Leu Ser Cys Leu Asp Arg Pro
              210              215              220

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

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 339 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

GCGGCCGCAG GTCTAGAATT CAATCGGGAG AGAGATACTG CCTGGTTCTT ACAGACACAG

60

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ATTATGTCAT CCTTGCAGCC TTCACCCAAA GTTGCTCCCT CCTTCTAGGG CATTTTGTTT	120
TCCTACTTAA TACCAAGTGT CAGCATGTTA GTAATAACA GGTGTCTCTA CCATTAGTCA	180
AAGGTGGGAG TTAAGCCTTT CATCTTTGTA GCTTTCTCCA GTACCTAACC ATGATTTACT	240
TCATGGGAAG TCCCTCAAAG TACTATTAAT TATCCTGTGT TCTCCTGCCT TGCCTCTTAA	300
CAAAAATTCT GCTGTTCTTG ATTATTTCCA TTTTACCAG	339

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 552 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

AAATANAAAT ANAACAAATT NTAGGGAAGG ACTAAACTGT CTAAAGAAAT GTAAAATCCA	60
AAGACTTGGA TTTTCAACCT ATATCAGAAG AACTTTTTTT TTCAGTCCC ATGTGAAATT	120
CTTNTAGGC CAAGGAAGGA CAAATACAAA TTTTGATTAC AAATTATTTT TAGAACTTTG	180
ACACCTACAC TTAAATTCTG AGTCATTAAA CAGGCCTACA TTTATCAACT GTGGAAATAT	240
CAGCCAGTTT TTGCAAACCT CTTCTTAGGA CACTAAGTTG TTTGCAGAAA TCACTAGCAT	300
TGACTGACTC AGCAACAATG TGGTTATATT CTTTGATTAA CTTAGTCCTT TTTCTTGGTC	360
AAGAGTCAGT AGACAGGACT GAAGCTTATG CCCCTTGCCC CCCACCACC ACTCCATTAC	420
TACCACCTTG GTTTAGCCAT CCTTTTCTTG ATCTGTTCTC CCCACTTCTA CTGTGCTACT	480
CTACAGACTT GCCCTGAATG TAAGAGCAAC AATTACCTTG TAAAGTCCAA GTTGGGGCAG	540
GTCACTCCCA AA	552

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 47 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

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

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 308 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

TTTTTTNGGA ATCACCAAAA TCAAGNGNGA TATTGTGTTT GCTGCCAGCC TNNANTTGTA	60
GAGTCAGCTA AAGGAATGTG NGATTTTAAA TTATTGACCA CCTGTTTGAT TACAGTTGAN	120
NACAAATGCC TGCAAGTGTG GATTTGGTTT TCCCANACAT TTTAATATGT ATTATATTTA	180
AATCAAACAT CATTCATAGA AAGCATATNA CANANATGTT TANACATAAG CATNACATTT	240
TTTTAATAAA AATGTANACA GGTGGGGCAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA	300
AAAAAAAAA	308

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 789 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

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CTCTCCTCTG GCTACTGGGT GCTCGTGGTG CATTTTACTC GGAGAGAGGC CATCAAGCAG      60
ATCGAGGTGC TGCAGCACGT GGCCACCAAC CTGGGGCGCA GCCGTGCCTG GCTGTACCTG      120
GCCCTCAACG ARAACTCCCT TGGARARACT ACCTGCGGTT GTTCCARGAR AAACCTGGGC      180
CTGCTGCATA AGTACTACGT CAAGAATGCC CTGGTCTGCA GCCACGATCA CCTGACGCTC      240
TTCCTGACCT TGGTGTCCGG GCTAGAGTTC ATTCGTTTCG AGCTGGATCT GGATGCCCCT      300
TACCTAGACC TGGCCCCCTA CATGCCCGAC TACTACAAAC CTCAGTACCT GCTGGACTTT      360
GAAGACCGCC TTCCAGCTC GGTCCACGGC TCAGACAGTC TGTCCCTCAA CTCTTTCAAC      420
TCCGTCACCT CCACCAACCT GGAGTGGGAT GACAGTGCGA TTGCCCCATC TAGTGAGGAT      480
TATGATTTTG GAGATGTGTT TCCAGCAGTG CCGTCTGTAC CCAGCACAGA CTGGGAAGAT      540
GGAGACCTCA CAGACACGGT CAGTGGTCCC CGCTCCACAG CCTCCGACCT GACCAGCAGC      600
AAGGCCTCCA CCAGGAGCCC CACCCAGCGC CAGAACCCTT TCAACGAGGA GCCGGCAGAG      660
ACTGTGTCCT CCTCTGACAC CACCCCCGTG CACACCACCT CTCAGGAGAA GGAGGAGGCC      720
CAGGCCCTGG ACCCGCCGGA TGCCTGCACG GAGCTCGAGG TCATCAGGGT CACCAAAAAA      780
AAAAAAAAA                                     789

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(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 151 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

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

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Ser	Val	Pro	Ser	Thr	Asp	Trp	Glu	Asp	Gly	Asp	Leu	Thr	Asp	Thr	Val	65	70	75	80
Ser	Gly	Pro	Arg	Ser	Thr	Ala	Ser	Asp	Leu	Thr	Ser	Ser	Lys	Ala	Ser	85	90	95	
Thr	Arg	Ser	Pro	Thr	Gln	Arg	Gln	Asn	Pro	Phe	Asn	Glu	Glu	Pro	Ala	100	105	110	
Glu	Thr	Val	Ser	Ser	Ser	Asp	Thr	Thr	Pro	Val	His	Thr	Thr	Ser	Gln	115	120	125	
Glu	Lys	Glu	Glu	Ala	Gln	Ala	Leu	Asp	Pro	Pro	Asp	Ala	Cys	Thr	Glu	130	135	140	
Leu	Glu	Val	Ile	Arg	Val	Thr										145	150		

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3443 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

AGAGACCCAA AGCCAAACT CAGCTGACAG GAATGTTTCA AAGGACACAA AGAGAGATGT	60
GGACTCAAAG TCACCGGGGA TGCCTTTATT TGAAGCAGAG GAAGGAGTTC TATCACGAAC	120
CCAGATATTT CCTACCACTA TTAAAGTCAT TGATCCAGAA TTTCTGGAGG AGCCACCTGC	180
ACTTGCATTT TTATATAAGG ATCTGTATGA AGAAGCAGTT GGAGAGAAAA AGAAGGAAGA	240
GGAGACAGCT TCTGAAGGTG ACAGTGTGAA TTCTGAGGCA TCATTTCCCA GCAGAAATTC	300
TGACACTGAT GATGGAACAG GAATATATTT TGAGAAGTAC ATACTCAAAG ATGACATTCT	360
CCATGACACA TCTCTAACTC AAAAGGACCA GGGCCAAGGT CTGGAARAAA AACRAGTTGG	420
TAAGGATGAT TCATACCAAC CGATAGCTGC AGAAGGGGAA ATTTGGGGAA AGTTTGGAAC	480
TATTTGCAGG GAGAAGAGTC TGGAAGAACA GAAAGGTGTT TATGGGGAAG GAGAATCAGT	540
AGACCATGTG GAGACCGTTG GTAACGTAGC GATGCAGAAG AAAGCTCCCA TCACAGAGGA	600
CGTCAGAGTG GCTACCCAGA AAATAAGTTA TGCGGTTCCA TTTGAAGACA CCCATCATGT	660

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TCTGGAGCGT GCAGATGAAG CAGGCAGTCA GGGTAATGAA GTCGGAAATG CAAGTCCAGA	720
GGTCAATCTG AATGTCCCAG TACAAGTGTC CTTCCCGGAG GAAGAATTTG CATCTGGTGC	780
AACTCATGTT CAAGAAACAT CACTAGAAGA ACCTAAAATC CTGGTCCCAC CTGAGCCAAG	840
TGAAGAGAGG CTCCGTAATA GCCCTGTTCA GGATGAGTAT GAATTTACAG AATCCCTGCA	900
TAATGAAGTG GTTCCTCAAG ACATATTATC AGAAGAACTG TCTTCAGAAT CCACACCTGA	960
AGATGTCTTA TCTCAAGGAA AGGAATCCTT TGAGCACATC AGTGAAAATG AATTTGCGAG	1020
TGAGGCAGAA CAAAGTACAC CTGCTGAACA AAAAGAGTTG GGCAGCGAGA GGAAAGAAGA	1080
AGACCAATTA TCATCTGAGG TAGTAACTGA AAAGGCACAA AAAGAGCTGA AAAAGTCCCA	1140
GATTGACACA TACTGTTACA CCTGCAAATG TCCAATTTCT GCCACTGACA AGGTGTTTGG	1200
CACCCACAAA GACCATGAAG TTTCAACGCT TGACACAGCT ATAAGTGCTG TAAAGGTTCA	1260
ATTAGCAGAA TTTCTAGAAA ATTTACAAGA AAAGTCCTTG AGGATTGAAG CCTTTGTTAG	1320
TGAGATAGAA TCCTTTTTTA ATACCATTGA GGAAAACTGT AGTAAAAATG AGAAAAGGCT	1380
AGAAGAACAG AATGAGGAAA TGATGAAGAA GGTTTTAGCA CAGTATGATG AGAAAGCCCA	1440
GAGCTTTGAG GAAGTGAAGA AGAAGAAGAT GGAGTTCCTG CATGAGCAGA TGGTCCACTT	1500
TCTGCAGAGC ATGGACACTG CCAAAGACAC CCTGGAGACC ATCGTGAGAG AAGCAGAGGA	1560
GCTTGATGAG GCCGTCTTCC TGACTTCGTT TGAGGAAATC AATGAAAGGT TGCTTTCTGC	1620
AATGGAGAGC ACTGCTTCTT TAGAGAAAAT GCCTGCTGCG TTTTCCCTTT TTGAACATTA	1680
TGATGACAGC TCGGCAAGAA GTGACCAGAT GTTAAAACAA GTGGCTGTTC CACAGCTTCC	1740
TAGATTAGAA CTCAGGAACC AAATTTTGCC ACCAGCACAA CAATTGCAGT TTAAGGAGC	1800
ATGAACAAGG AAGATGTCAT TGATTCATTT CAGGTTTACT GCATGGAGGA GCCACAAGAT	1860
GATCAAGAAG TAAATGAGTT GGTAGAAGAA TACAGACTGA CAGTGAAAGA AAGCTACTGC	1920
ATTTTTGAAG ATCTGGAACC TGACCGATGC TATCAAGTGT GGGTGATGGC TGTGAACTTC	1980
ACTGGATGTA GCCTGCCCAG TGAAAGGGCC ATTTTTAGGA CAGCACCTC CACCCCTGTG	2040
ATCCGCGCTG AGGACTGTAC TGTGTGTTGG AACACAGCCA CTATCCGATG GCGGCCACC	2100
ACCCAGAGG CCACGGAGAC CTACACTCTG GAGTACTGCA GACAGCACTC TCCTGAGGGA	2160
GAGGGCCTCA GATCTTTCTC TGAATCAAA GGACTCCAGC TGAAAGTTAA CCTCCAACCC	2220
AATGATAACT ACTTTTTTTA TGTGAGGGCC ATCAATGCAT TTGGGACAAG TGAACAGAGT	2280
GAAGCTGCTT TCATCTCCAC CAGAGGAACC AGATTTCTCT TGTGAGAGA AACAGCTCAT	2340

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CCTGCTCTAC ACATTTTCCTC AAGTGGGACA GTGATCAGCT TTGGTGAGAG GAGACGGCTG      2400
ACGGAAATCC CGTCAGTGCT GGGTGAGGAG CTGCCTTCCT GTGGCCAGCA TTACTGGGAA      2460
ACCACAGTCA CAGACTGCCC AGCATATCGA CTCGGCATCT GCTCCAGCTC GGCTGTGCAG      2520
GCAGGTGCCC TAGGACAAGG GGAGACCTCA TGGTACATGC ACTGCTCTGA GCCACAGAGA      2580
TACACATTTT TCTACAGTGG TATTGTGAGT GATGTTTCATG TGACTGAGCG TCCAGCCAGA      2640
GTGGGCATCC TGCTGGACTA CAACAACCAG AGATTATCTT CATCAACGCA GAGAGCGAGC      2700
AGTTGCTCTT CATCATCAGG CACAGGTTTA ATGAGGGTGT CCACCCTGCC TTTGCCCTGG      2760
AGAAACCTGG AAAATGTACT TTGCACCTGG GGATAGAGCC CCCGGATTCT GTAAGGCACA      2820
AGTGATCCTT GGCTTTCAGA ATTTGCAAGA ACAGCGATTT GAATTTTGGG GGGGTCTGCT      2880
GTTTCATTCCT TTAGGTGCTA TACATTATTC AAAAAGTCTC CCGCGCATTT GCACTAATGA      2940
TGGCTGCATG CATAGCAATC AGCATGTGAG CAAAATCGAC AAGAAAACCT TGACTTTACA      3000
GAGCAGTGTG TGAGTAAACA GAATGAAAAC AACAACCTCC ACTCTTTAGT TTATATAAGT      3060
TTGAGTTCTT TCCTAAATTA AAAGATCTAC ACTTGAGTTG GGAACCGAAA GAGAAAAATG      3120
GACTTCCATC TGTTTTACTG GTAAAGGAAA TCCTCTGATG GACAGGTCAG AGTGAAGGAA      3180
GGTTGTGCTG GTAAGACATC TCTGACGAAG AGCCATGGAT GCTTTCACCA AAATGTCACC      3240
TCGCTGCACT AAAGGATGAT GAATCCTAAT CATTAAAGGA ATTGTTTCAG CTGATTTAAA      3300
TTTATAATGA ACTCTTTTGT AATAATGTAT ACTGTAGAAC ATGAGTCTCT CCTCCCTAAA      3360
ATTTTAAATG TAGAAAAGTG CTATATATTA GAAATTTCCA TTTTGTTAAA TAAATGGTTA      3420
GAGTCTATAA AAAAAAAAAA AAA                                     3443

```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 574 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

```

Met Pro Leu Phe Glu Ala Glu Glu Gly Val Leu Ser Arg Thr Gln Ile
1           5           10           15

```

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

305		310		315		320									
Pro	Ala	Glu	Gln	Lys	Glu	Leu	Gly	Ser	Glu	Arg	Lys	Glu	Glu	Asp	Gln
				325					330					335	
Leu	Ser	Ser	Glu	Val	Val	Thr	Glu	Lys	Ala	Gln	Lys	Glu	Leu	Lys	Lys
			340					345					350		
Ser	Gln	Ile	Asp	Thr	Tyr	Cys	Tyr	Thr	Cys	Lys	Cys	Pro	Ile	Ser	Ala
		355					360					365			
Thr	Asp	Lys	Val	Phe	Gly	Thr	His	Lys	Asp	His	Glu	Val	Ser	Thr	Leu
	370					375					380				
Asp	Thr	Ala	Ile	Ser	Ala	Val	Lys	Val	Gln	Leu	Ala	Glu	Phe	Leu	Glu
385					390					395					400
Asn	Leu	Gln	Glu	Lys	Ser	Leu	Arg	Ile	Glu	Ala	Phe	Val	Ser	Glu	Ile
				405					410					415	
Glu	Ser	Phe	Phe	Asn	Thr	Ile	Glu	Glu	Asn	Cys	Ser	Lys	Asn	Glu	Lys
			420					425					430		
Arg	Leu	Glu	Glu	Gln	Asn	Glu	Glu	Met	Met	Lys	Lys	Val	Leu	Ala	Gln
		435					440					445			
Tyr	Asp	Glu	Lys	Ala	Gln	Ser	Phe	Glu	Glu	Val	Lys	Lys	Lys	Lys	Met
	450					455					460				
Glu	Phe	Leu	His	Glu	Gln	Met	Val	His	Phe	Leu	Gln	Ser	Met	Asp	Thr
465					470					475					480
Ala	Lys	Asp	Thr	Leu	Glu	Thr	Ile	Val	Arg	Glu	Ala	Glu	Glu	Leu	Asp
				485					490					495	
Glu	Ala	Val	Phe	Leu	Thr	Ser	Phe	Glu	Glu	Ile	Asn	Glu	Arg	Leu	Leu
		500						505					510		
Ser	Ala	Met	Glu	Ser	Thr	Ala	Ser	Leu	Glu	Lys	Met	Pro	Ala	Ala	Phe
		515					520					525			
Ser	Leu	Phe	Glu	His	Tyr	Asp	Asp	Ser	Ser	Ala	Arg	Ser	Asp	Gln	Met
	530					535					540				
Leu	Lys	Gln	Val	Ala	Val	Pro	Gln	Leu	Pro	Arg	Leu	Glu	Leu	Arg	Asn
545					550					555					560
Gln	Ile	Leu	Pro	Pro	Ala	Gln	Gln	Leu	Gln	Phe	Thr	Gly	Ala		
				565					570						

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1199 base pairs
 (B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

RGACTTGTTG CCAGTGATAC CAAAACAGAC TTTTCCCAAG CAGTGCCTCA CATGTCTGCT	60
GGTGTGGCTT TGGGATTCTC CTGCCCCACC CCCCCGTCCA TGGCAGCCCC CTCCCCAAGG	120
CTTTGCTCAC ACCTGAGACA GGAAGGAGGA AGGGGATCCA ATAGGAATAT GGGCCCCGGA	180
GGGGAAGTCA TGCACCCCCA AGCCACCACC CCCCAGCCTT CCACGCACAT CTCCTGGYTG	240
GAAGAGAGCC CTCCAAAAG GGGACACAGG CTGCCCCGGC CCCTCAACTG CATCCACACC	300
CCATCCTCTC ATCTTGGGTC CCAGCCAGGC CCCCCAAAA CCAAAGCCCC CTCAAGTCCT	360
GGGGTCCCAG CCTGTGCCCC CAGCTTCCTG CCCACCCAGC CCTGAGCATT CTCACACAGA	420
GAAAGAACAA GCAAGGGCTC CAGGGGGACA GGATGGGGCA GGGCATAACAG TGGGGGGTGG	480
GGGGGCAGCT GGGAGGAGGG AGGGACAAAA CAAAACATTT TCCTTTGGGT TTTTTTTTTC	540
TTTCTTTTTT CTCCCCTTTA CTCTTTGGGT GGTGTTGCTT TTCCTTTCCT TTTCCCTTTG	600
AGATTTTTTT GTTGTTGTTT CCTTTTTGTA TTTTACTGAT ATCACCAGGA TAGTTTACTC	660
TCCTTCTAGC TTTCTGCTTA CCGCACACTG GATAACACAC ACATACACAC CCACAAAAAT	720
GCTCATGAAC CCAATCCGGA GAAGGTTCCT GCAGGTCCCC CACCCTCCCC TCCTCCTCCT	780
ACTTCTCCTC TTGACAGCGA GGACAGGAGG GGGACAAGGG GACACCTGGG CAGACCCGCC	840
GGCTCTCCCC CCACCCCACC CCGCCCCTCA CATCATACTC CAATCATAAC CTTGTATATT	900
ACGCAGTCAT TTTGGTTTTT GCGGACGCGC CTACCTAAGT ACCATTTACA GAAAGTGACT	960
CTGGCTGTCA TTATTTTGTT TATTTGTTCC CTATGCAAAA AAAAAATGAA AATGAAAAAA	1020
GGGGGATTCC ATAAAAGATT CAATAAAAGA CAAACAAAAA AAAAAGAAAA AAGAAAAAAA	1080
TGTATAAAAA TTAAACAAGC TATGCTTCGA CTCAAAAAAA AAAAAAAAAA AAAAAAAAAA	1140
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA	1199

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 56 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

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	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			
Ala	Pro	His	Ile	Ile	Leu	Gln	Ser								
		50				55									

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 839 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

GAATGAAAAT CCAGGTGTTT GTCATTCATC AGCAACAGGT GATCCCCATT GCAGGCAGCC	60
GGAACCGACG TCTCCTGGAC CACTGAGCTG GCTGTTCTCA TTACTGCCCT TTCCGCCAG	120
GCTGGCGGTG ACTCACCGTG AGACAAGTCA GCTAGGTGTT CAGGACAGGG ATTCAGAGT	180
ATTTTGTCC AAAGAGGAAA GGGATGATTT CTACGGATCA CTACCAGTTG GTTACTGTT	240
AGCTNCATCG TGTGATCAC ACCAAGTCCT TGCCAATTG GTTTTCTAAG TATTTTCACG	300
CCTTCTCCTC GTGTCCGCGT CACTGCTCTG ATTCAGGCC TTGTCATTC TCATCTTTGC	360
CATTTTAGTA GTTTTGGAT TGGGCTCCCG GCTGCTAATT TTGTCCCCTT TTCCACTATC	420
TTCCACATTG TCACCGCAGT CATGTTTCTA AGGCAGAATC TCACTGTGCC CCTCATCGTG	480
TTGGGTGACT TSTGGTGGCA TCCCGTCACC CTCAGGACAA CCTTTCCTGG GGCCTGCCCG	540

WO 99/20644

PCT/US98/22034

CTCTGCTCTT GCTGCTGCCT CGCTGTCCCC CTCCTCCCTC CTGTGGTTTA TATTCCAGGA 600
 ATTCTGAATT AGTTGCACCG TGCTCTCATA TTTACTGCAA GAATAGACCA GTGGTTCTCC 660
 AGCTTTTCTG CACTCTGGAA TCACCTGGGG GTCTTTAAAA AACACTGCCT GGCTCCTAGT 720
 CCTAAATTG GAGATTTAAC TGGACTTACA GTTTTTCAAA GCACCCCAA AGATTCTAAT 780
 GTGCAGCAAA GTTTGGGAAC CACTGGTATA GACTGTCTTC TGCTTGTTTT CTTGAAAAA 839

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 56 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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

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

(2) INFORMATION FOR SEQ ID NO:29:

(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:29:

ANTATCCCAC CAGCTTCTCA CAGGTGTCA

29

(2) INFORMATION FOR SEQ ID NO:30:

(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:30:

GNAGGCATCA CTGTGGCTAT TTCAATCTC

29

(2) INFORMATION FOR SEQ ID NO:31:

(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:31:

TNCCATCTAC CGCAACTCTC AGTTCGAGA

29

(2) INFORMATION FOR SEQ ID NO:32:

(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:32:

TNAGTGTAGT GACAGTGGTG ACATCCTTT

29

(2) INFORMATION FOR SEQ ID NO:33:

- (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:33:

TGAAGGGGTC TGAAAAGGGC AGATGAG

27

- (2) INFORMATION FOR SEQ ID NO:34:

- (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:34:

TNTTGGTGGA GATGCCATCC GGAACCTCA

29

- (2) INFORMATION FOR SEQ ID NO:35:

- (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:35:

GNTCTTGGGA TCGTCGCCC TGCAGATAA

29

- (2) INFORMATION FOR SEQ ID NO:36:

(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:36:

GNAAGCCGAC AAGTTTCGTC TTCCTATAA

29

(2) INFORMATION FOR SEQ ID NO:37:

(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:37:

GNTAAACCAA GGTGGTAGTA ATGGAGTGG

29

(2) INFORMATION FOR SEQ ID NO:38:

(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:38:

GNTTGGTGGA GGTGACGGAG TTGAAAGAG

29

(2) INFORMATION FOR SEQ ID NO:39:

(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:39:

GNCTCCTCCA GAAATTCTGG ATCAATGAC

29

(2) INFORMATION FOR SEQ ID NO:40:

(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:40:

TCCTCCTACT TCTCCTCTTG ACAGCGA

27

(2) INFORMATION FOR SEQ ID NO:41:

(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:41:

TNCCTTAGAA ACATGACTGC GGTGACAAT

29

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 113 to nucleotide 742;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 179 to nucleotide 742;
 - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 568;
 - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;
 - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;
 - (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;
 - (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;
 - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
 - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;
 - (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
 - (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
 - (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

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 53 to amino acid 129;
 - (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 AC41_1 deposited under accession number ATCC 98101;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 53 to amino acid 129.

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. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.
14. A composition comprising an isolated polynucleotide selected from the group consisting of:
 - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 161 to nucleotide 1126;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 218 to nucleotide 1126;
 - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 553;
 - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101;
 - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;
 - (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101;
 - (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

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:4;
 - (b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131;
 - (c) fragments of the amino acid sequence of SEQ ID NO:4; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;
- the protein being substantially free from other mammalian proteins.

16. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:3.

17. 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 827 to nucleotide 994;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 869 to nucleotide 994;

- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 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).

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:6;
 - (b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20;
 - (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 AJ143_1 deposited under accession number ATCC 98101;
- the protein being substantially free from other mammalian proteins.

19. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.
20. A composition comprising an isolated polynucleotide selected from the group consisting of:
 - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 91 to nucleotide 204;
 - (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;
 - (d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;
 - (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;
 - (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;
 - (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;
 - (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 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:8;
 - (b) fragments of the amino acid sequence of SEQ ID NO:8; and
 - (c) the amino acid sequence encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;
- the protein being substantially free from other mammalian proteins.

22. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.
23. 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 60 to nucleotide 230;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 323;
 - (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;
 - (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;
 - (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;
 - (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;
 - (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;
 - (i) a polynucleotide encoding a protein comprising a fragment of the

amino acid sequence of SEQ ID NO:10 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).

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:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone

AK684_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

25. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:9.

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

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 812 to nucleotide 2731;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 944 to nucleotide 2731;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 855 to nucleotide 1186;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;

- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

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:12;
 - (b) the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125;
 - (c) fragments of the amino acid sequence of SEQ ID NO:12; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;
- the protein being substantially free from other mammalian proteins.

28. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:11.

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

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 2196 to nucleotide 2708;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 489 to nucleotide 890;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX56_28 deposited under accession number ATCC 98180;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX56_28 deposited under accession number ATCC 98180;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 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).

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:14;
 - (b) fragments of the amino acid sequence of SEQ ID NO:14; and
 - (c) the amino acid sequence encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;
- the protein being substantially free from other mammalian proteins.

31. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:13.

32. 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 51 to nucleotide 1319;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 126 to nucleotide 1319;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 409 to nucleotide 495;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

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:16;
- (b) fragments of the amino acid sequence of SEQ ID NO:16; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

AX92_3 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

34. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:15.

35. 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 210 to nucleotide 350;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 300 to nucleotide 350;
- (d) a polynucleotide comprising the nucleotide sequence of the full-

length protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

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

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

(b) fragments of the amino acid sequence of SEQ ID NO:19; and

(c) the amino acid sequence encoded by the cDNA insert of clone

BF245_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

37. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:18, SEQ ID NO:17 or SEQ ID NO:20 .

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

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 322 to nucleotide 774;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 149 to nucleotide 477;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 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:22;
 - (b) the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121;
 - (c) fragments of the amino acid sequence of SEQ ID NO:22; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;
- the protein being substantially free from other mammalian proteins.

40. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:21.

41. 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 80 to nucleotide 1801;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 1 to nucleotide 421;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BM46_10 deposited under accession number ATCC 98152;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BM46_10 deposited under accession number ATCC 98152;

- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:24 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:24;
 - (b) the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112;
 - (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 BM46_10 deposited under accession number ATCC 98152;
- the protein being substantially free from other mammalian proteins.

43. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:23.

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

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 719 to nucleotide 886;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:25 from nucleotide 812 to nucleotide 886;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 1 to nucleotide 853;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:26;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:26 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

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

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

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:26;

(b) fragments of the amino acid sequence of SEQ ID NO:26; and

(c) the amino acid sequence encoded by the cDNA insert of clone

J317_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

46. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:25.
47. A composition comprising an isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 442 to nucleotide 609;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 1 to nucleotide 483;
 - (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone O289_1 deposited under accession number ATCC 98101;
 - (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;
 - (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone O289_1 deposited under accession number ATCC 98101;
 - (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;
 - (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:28;
 - (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:28 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:

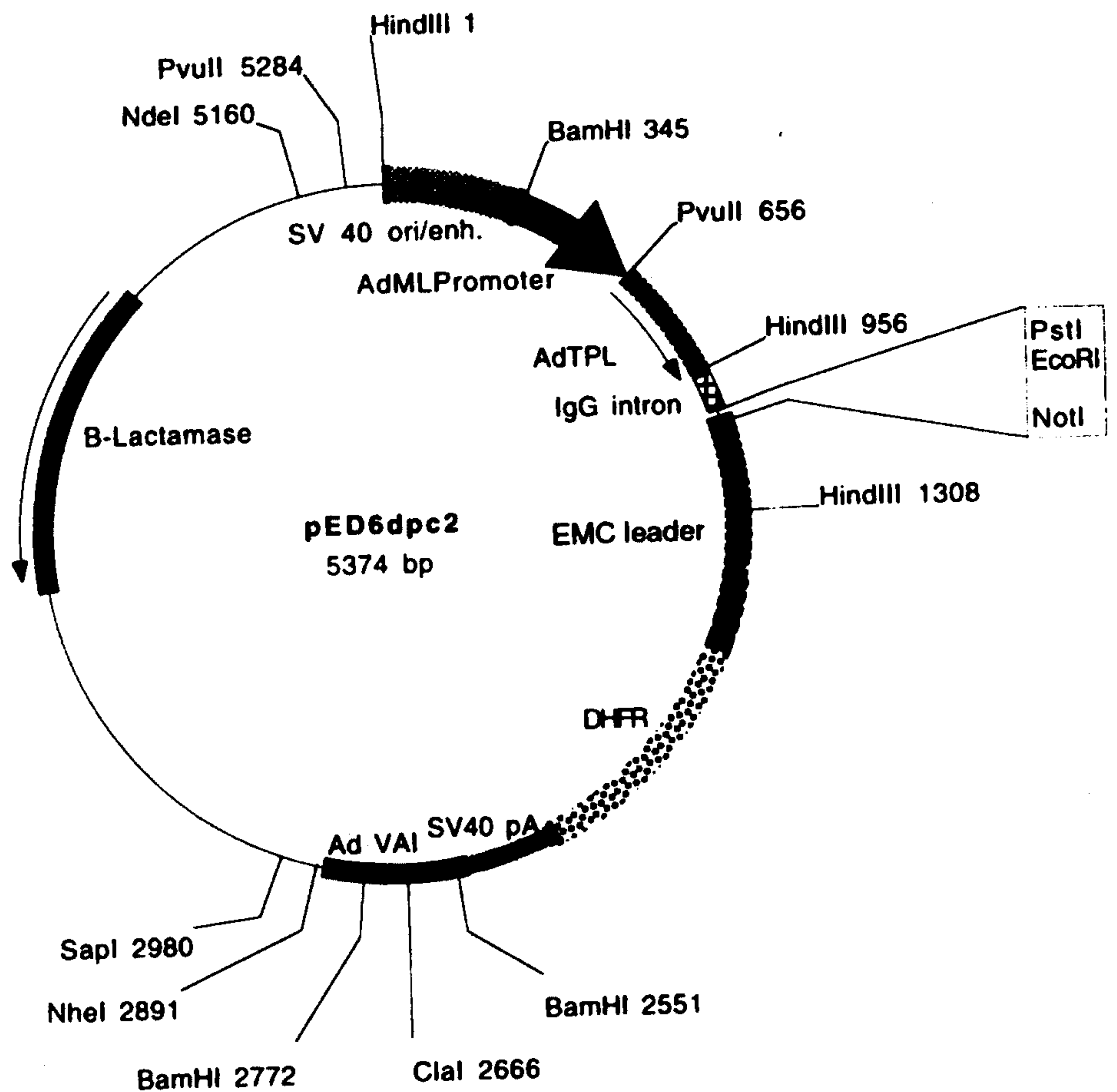
- (a) the amino acid sequence of SEQ ID NO:28;
- (b) fragments of the amino acid sequence of SEQ ID NO:28; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

O289_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

49. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:27.

FIGURE 1A

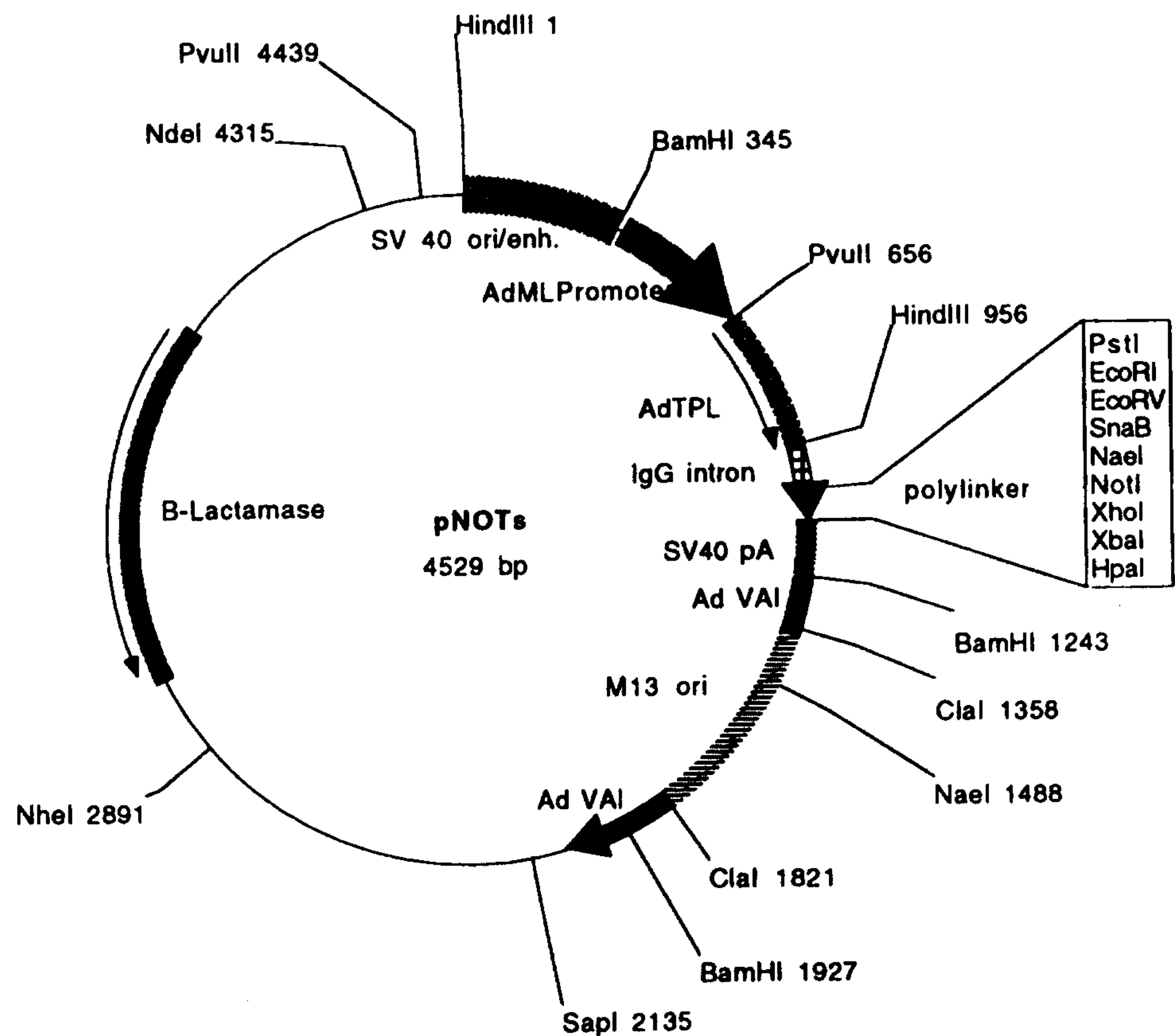


Plasmid name: pED6dpc2

Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs
Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al,1989. Mol.Cell.Biol.9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the ClaI site. SST cDNAs are cloned between EcoRI and NotI

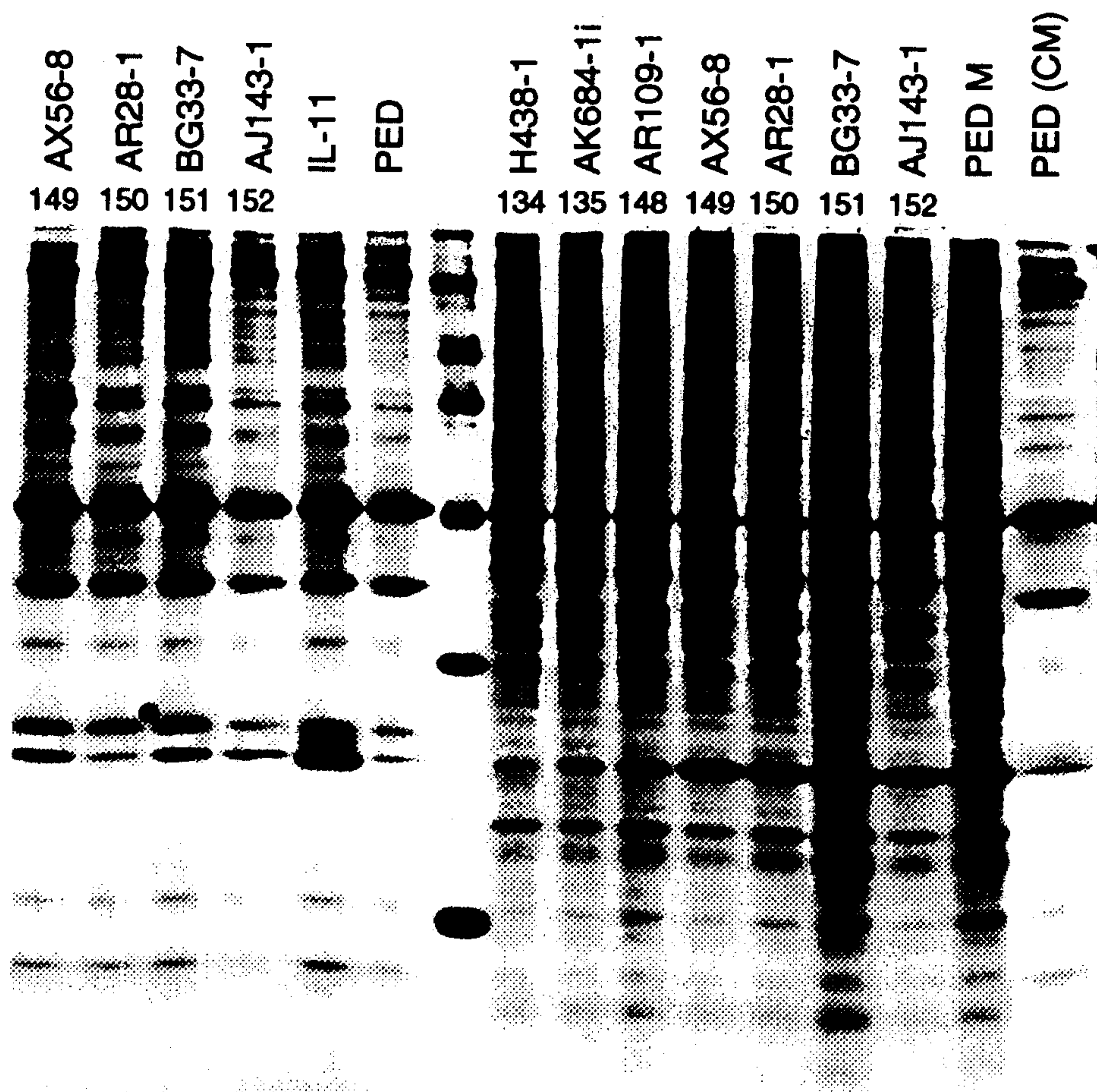


Figure 2

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