



- (72) JACOBS, KENNETH, US
(72) MCCOY, JOHN M., US
(72) LAVALLIE, EDWARD R., US
(72) COLLINS-RACIE, LISA A., US
(72) EVANS, CHERYL, US
(72) MERBERG, DAVID, US
(72) TREACY, MAURICE, US
(72) SPAULDING, VIKKI, US
(71) GENETICS INSTITUTE, INC., US
(51) Int.Cl.⁶ C07K 14/47, C12N 15/63, C12N 15/12, C12N 15/11,
C12N 15/10, C12N 5/10, C07K 14/00, C07K 7/00, A61K 38/00
(30) 1997/11/21 (08/976,112) US
(30) 1998/11/19 (09/196,027) US
(54) **PROTEINES SECRETEES ET POLYNUCLEOTIDES LES
CODANT**
(54) **SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING
THEM**

(57) Cette invention a trait à de nouveaux polynucléotides ainsi qu'aux protéines codées par ces polynucléotides.

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



PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 14/47, 14/00, 7/00, C12N 5/10, 15/10, 15/11, 15/12, 15/63, A61K 38/00	A1	(11) International Publication Number: WO 99/26973 (43) International Publication Date: 3 June 1999 (03.06.99)
(21) International Application Number: PCT/US98/24944 (22) International Filing Date: 20 November 1998 (20.11.98) (30) Priority Data: 08/976,112 21 November 1997 (21.11.97) US 09/196,027 19 November 1998 (19.11.98) US (71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 CambridgePark Drive, Cambridge, MA 02140 (US). (72) Inventors: JACOBS, Kenneth; 151 Beaumont Avenue, Newton, MA 02160 (US). MCCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). LAVALLIE, Edward, R.; 113 Ann Lee Road, Harvard, MA 01451 (US). COLLINS-RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). EVANS, Cheryl; 307 Brighton Drive, Beverly, MA 01915 (US). MERBERG, David; 2 Orchard Drive, Acton, MA 01720 (US). TREACY, Maurice; 93 Walcott Road, Chestnut Hill, MA 02167 (US). SPAULDING, Vikki; 11 Meadowbank Road, Billerica, MA 01821 (US). (74) Agent: SPRUNGER, Suzanne, A.; American Home Products Corporation, Patent & Trademark Dept. - 2B, One Campus Drive, Parsippany, NJ 07054 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM (57) Abstract Novel polynucleotides and the proteins encoded thereby are disclosed.		

WO 99/26973

PCT/US98/24944

SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

5 This application is (1) a continuation-in-part of application Ser. No. 09/XXX,XXX, filed November 19, 1998, which is a continuation-in-part of application Ser. No. 08/976,112, filed November 21, 1997, which is a continuation-in-part of application Ser. No. 08/702,344, filed August 23, 1996, and issued as U.S. Patent No. 5,723,315 on March 3, 1998; and (2) a continuation-in-part of application Ser. No. 08/976,112, filed November
10 21, 1997, which is a continuation-in-part of application Ser. No. 08/702,344, filed August 23, 1996, and issued as U.S. Patent No. 5,723,315 on March 3, 1998; all of which are incorporated by reference herein.

FIELD OF THE INVENTION

15 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

20 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
25 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
30 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.

WO 99/26973

PCT/US98/24944

SUMMARY OF THE INVENTION

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

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 54 to nucleotide 1283;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 648 to nucleotide 1283;
- 10 (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 458 to nucleotide 947;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AY421_2 deposited under accession number ATCC 98145;
- 15 (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AY421_2 deposited under accession number ATCC 98145;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AY421_2 deposited under accession number ATCC 98145;
- 20 (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AY421_2 deposited under accession number ATCC 98145;
- (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
- 30 (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:1 from nucleotide 54 to nucleotide 1283; the nucleotide sequence of SEQ ID NO:1 from nucleotide 648 to nucleotide 1283; the nucleotide sequence of SEQ ID NO:1 from

WO 99/26973

PCT/US98/24944

nucleotide 458 to nucleotide 947; the nucleotide sequence of the full-length protein coding sequence of clone AY421_2 deposited under accession number ATCC 98145; or the nucleotide sequence of the mature protein coding sequence of clone AY421_2 deposited under accession number ATCC 98145. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AY421_2 deposited under accession number ATCC 98145. 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 180 to amino acid 298.

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 180 to amino acid 298;
- (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 AY421_2 deposited under accession number ATCC 98145;

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 180 to amino acid 298.

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 720 to nucleotide 974;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 715 to nucleotide 947;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BV278_2 deposited under accession number ATCC 98145;

WO 99/26973

PCT/US98/24944

- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BV278_2 deposited under accession number ATCC 98145;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV278_2 deposited under accession number ATCC 98145;
- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BV278_2 deposited under accession number ATCC 98145;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 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:3 from nucleotide 720 to nucleotide 974; the nucleotide sequence of SEQ ID NO:3 from nucleotide 715 to nucleotide 947; the nucleotide sequence of the full-length protein coding sequence of clone BV278_2 deposited under accession number ATCC 98145; or the nucleotide sequence of the mature protein coding sequence of clone BV278_2 deposited under accession number ATCC 98145. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BV278_2 deposited under accession number ATCC 98145. 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 76.

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;

WO 99/26973

PCT/US98/24944

(b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 76;

(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
5 BV278_2 deposited under accession number ATCC 98145;

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 76.

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

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 36 to nucleotide 968;

15 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 340 to nucleotide 717;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone C544_1 deposited under accession number ATCC 98145;

20 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone C544_1 deposited under accession number ATCC 98145;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone C544_1 deposited under accession number ATCC 98145;

25 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone C544_1 deposited under accession number ATCC 98145;

(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
30 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

WO 99/26973

PCT/US98/24944

(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 36 to nucleotide 968; the nucleotide sequence of SEQ ID NO:5 from
 5 nucleotide 340 to nucleotide 717; the nucleotide sequence of the full-length protein coding sequence of clone C544_1 deposited under accession number ATCC 98145; or the nucleotide sequence of the mature protein coding sequence of clone C544_1 deposited under accession number ATCC 98145. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of
 10 clone C544_1 deposited under accession number ATCC 98145. 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 103 to amino acid 227.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ
 15 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;
- 20 (b) the amino acid sequence of SEQ ID NO:6 from amino acid 103 to amino acid 227;
- (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 C544_1 deposited under accession number ATCC 98145;

25 the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 103 to amino acid 227.

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

- 30 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 151 to nucleotide 1398;

WO 99/26973

PCT/US98/24944

- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 637 to nucleotide 1398;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 255 to nucleotide 429;
- 5 (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CC332_33 deposited under accession number ATCC 98145;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CC332_33 deposited under accession number ATCC 98145;
- 10 (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CC332_33 deposited under accession number ATCC 98145;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CC332_33 deposited under accession number ATCC 98145;
- 15 (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 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:7 from nucleotide 151 to nucleotide 1398; the nucleotide sequence of SEQ ID NO:7 from nucleotide 637 to nucleotide 1398; the nucleotide sequence of SEQ ID NO:7 from nucleotide 255 to nucleotide 429; the nucleotide sequence of the full-length protein coding sequence of clone CC332_33 deposited under accession number ATCC 98145; or the
- 30 nucleotide sequence of the mature protein coding sequence of clone CC332_33 deposited under accession number ATCC 98145. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CC332_33 deposited under accession number ATCC 98145. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein

WO 99/26973

PCT/US98/24944

comprising the amino acid sequence of SEQ ID NO:8 from amino acid 36 to amino acid 93.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

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:8;
- (b) the amino acid sequence of SEQ ID NO:8 from amino acid 36 to
10 amino acid 93;
- (c) fragments of the amino acid sequence of SEQ ID NO:8; and
- (d) the amino acid sequence encoded by the cDNA insert of clone
CC332_33 deposited under accession number ATCC 98145;

the protein being substantially free from other mammalian proteins. Preferably such
15 protein comprises the amino acid sequence of SEQ ID NO:8 or the amino acid sequence of SEQ ID NO:8 from amino acid 36 to amino acid 93.

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
20 NO:9;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID
NO:9 from nucleotide 89 to nucleotide 436;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID
NO:9 from nucleotide 212 to nucleotide 436;
- 25 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CC365_40 deposited under accession number ATCC 98145;
- (e) a polynucleotide encoding the full-length protein encoded by the
cDNA insert of clone CC365_40 deposited under accession number ATCC 98145;
- 30 (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CC365_40 deposited under accession number ATCC 98145;
- (g) a polynucleotide encoding the mature protein encoded by the
cDNA insert of clone CC365_40 deposited under accession number ATCC 98145;

WO 99/26973

PCT/US98/24944

- (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;
- 5 (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
- 10 to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 89 to nucleotide 436; the nucleotide sequence of SEQ ID NO:9 from nucleotide 212 to nucleotide 436; the nucleotide sequence of the full-length protein coding sequence of clone CC365_40 deposited under accession number ATCC 98145; or the

15 nucleotide sequence of the mature protein coding sequence of clone CC365_40 deposited under accession number ATCC 98145. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein

20 comprising the amino acid sequence of SEQ ID NO:10 from amino acid 17 to amino acid 116.

Other embodiments provide the gene corresponding to the cDNA sequences of SEQ ID NO:9 and SEQ ID NO:11.

In other embodiments, the present invention provides a composition comprising

25 a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:10;
- (b) the amino acid sequence of SEQ ID NO:10 from amino acid 17 to amino acid 116;
- 30 (c) fragments of the amino acid sequence of SEQ ID NO:10; and
- (d) the amino acid sequence encoded by the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145;

WO 99/26973

PCT/US98/24944

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10 or the amino acid sequence of SEQ ID NO:10 from amino acid 17 to amino acid 116.

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

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 21 to nucleotide 410;
- 10 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 144 to nucleotide 410;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 68 to nucleotide 368;
- (e) a polynucleotide comprising the nucleotide sequence of the full-
15 length protein coding sequence of clone CC365_40 deposited under accession number ATCC 98145;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145;
- (g) a polynucleotide comprising the nucleotide sequence of a mature
20 protein coding sequence of clone CC365_40 deposited under accession number ATCC 98145;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145;
- (i) a polynucleotide encoding a protein comprising the amino acid
25 sequence of SEQ ID NO:33;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:33 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:33;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of
30 (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

WO 99/26973

PCT/US98/24944

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:32 from nucleotide 21 to nucleotide 410; the nucleotide sequence of SEQ ID NO:32 from nucleotide 144 to nucleotide 410; the nucleotide sequence of SEQ ID NO:32 from nucleotide 68 to nucleotide 368; the nucleotide sequence of the full-length protein coding sequence of clone CC365_40 deposited under accession number ATCC 98145; or the nucleotide sequence of a mature protein coding sequence of clone CC365_40 deposited under accession number ATCC 98145. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:33 from amino acid 17 to amino acid 116. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:33 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:33, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:33 having biological activity, the fragment comprising the amino acid sequence from amino acid 60 to amino acid 69 of SEQ ID NO:33.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:32.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

- (a) a process comprising the steps of:
 - (i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:
 - (aa) SEQ ID NO:32, but excluding the poly(A) tail at the 3' end of SEQ ID NO:32; and
 - (ab) the nucleotide sequence of the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145; and
 - (ii) hybridizing said probe(s) to human DNA; and
 - (iii) isolating the DNA polynucleotide detected with the probe(s);

and

WO 99/26973

PCT/US98/24944

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

5 (ba) SEQ ID NO:32, but excluding the poly(A) tail at the 3' end of SEQ ID NO:32; and

(bb) the nucleotide sequence of the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145; and

(ii) hybridizing said primer(s) to human DNA;

10 (iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide product of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:32, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:32 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:32, but excluding the poly(A) tail at the 3' end of SEQ ID NO:32. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:32 from nucleotide 21 to nucleotide 410, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:32 from nucleotide 21 to nucleotide 410, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:32 from nucleotide 21 to nucleotide 410. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:32 from nucleotide 144 to nucleotide 410, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:32 from nucleotide 144 to nucleotide 410, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:32 from nucleotide 144 to nucleotide 410. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:32 from nucleotide 68 to nucleotide 368, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:32 from nucleotide 68 to nucleotide 368, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:32 from nucleotide 68 to nucleotide 368.

WO 99/26973

PCT/US98/24944

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:33;
 - 5 (b) the amino acid sequence of SEQ ID NO:33 from amino acid 17 to amino acid 116;
 - (c) fragments of the amino acid sequence of SEQ ID NO:33 comprising eight consecutive amino acids of SEQ ID NO:33; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone
10 CC365_40 deposited under accession number ATCC 98145;
- the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:33 or the amino acid sequence of SEQ ID NO:33 from amino acid 17 to amino acid 116. In further preferred embodiments, the present invention provides a protein comprising a fragment of the
15 amino acid sequence of SEQ ID NO:33 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:33, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:33 having biological activity, the fragment comprising the amino acid sequence from amino acid 60 to amino acid 69 of SEQ ID NO:33.

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:12;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID
25 NO:12 from nucleotide 769 to nucleotide 966;
- (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CG68_4 deposited under accession number ATCC 98145;
- (d) a polynucleotide encoding the full-length protein encoded by the
30 cDNA insert of clone CG68_4 deposited under accession number ATCC 98145;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CG68_4 deposited under accession number ATCC 98145;

WO 99/26973

PCT/US98/24944

- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CG68_4 deposited under accession number ATCC 98145;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;
- 5 (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein
- 10 of (g) or (h) above ; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:12 from nucleotide 769 to nucleotide 966; the nucleotide sequence of the full-length

15 protein coding sequence of clone CG68_4 deposited under accession number ATCC 98145; or the nucleotide sequence of the mature protein coding sequence of clone CG68_4 deposited under accession number ATCC 98145. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CG68_4 deposited under accession number ATCC 98145. In yet other preferred

20 embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13 from amino acid 18 to amino acid 57.

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

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:13;
- (b) the amino acid sequence of SEQ ID NO:13 from amino acid 18 to
- 30 amino acid 57;
- (c) fragments of the amino acid sequence of SEQ ID NO:13; and
- (d) the amino acid sequence encoded by the cDNA insert of clone CG68_4 deposited under accession number ATCC 98145;

WO 99/26973

PCT/US98/24944

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:13 or the amino acid sequence of SEQ ID NO:13 from amino acid 18 to amino acid 57.

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

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14 from nucleotide 1042 to nucleotide 1389;
- 10 (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone D329_1 deposited under accession number ATCC 98145;
- (d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone D329_1 deposited under accession number ATCC 98145;
- 15 (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone D329_1 deposited under accession number ATCC 98145;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone D329_1 deposited under accession number ATCC 98145;
- 20 (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:15;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:15 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- 25 (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

30 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:14 from nucleotide 1042 to nucleotide 1389; the nucleotide sequence of the full-length protein coding sequence of clone D329_1 deposited under accession number ATCC 98145; or the nucleotide sequence of the mature protein coding sequence of clone D329_1 deposited under accession number ATCC 98145. In other preferred embodiments, the

WO 99/26973

PCT/US98/24944

polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone D329_1 deposited under accession number ATCC 98145.

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

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:15;
- (b) fragments of the amino acid sequence of SEQ ID NO:15; and
- 10 (c) the amino acid sequence encoded by the cDNA insert of clone D329_1 deposited under accession number ATCC 98145;

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

15 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:18;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 279 to nucleotide 515;
- 20 (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone H698_3 deposited under accession number ATCC 98145;
- (d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone H698_3 deposited under accession number ATCC 98145;
- 25 (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H698_3 deposited under accession number ATCC 98145;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H698_3 deposited under accession number ATCC 98145;
- 30 (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:19;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;

WO 99/26973

PCT/US98/24944

(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:18 from nucleotide 279 to nucleotide 515; the nucleotide sequence of the full-length protein coding sequence of clone H698_3 deposited under accession number ATCC 98145; 10 or the nucleotide sequence of the mature protein coding sequence of clone H698_3 deposited under accession number ATCC 98145. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone H698_3 deposited under accession number ATCC 98145.

Other embodiments provide the gene corresponding to the cDNA sequences of 15 SEQ ID NO:17 and SEQ ID NO:18.

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: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 H698_3 deposited under accession number ATCC 98145;

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

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:21;
- 30 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 199 to nucleotide 1155;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 304 to nucleotide 1155;

WO 99/26973

PCT/US98/24944

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone H963_20 deposited under accession number ATCC 98145;

5 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone H963_20 deposited under accession number ATCC 98145;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H963_20 deposited under accession number ATCC 98145;

10 (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H963_20 deposited under accession number ATCC 98145;

(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;

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

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

20 (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 199 to nucleotide 1155; the nucleotide sequence of SEQ ID NO:21 from nucleotide 304 to nucleotide 1155; the nucleotide sequence of the full-length protein coding sequence of clone H963_20 deposited under accession number ATCC 98145; or the
25 nucleotide sequence of the mature protein coding sequence of clone H963_20 deposited under accession number ATCC 98145. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone H963_20 deposited under accession number ATCC 98145. In yet other preferred
30 embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22 from amino acid 19 to amino acid 84.

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

WO 99/26973

PCT/US98/24944

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;
- 5 (b) the amino acid sequence of SEQ ID NO:22 from amino acid 19 to amino acid 84;
- (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 H963_20 deposited under accession number ATCC 98145;
- 10 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 19 to amino acid 84.

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

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

- (a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and
- (b) purifying the protein from the culture.
- 20 The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

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

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

30

BRIEF DESCRIPTION OF THE DRAWINGS

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

WO 99/26973

PCT/US98/24944

DETAILED DESCRIPTIONISOLATED 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
5 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
10 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
15 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.

20 Clone "AY421_2"

A polynucleotide of the present invention has been identified as clone "AY421_2". AY421_2 was isolated from a human adult retina 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
25 analysis of the amino acid sequence of the encoded protein. AY421_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AY421_2 protein").

The nucleotide sequence of AY421_2 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the
30 predicted amino acid sequence of the AY421_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2. Amino acids 186 to 198 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 199, or are a transmembrane domain.

WO 99/26973

PCT/US98/24944

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AY421_2 should be approximately 1500 bp.

The nucleotide sequence disclosed herein for AY421_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AY421_2 demonstrated at least some similarity with sequences identified as AA016992 (ze33d02.r1 Soares retina N2b4HR Homo sapiens cDNA clone 360771 5' similar to WP T06D8.5 CE02326 YER141W), H60299 (yr41b09.r1 Homo sapiens cDNA clone 207833 5'), L38643 (Saccharomyces cerevisiae cytochrome oxidase assembly), N25978 (yx88b04.s1 Homo sapiens cDNA clone 268783 3'), and R59851 (yh07a09.r1 Homo sapiens cDNA). The predicted amino acid sequence disclosed herein for AY421_2 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AY421_2 protein demonstrated at least some similarity to sequences identified as L38643 (YSCCOX15A_1 cytochrome oxidase assembly factor [Saccharomyces cerevisiae]) and Z49130 (CET06D8_5 T06D8.5 [Caenorhabditis elegans]). Based upon sequence similarity, AY421_2 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts six potential transmembrane domains within the AY421_2 protein sequence, centered around amino acids 80, 193, 237, 274, 336, and 376 of SEQ ID NO:2.

Clone "BV278_2"

A polynucleotide of the present invention has been identified as clone "BV278_2". BV278_2 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. BV278_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BV278_2 protein").

The nucleotide sequence of BV278_2 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 BV278_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BV278_2 should be approximately 2300 bp.

WO 99/26973

PCT/US98/24944

The nucleotide sequence disclosed herein for BV278_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BV278_2 demonstrated at least some similarity with sequences identified as AA359704 (EST68845 Fetal lung II Homo sapiens cDNA 5' end). Based upon
 5 sequence similarity, BV278_2 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the BV278_2 protein sequence centered around amino acid 19 of SEQ ID NO:4.

10 Clone "C544_1"

A polynucleotide of the present invention has been identified as clone "C544_1". C544_1 was isolated from a human adult blood (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
 15 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. C544_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "C544_1 protein").

The nucleotide sequence of C544_1 as presently determined is reported in SEQ ID
 20 NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the C544_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone C544_1 should be approximately 1250 bp.

25 The nucleotide sequence disclosed herein for C544_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. C544_1 demonstrated at least some similarity with sequences identified as AA029713 (ze95f03.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 366749 3'), T53653 (ya98b10.s1 Homo sapiens cDNA clone 69691 3'), T85425
 30 (yd76d07.r1 Homo sapiens cDNA clone 114157 5'), and Z97634 (Human DNA sequence *** SEQUENCING IN PROGRESS *** from clone 367G8; HTGS phase 1). Based upon sequence similarity, C544_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts seven potential transmembrane domains within the C544_1 protein sequence, centered around amino

WO 99/26973

PCT/US98/24944

acids 80, 110, 150, 170, 190, 220, and 260 of SEQ ID NO:6. C544_1 protein also contains an EGF domain motif around amino acid 50 of SEQ ID NO:6. A single EGF domain has been shown to exist in other proteins including, but not limited to, human teratocarcinoma-derived growth factor 1, tissue plasminogen activator (TPA), and
5 coagulation factors VII, IX, and X. A common feature of EGF repeats is that they are found in the extracellular domain of membrane-bound proteins or in proteins known to be secreted.

Clone "CC332_33"

10 A polynucleotide of the present invention has been identified as clone "CC332_33". CC332_33 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. CC332_33 is a full-length
15 clone, including the entire coding sequence of a secreted protein (also referred to herein as "CC332_33 protein").

The nucleotide sequence of CC332_33 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 CC332_33 protein corresponding to the foregoing
20 nucleotide sequence is reported in SEQ ID NO:8. Amino acids 150 to 162 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 163, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CC332_33 should be approximately 4400 bp.

25 The nucleotide sequence disclosed herein for CC332_33 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CC332_33 demonstrated at least some similarity with sequences identified as N63467 (yy61d06.s1 Homo sapiens cDNA clone 278027 3'). Based upon sequence similarity, CC332_33 proteins and each similar protein or peptide may share at
30 least some activity. The TopPredII computer program predicts a potential transmembrane domain within the CC332_33 protein sequence, centered around amino acid 10 of SEQ ID NO:8, which could also function as a secretory signal sequence.

WO 99/26973

PCT/US98/24944

Clone "CC365_40"

A polynucleotide of the present invention has been identified as clone "CC365_40". CC365_40 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
5 identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CC365_40 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CC365_40 protein").

The nucleotide sequence of the 5' portion of CC365_40 as previously determined
10 is reported in SEQ ID NO:9. The predicted reading frame for the coding region of SEQ ID NO:9 is indicated in SEQ ID NO:10. The predicted amino acid sequence of the CC365_40 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10. Amino acids 29 to 41 of SEQ ID NO:10 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 42. Due to the
15 hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the CC365_40 protein. Additional nucleotide sequence from the 3' portion of CC365_40, including the polyA tail, is reported in SEQ ID NO:11.

The nucleotide sequence of CC365_40 as presently determined is reported in SEQ
20 ID NO:32, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CC365_40 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:33. Amino acids 29 to 41 of SEQ ID NO:33 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 42. Due to the hydrophobic nature
25 of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the CC365_40 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CC365_40 should be approximately 1380 bp.

30 The nucleotide sequence disclosed herein for CC365_40 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CC365_40 demonstrated at least some similarity with sequences identified as AA799783 (EST189280 Normalized rat heart, Bento Soares Rattus sp. cDNA clone RHEAF28 3' end, mRNA sequence), H33410 (EST109372 Rattus sp. cDNA 5' end),

WO 99/26973

PCT/US98/24944

and W21840 (58b3 Human retina cDNA Tsp509I-cleaved sublibrary Homo sapiens cDNA). The predicted amino acid sequence disclosed herein for CC365_40 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CC365_40 protein demonstrated at least some similarity
5 to sequences identified as U13625 (cytochrome b [Pezoporus wallicus]). Based upon sequence similarity, CC365_40 proteins and each similar protein or peptide may share at least some activity.

Clone "CG68_4"

10 A polynucleotide of the present invention has been identified as clone "CG68_4". CG68_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. CG68_4 is a full-length clone,
15 including the entire coding sequence of a secreted protein (also referred to herein as "CG68_4 protein").

The nucleotide sequence of CG68_4 as presently determined is reported in SEQ ID NO:12. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CG68_4 protein corresponding to the foregoing
20 nucleotide sequence is reported in SEQ ID NO:13.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CG68_4 should be approximately 1080 bp.

The predicted amino acid sequence disclosed herein for CG68_4 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX
25 search protocol. The predicted CG68_4 protein demonstrated at least some similarity to sequences identified as M29854 (interleukin 4 receptor (IL-4) precursor). Based upon sequence similarity, CG68_4 proteins and each similar protein or peptide may share at least some activity.

30 Clone "D329_1"

A polynucleotide of the present invention has been identified as clone "D329_1". D329_1 was isolated from a human adult blood (peripheral blood mononuclear cells treated with concanavalin A and phorbol myristate acetate) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or

WO 99/26973

PCT/US98/24944

was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. D329_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "D329_1 protein").

5 The nucleotide sequence of the 5' portion of D329_1 as presently determined is reported in SEQ ID NO:14. What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:15. The predicted amino acid sequence of the D329_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:15. Additional nucleotide sequence from the 3' portion of D329_1, including
10 the polyA tail, is reported in SEQ ID NO:16.

 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone D329_1 should be approximately 3100 bp.

 The nucleotide sequence disclosed herein for D329_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and
15 FASTA search protocols. D329_1 demonstrated at least some similarity with sequences identified as W46599 (zc32g12.r1 Soares senescent fibroblasts NbHSF Homo sapiens cDNA). The predicted amino acid sequence disclosed herein for D329_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted D329_1 protein demonstrated at least some similarity to
20 sequences identified as U40941 (coded for by C. elegans cDNA CEESB82F). Based upon sequence similarity, D329_1 proteins and each similar protein or peptide may share at least some activity.

Clone "H698_3"

25 A polynucleotide of the present invention has been identified as clone "H698_3". H698_3 was isolated from a human adult blood (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
30 transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. H698_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "H698_3 protein").

 The nucleotide sequence of the 5' portion of H698_3 as presently determined is reported in SEQ ID NO:17. An additional internal nucleotide sequence from H698_3 as

WO 99/26973

PCT/US98/24944

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 such internal sequence is reported in SEQ ID NO:19. Additional nucleotide sequence from the 3' portion of H698_3, including the polyA tail, is reported in SEQ ID NO:20.

5 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone H698_3 should be approximately 1400 bp.

 The nucleotide sequence disclosed herein for H698_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. H698_3 demonstrated at least some similarity with sequences
 10 identified as N69846 (za67e04.s1 Homo sapiens cDNA clone 297630 3' similar to SW RT05_YEAST P33759 PROBABLE MITOCHONDRIAL 40S RIBOSOMAL PROTEIN S5), W36396 (mb75e09.r1 Soares mouse p3NMF19.5 Mus musculus cDNA clone 335272 5'), and W81295 (zd85h08.r1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 347487 5'). The predicted amino acid sequence disclosed herein for H698_3 was searched against
 15 the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted H698_3 protein demonstrated at least some similarity to sequences identified as L20296 (homology with a procaryotic 30S ribosomal protein S5 [Saccharomyces cerevisiae]) and Z69727 (unknown [Schizosaccharomyces pombe]). Based upon sequence similarity, H698_3 proteins and each similar protein or peptide may share
 20 at least some activity. H698_3 shares sequence similarity with several other ribosomal proteins and with polynucleotide sequences that encode ribosomal proteins or proteins similar to ribosomal proteins.

Clone "H963_20"

25 A polynucleotide of the present invention has been identified as clone "H963_20". H963_20 was isolated from a human adult blood (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
 30 transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. H963_20 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "H963_20 protein").

 The nucleotide sequence of H963_20 as presently determined is reported in SEQ ID NO:21. What applicants presently believe to be the proper reading frame and the

WO 99/26973

PCT/US98/24944

predicted amino acid sequence of the H963_20 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:22. Amino acids 23 to 35 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 36, or are a transmembrane domain.

5 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone H963_20 should be approximately 1240 bp.

The nucleotide sequence disclosed herein for H963_20 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. H963_20 demonstrated at least some similarity with sequences
10 identified as AA184698 (mt58f09.r1 Soares 2NbMT Mus musculus cDNA clone 634121 5' similar to TR G285995 G285995 ORF, COMPLETE CDS.). The predicted amino acid sequence disclosed herein for H963_20 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted H963_20 protein demonstrated at least some similarity to sequences identified as D13626
15 (KIAA0001 [Homo sapiens]), U33447 (putative G-protein-coupled receptor [Homo sapiens]), and W04246 (Human G-protein coupled receptor GPR3). Based upon sequence similarity, H963_20 proteins and each similar protein or peptide may share at least some activity.

20 Deposit of Clones

Clones AY421_2, BV278_2, C544_1, CC332_33, CC365_40, CG68_4, D329_1, H698_3, and H963_20 were deposited on August 22, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the accession number ATCC 98145, from which each clone comprising a particular
25 polynucleotide is obtainable. 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
30 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. 1. 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

WO 99/26973

PCT/US98/24944

(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 be
 5 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.

Bacterial cells containing a particular clone can be obtained from the composite
 10 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 oligonucleotide probe that was used to isolate each full-length clone is identified below,
 15 and should be most reliable in isolating the clone of interest.

<u>Clone</u>	<u>Probe Sequence</u>
AY421_2	SEQ ID NO:23
BV278_2	SEQ ID NO:24
20 C544_1	SEQ ID NO:25
CC332_33	SEQ ID NO:26
CC365_40	SEQ ID NO:27
CG68_4	SEQ ID NO:28
D329_1	SEQ ID NO:29
25 H698_3	SEQ ID NO:30
H963_20	SEQ ID NO:31

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
 30 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:

WO 99/26973

PCT/US98/24944

- (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).
- 5 The oligonucleotide should preferably be labeled with γ -³²P ATP (specific activity 6000 Ci/mmole) 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
- 10 by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be

15 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 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other

20 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

25 NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at 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

30 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.

WO 99/26973

PCT/US98/24944

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
5 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
10 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
15 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
20 (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. "Corresponding genes" are the regions of the genome that are
25 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
30 sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding

WO 99/26973

PCT/US98/24944

sequences, if any, present in the genome of the organism from which the gene was isolated.

The chromosomal location corresponding to the polynucleotide sequences disclosed herein may also be determined, for example by hybridizing appropriately
5 labeled polynucleotides of the present invention to chromosomes *in situ*. It may also be possible to determine the corresponding chromosomal location for a disclosed polynucleotide by identifying significantly similar nucleotide sequences in public databases, such as expressed sequence tags (ESTs), that have already been mapped to particular chromosomal locations. For at least some of the polynucleotide sequences
10 disclosed herein, public database sequences having at least some similarity to the polynucleotide of the present invention have been listed by database accession number. Searches using the GenBank accession numbers of these public database sequences can then be performed at an Internet site provided by the National Center for Biotechnology Information having the address <http://www.ncbi.nlm.nih.gov/UniGene/>, in order to
15 identify "UniGene clusters" of overlapping sequences. Many of the "UniGene clusters" so identified will already have been mapped to particular chromosomal sites.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense
20 polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* 15(7): 250-254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* 62(1): 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed
25 herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein).
30 In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of

WO 99/26973

PCT/US98/24944

transposable elements (Plasterk, 1992, *Bioessays* 14(9): 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90(16): 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614,396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information. For example, the TopPredII computer program can be used to predict the location of transmembrane domains in an amino acid sequence, domains which are described by the location of the center of the transmembrane domain, with at least ten transmembrane amino acids on each side of the reported central residue(s).

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 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 of the disclosed proteins.

In particular, sequence identity may be determined using WU-BLAST (Washington University BLAST) version 2.0 software, which builds upon WU-BLAST

WO 99/26973

PCT/US98/24944

version 1.4, which in turn is based on the public domain NCBI-BLAST version 1.4 (Altschul and Gish, 1996, Local alignment statistics, Doolittle *ed.*, *Methods in Enzymology* **266**: 460-480; Altschul *et al.*, 1990, Basic local alignment search tool, *Journal of Molecular Biology* **215**: 403-410; Gish and States, 1993, Identification of protein coding
5 regions by database similarity search, *Nature Genetics* **3**: 266-272; Karlin and Altschul, 1993, Applications and statistics for multiple high-scoring segments in molecular sequences, *Proc. Natl. Acad. Sci. USA* **90**: 5873-5877; all of which are incorporated by reference herein). WU-BLAST version 2.0 executable programs for several UNIX platforms can be downloaded from <ftp://blast.wustl.edu/blast/executables>. The complete
10 suite of search programs (BLASTP, BLASTN, BLASTX, TBLASTN, and TBLASTX) is provided at that site, in addition to several support programs. WU-BLAST 2.0 is copyrighted and may not be sold or redistributed in any form or manner without the express written consent of the author; but the posted executables may otherwise be freely used for commercial, nonprofit, or academic purposes. In all search programs in the suite
15 -- BLASTP, BLASTN, BLASTX, TBLASTN and TBLASTX -- the gapped alignment routines are integral to the database search itself, and thus yield much better sensitivity and selectivity while producing the more easily interpreted output. Gapping can optionally be turned off in all of these programs, if desired. The default penalty (Q) for a gap of length one is Q=9 for proteins and BLASTP, and Q=10 for BLASTN, but may be changed to any
20 integer value including zero, one through eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. The default per-residue penalty for extending a gap (R) is R=2 for proteins and BLASTP, and R=10 for BLASTN, but may be changed to any integer value including zero, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one
25 through one hundred, etc. Any combination of values for Q and R can be used in order to align sequences so as to maximize overlap and identity while minimizing sequence gaps. The default amino acid comparison matrix is BLOSUM62, but other amino acid comparison matrices such as PAM can be utilized.

Species homologues of the disclosed polynucleotides and proteins are also
30 provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or

WO 99/26973

PCT/US98/24944

polynucleotide. Preferably, polynucleotide species homologues have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, and protein species homologues have at least 30% sequence identity (more preferably, at least 45% identity; most preferably at least 60% identity) with the given protein, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides or the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Species homologues 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. Preferably, species homologues are those isolated from mammalian species. Most preferably, species homologues are those isolated from certain mammalian species such as, for example, *Pan troglodytes*, *Gorilla gorilla*, *Pongo pygmaeus*, *Hylobates concolor*, *Macaca mulatta*, *Papio papio*, *Papio hamadryas*, *Cercopithecus aethiops*, *Cebus capucinus*, *Aotus trivirgatus*, *Sanguinus oedipus*, *Microcebus murinus*, *Mus musculus*, *Rattus norvegicus*, *Cricetulus griseus*, *Felis catus*, *Mustela vison*, *Canis familiaris*, *Oryctolagus cuniculus*, *Bos taurus*, *Ovis aries*, *Sus scrofa*, and *Equus caballus*, for which genetic maps have been created allowing the identification of syntenic relationships between the genomic organization of genes in one species and the genomic organization of the related genes in another species (O'Brien and Seuánez, 1988, *Ann. Rev. Genet.* 22: 323-351; O'Brien *et al.*, 1993, *Nature Genetics* 3:103-112; Johansson *et al.*, 1995, *Genomics* 25: 682-690; Lyons *et al.*, 1997, *Nature Genetics* 15: 47-56; O'Brien *et al.*, 1997, *Trends in Genetics* 13(10): 393-399; Carver and Stubbs, 1997, *Genome Research* 7:1123-1137; all of which are incorporated by reference herein).

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotides which also encode proteins which are identical or have significantly similar sequences to those encoded by the disclosed polynucleotides. Preferably, allelic variants have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps. Allelic variants may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from individuals of the appropriate species.

WO 99/26973

PCT/US98/24944

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
5 highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent 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.

WO 99/26973

PCT/US98/24944

	Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) [‡]	Hybridization Temperature and Buffer [†]	Wash Temperature and Buffer [†]
5	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
10	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
15	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).

WO 99/26973

PCT/US98/24944

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.,
5 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
10 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
15 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
20 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
25 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.

30 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

WO 99/26973

PCT/US98/24944

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. 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

WO 99/26973

PCT/US98/24944

methyle or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance
5 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 are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

10 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 virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith,
15 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
20 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, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another
25 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
30 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.

WO 99/26973

PCT/US98/24944

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

10 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
15 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"
20 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
25 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.

30 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

WO 99/26973

PCT/US98/24944

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

WO 99/26973

PCT/US98/24944

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
5 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
10 7, Immunologic studies in Humans); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bertagnolli et al., *J. Immunol.* 145:1706-1712, 1990; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Bertagnolli, et al., *J. Immunol.* 149:3778-3783, 1992; Bowman et al., *J. Immunol.* 152: 1756-1761, 1994.

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

Assays for proliferation and differentiation of hematopoietic and lymphopoietic
20 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*
25 336:690-692, 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*
30 *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.

WO 99/26973

PCT/US98/24944

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

Immune Stimulating or Suppressing Activity

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

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for

WO 99/26973

PCT/US98/24944

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 regulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune 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 matter 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

WO 99/26973

PCT/US98/24944

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 erythmatosis 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

WO 99/26973

PCT/US98/24944

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

Alternatively, anti-viral immune responses may be enhanced in an infected patient
5 by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic
10 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*.

In another application, up regulation or enhancement of antigen function
15 (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.
20 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
25 to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II
30 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 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.

WO 99/26973

PCT/US98/24944

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.

10 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.

25 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.

30 Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter

WO 99/26973

PCT/US98/24944

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

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those
 5 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
 10 et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

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

Assays for proteins that influence early steps of T-cell commitment and
 20 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

25 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,
 30 thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent

WO 99/26973

PCT/US98/24944

myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of

5 hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or

10 *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

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

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

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

20 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359,

25 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 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,

30

WO 99/26973

PCT/US98/24944

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

Tissue Growth Activity

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

A protein of the present invention, which induces cartilage and/or bone growth
10 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. *De novo* bone formation induced by an osteogenic agent contributes to the repair of
15 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
20 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.

25 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
30 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

WO 99/26973

PCT/US98/24944

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
5 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
10 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
15 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
20 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
25 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)
30 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.

WO 99/26973

PCT/US98/24944

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
5 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
10 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
15 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
20 activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and 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
25 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,
30 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:

WO 99/26973

PCT/US98/24944

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.

5

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.

10 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

15 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

20 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

25 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

30 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.

WO 99/26973

PCT/US98/24944

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).

10 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 15 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.

30 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

WO 99/26973

PCT/US98/24944

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, 5 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 10 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 15 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 20 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 25 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.

30 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

WO 99/26973

PCT/US98/24944

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.

5 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
10 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
15 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.

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
20 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.

Additionally, proteins of the present invention with cadherin activity, and
25 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
30 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

WO 99/26973

PCT/US98/24944

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
 5 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.

10 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 antibody-dependent cell-mediated cytotoxicity (ADCC)). A protein may exhibit its tumor
 15 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.

20

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting
 25 (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism,
 30 anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting

WO 99/26973

PCT/US98/24944

differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

10 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
15 "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11,
20 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,
25 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.

30 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.

WO 99/26973

PCT/US98/24944

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 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.

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 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 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

WO 99/26973

PCT/US98/24944

administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

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

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred

WO 99/26973

PCT/US98/24944

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
5 pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone.
10 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
15 increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μ g to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1 μ g to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the
20 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
25 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
30 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

WO 99/26973

PCT/US98/24944

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
5 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
10 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
15 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
20 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
25 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
30 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-

WO 99/26973

PCT/US98/24944

aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns.

- 5 In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, 10 ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 15 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

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

- 25 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.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering 30 various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in

WO 99/26973

PCT/US98/24944

the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline
5 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, without
10 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.

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

WO 99/26973

PCT/US98/24944

SEQUENCE LISTING

<110> Jacobs, Kenneth
 McCoy, John M.
 LaVallie, Edward R.
 Collins-Racie, Lisa A.
 Evans, Cheryl
 Merberg, David
 Treacy, Maurice
 Spaulding, Vikki
 Genetics Institute, Inc.

<120> SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

<130> 6009A-PCT

<140>

<141>

<160> 33

<170> PatentIn Ver. 2.0

<210> 1

<211> 1673

<212> DNA

<213> Homo sapiens

<400> 1

```

ggagaccaca gagccctggg ttgtggaaga ggtggctggt ccctgtcatc agtatgcagc 60
gattgctctt tccgccgttg agggccttga aggggaggca gtatctgccg ctectggctc 120
ctagggcagc gcctagagca cagtgtgatt gcatcaggcg ccctttgagg ccagggcaat 180
acagcaccat ctctgaagta gctttgcaat ctggaagggg tacagtgtcc ctccctcaa 240
aggctgctga gcggttggtg ggccgatggc tcctggtctg cagtggaaaca gtggctggag 300
cagttattct tgggtggagta actagggtga cagagtctgg cctctcgatg gtagattggc 360
atttaataaa ggagatgaag ccacctacaa gccaaagagga atgggaagca gaattccaaa 420
gataccagca atttccagaa tttaaaatct tgaatcatga tatgacactg acagaattca 480
agttcatctg gtacatggag tactcacacc gaatgtgggg tcgccttgta ggccttgta 540
acatcctgcc tgctgcctac ttttgagaa agggctggct cagccgtggc atgaaaggac 600
gtgttcttgc cctctgtggc ctctgtctgt tccaggggtc gttgggatgg tatatggtga 660
aaagtggact agaagaaaaa tcagactccc atgacatccc tcgggtcagt cagtaccgcc 720
ttgctgccc cctgggatca gccctggttc tttattgtgc cagcttggtg acctactgt 780
cactgctact ccctccgcac aagttgcttg aaaccaccca actcctacag ttgagacgat 840
ttgctcatgg aacagcaggt ctggtgttcc ttacggccct ctacaggggt tttgtggcag 900
ggctagatgc tgggcttggt tataactcct tccccaaaat gggagaatcc tggatcccgg 960
aggacctctt taccttctcc cccatcctga ggaatgtttt tgagaatccc accatggtgc 1020
agtttgatca ccggattctg ggaatcactt cagtcactgc cattacagtg ctctacttcc 1080
tctctcgga aattcccctt cctaaaagga ccaaatggc agcagtgact ctgctggctt 1140
tggcgtatac acaggtgggc ttgggcatca gcacgtgct gatgtatgtc ccaactcctc 1200
tggccgccac tcaccagtca ggctccttgg ctttgctcac tgggtgctctt tggctgatga 1260
atgaactccg aaaagtccca aatgattct taaaggacca gcctcctggg actgtgactg 1320
cttttgaaag ctcttcaaag atcataaaaa cttgggcttt tctacaaaat gaccttgaca 1380
taccaagtgg tttccaaatg gtcaacttac ttaaaaatct tttcctgttt tgagatagtc 1440
actggatcaa gaatgcatta agtgtggtta ccctaaatgt tcccttttaa atctgctttt 1500
catgttgaaa atcagtttta atgtagagaa agaaatgtct gccatttgct gcttaaaaaa 1560
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 1673

```

<210> 2

<211> 410

WO 99/26973

PCT/US98/24944

<212> PRT

<213> Homo sapiens

<400> 2

```

Met Gln Arg Leu Leu Phe Pro Pro Leu Arg Ala Leu Lys Gly Arg Gln
  1              5              10              15

Tyr Leu Pro Leu Leu Ala Pro Arg Ala Ala Pro Arg Ala Gln Cys Asp
          20              25              30

Cys Ile Arg Arg Pro Leu Arg Pro Gly Gln Tyr Ser Thr Ile Ser Glu
          35              40              45

Val Ala Leu Gln Ser Gly Arg Gly Thr Val Ser Leu Pro Ser Lys Ala
          50              55              60

Ala Glu Arg Val Val Gly Arg Trp Leu Leu Val Cys Ser Gly Thr Val
          65              70              75              80

Ala Gly Ala Val Ile Leu Gly Gly Val Thr Arg Leu Thr Glu Ser Gly
          85              90              95

Leu Ser Met Val Asp Trp His Leu Ile Lys Glu Met Lys Pro Pro Thr
          100             105             110

Ser Gln Glu Glu Trp Glu Ala Glu Phe Gln Arg Tyr Gln Gln Phe Pro
          115             120             125

Glu Phe Lys Ile Leu Asn His Asp Met Thr Leu Thr Glu Phe Lys Phe
          130             135             140

Ile Trp Tyr Met Glu Tyr Ser His Arg Met Trp Gly Arg Leu Val Gly
          145             150             155             160

Leu Val Asn Ile Leu Pro Ala Ala Tyr Phe Trp Arg Lys Gly Trp Leu
          165             170             175

Ser Arg Gly Met Lys Gly Arg Val Leu Ala Leu Cys Gly Leu Val Cys
          180             185             190

Phe Gln Gly Leu Leu Gly Trp Tyr Met Val Lys Ser Gly Leu Glu Glu
          195             200             205

Lys Ser Asp Ser His Asp Ile Pro Arg Val Ser Gln Tyr Arg Leu Ala
          210             215             220

Ala His Leu Gly Ser Ala Leu Val Leu Tyr Cys Ala Ser Leu Trp Thr
          225             230             235             240

Ser Leu Ser Leu Leu Leu Pro Pro His Lys Leu Pro Glu Thr His Gln
          245             250             255

Leu Leu Gln Leu Arg Arg Phe Ala His Gly Thr Ala Gly Leu Val Phe
          260             265             270

Leu Thr Ala Leu Ser Gly Ala Phe Val Ala Gly Leu Asp Ala Gly Leu
          275             280             285

Val Tyr Asn Ser Phe Pro Lys Met Gly Glu Ser Trp Ile Pro Glu Asp
          290             295             300

```

WO 99/26973

PCT/US98/24944

Leu Phe Thr Phe Ser Pro Ile Leu Arg Asn Val Phe Glu Asn Pro Thr
 305 310 315 320

Met Val Gln Phe Asp His Arg Ile Leu Gly Ile Thr Ser Val Thr Ala
 325 330 335

Ile Thr Val Leu Tyr Phe Leu Ser Arg Lys Ile Pro Leu Pro Lys Arg
 340 345 350

Thr Lys Met Ala Ala Val Thr Leu Leu Ala Leu Ala Tyr Thr Gln Val
 355 360 365

Gly Leu Gly Ile Ser Thr Leu Leu Met Tyr Val Pro Thr Pro Leu Ala
 370 375 380

Ala Thr His Gln Ser Gly Ser Leu Ala Leu Leu Thr Gly Ala Leu Trp
 385 390 395 400

Leu Met Asn Glu Leu Arg Lys Val Pro Lys
 405 410

<210> 3

<211> 2190

<212> DNA

<213> Homo sapiens

<400> 3

taggccatga aggccggcct tcatggccta aaatgtttca agaacaacac attgatattgt 60
 ggaaatattc tataaggttt tcttttgttc ccttagaatt cattggaggg atgcagtaaa 120
 aactgtagta gaaaccttga aacacccata tgtgaaaagg tctgtggaaa ttgaggcctc 180
 tacattaaaa gtgcagaacc aactgtttta cagtcaaagt gctaggaaac ctgataggat 240
 acttcccttt ggcacaaaaa caccctgggt gctacatata ggagcatgac ctttggtgaa 300
 tatgtggcac taattttttt taccttaatc atattcttgt caagtaggca acccattgcc 360
 ccttgagac cacaccagcc ctgtaagttc tcaccagcag catggagatt aggaagaggg 420
 gctgctgtga ccaggagata cacacggcct taagtaactg agagcctaaa gaaagtaacc 480
 cagggagtcc ggtccagttt taatatttgt ggatttggtg tcacacacat tgtttagtcc 540
 tgaaactaaa acctatttta taaatagtag ggttaattcc tcgaaacaat ttctttatta 600
 ataatgtcc tgtgggttta gaaatatcag gtaaatattt gaatacagaa tgatgattgc 660
 aattactgtt acaagcgtga aacacaaact tcagatcaaa tctagagttg cttcatttaa 720
 tgcattgctag caacagcctt aactttggat tcagttattt gaaacacttt tccggcatct 780
 ttccctttct aatgttgtgg ggtggaaacc ggatggcaaa tcaactgtgag ccggatacct 840
 cagcacagtc caccttgtgt gtgacttcac aaatggggga cttcacaat ggggtaactg 900
 aatgttatta ctttcaaatt ttgacatgga gcattatgat caaggaaatg gagctgcctt 960
 atacattaaa cccgtgattt aatcctattg acattttcat agccatgcct ccagatttta 1020
 tctttttggc aaaattctga ttccacagtt tggctctgatt gaaataaata ttccctggac 1080
 gtctggctaa aaattttgct aacaatccca gaggtgccat tttcttatta ataaatttca 1140
 ttggagcctt atttcttact atattcaatt tcgtttcaaa cctgcaagtc cctgggatgg 1200
 tcccacgact agggcctgca catttcttac aatggcaaag cattttttta aatttagggg 1260
 caggttgaaa aattctagga ctaattctgt agagaggagg gactgttaac taacgtgagt 1320
 ggggacagag gagtaggtta ccacatttgg agcagtaata gatgcaaacg atgtaaattt 1380
 gaaatttgcc cttttagtta aagaaggagc ctgcaaagtc catttctctg ttttcagccc 1440
 tgtcagtcac ccatttagga tgttggtgca gtactgcttg agcagaatgt gtaagaaagt 1500
 aataatgaaa gcaaaagtat gtcagacagt tacttcttcc acatgggttag aggcattgta 1560
 ttttcagcac tgtgtgttac agaaatgtca ggaatggtgt attataacgt gtgcaagata 1620
 atgtcagtgt gcacagaggg tcttttttcc ttatctgatt agtactgtta atgttcaaag 1680
 aataaaaatg gttttacatt tagattctga gatagcaaaa cctgattttt caaccatgac 1740
 ctgcatgaga gaagcatcct aggaagtctt agatcatact tttgagtttt taattttaat 1800
 ttatatagtg tttttttatg tcttaatttt tttgtgaact ggtgtaaatt gttaatgcat 1860

WO 99/26973

PCT/US98/24944

ataagcttgt gtatttttct aaatagtttt gtgattttatt tcttgcccca tatgtaaata 1920
 tttagagtct catttcttgc aaacttattt gaagctgagt tgtgggtttg ggttttgttt 1980
 gtttcttttg ttgcagggtg ggggtggggg tggcagggga gggaggaagg gatttttcta 2040
 cctggagatg gagatatctt gtggttttaa gcaaatgtcc cactgaaagt gattcaaata 2100
 tcaacagaat tatttcaggt taaaacaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2160
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2190

<210> 4

<211> 85

<212> PRT

<213> Homo sapiens

<400> 4

Met His Ala Ser Asn Ser Leu Asn Phe Gly Phe Ser Tyr Leu Lys His
 1 5 10 15

Phe Ser Gly Ile Phe Pro Phe Leu Met Leu Trp Gly Gly Asn Arg Met
 20 25 30

Ala Asn His Cys Glu Pro Asp Thr Ser Ala Gln Ser Thr Leu Cys Val
 35 40 45

Thr Ser Gln Met Gly Asp Phe Thr Asn Gly Val Thr Glu Cys Tyr Tyr
 50 55 60

Phe Gln Ile Leu Thr Trp Ser Ile Met Ile Lys Glu Met Glu Leu Pro
 65 70 75 80

Tyr Thr Leu Asn Pro
 85

<210> 5

<211> 1087

<212> DNA

<213> Homo sapiens

<400> 5

cagagacaga caactggtac ctctccctgc agctcatgtg ccctgagaat gctgaggact 60
 gtgagcaggc tgtggteccac gtggagacca ccttgtagct ggtgccctgt ttgaacgatt 120
 gtggacccta tggccagtgc ctctgctcc gcagacacag ctacctgtat gccagctgca 180
 gctgcaaggc aggctggcgt ggggtggagct gcacggacaa cagcacagcc cagacggtgg 240
 cccagcagag ggcggccaca ctgctgctca cgctcagcaa cctcatgttc ctggccccc 300
 tcgccgtctc agtgccggcg ttcttctctg tggaggcctc cgtctacgcc tacaccatgt 360
 tcttctccac gttctaccac gcctgcgacc agcccgggga ggcgggtgctg tgcctcctca 420
 gctacgacac gctgcagtac tgcgacttct tgggctccgg ggcggccatc tgggtcacca 480
 tcctgtgcat ggcacggctc aagacagtc tgaaatacgt gctgtttctt ctgggtacac 540
 tggctatcgc catgtccttg cagctggacc gcaggggcat gtggaacatg ctggggccct 600
 gcctctttgc ctctgtgatc atggcctcca tgtgggctta ccgctgcggg caccggcgcc 660
 agtgctaccc cacctcgtgg cagcgtggtg ccttctacct cctgcccggc gtctctaygg 720
 cctctgtggg catcgccatc tacacctcca tgatgactag cgacaactac ttactaacia 780
 cccacagcat tcttggcaac atcctgctgg ccgggagcgc agccttgytg ctgccgccac 840
 ctgaccagcc cgccgagccc tggggcctgy tgcagaaat tccctgcca ctatcagatc 900
 tgcaagaacg atcgggagga actgtacgca gtgacgtgac actggcctgg ggacagctgc 960
 tgctctgatg acctcttcag ccaggagctg tatcgagggg gaggcgctg gtccagccyt 1020
 ggacagattg atttccagct gaataaattg gcctagatac cctcaaaaaa aaaaaaaaaa 1080
 aaaaaaa 1087

<210> 6

<211> 310

WO 99/26973

PCT/US98/24944

<212> PRT

<213> Homo sapiens

<220>

<221> UNSURE

<222> (228)

<220>

<221> UNSURE

<222> (279)

<400> 6

Met Cys Pro Glu Asn Ala Glu Asp Cys Glu Gln Ala Val Val His Val
 1 5 10 15

Glu Thr Thr Leu Tyr Leu Val Pro Cys Leu Asn Asp Cys Gly Pro Tyr
 20 25 30

Gly Gln Cys Leu Leu Leu Arg Arg His Ser Tyr Leu Tyr Ala Ser Cys
 35 40 45

Ser Cys Lys Ala Gly Trp Arg Gly Trp Ser Cys Thr Asp Asn Ser Thr
 50 55 60

Ala Gln Thr Val Ala Gln Gln Arg Ala Ala Thr Leu Leu Leu Thr Leu
 65 70 75 80

Ser Asn Leu Met Phe Leu Ala Pro Ile Ala Val Ser Val Arg Arg Phe
 85 90 95

Phe Leu Val Glu Ala Ser Val Tyr Ala Tyr Thr Met Phe Phe Ser Thr
 100 105 110

Phe Tyr His Ala Cys Asp Gln Pro Gly Glu Ala Val Leu Cys Ile Leu
 115 120 125

Ser Tyr Asp Thr Leu Gln Tyr Cys Asp Phe Leu Gly Ser Gly Ala Ala
 130 135 140

Ile Trp Val Thr Ile Leu Cys Met Ala Arg Leu Lys Thr Val Leu Lys
 145 150 155 160

Tyr Val Leu Phe Leu Leu Gly Thr Leu Val Ile Ala Met Ser Leu Gln
 165 170 175

Leu Asp Arg Arg Gly Met Trp Asn Met Leu Gly Pro Cys Leu Phe Ala
 180 185 190

Phe Val Ile Met Ala Ser Met Trp Ala Tyr Arg Cys Gly His Arg Arg
 195 200 205

Gln Cys Tyr Pro Thr Ser Trp Gln Arg Trp Ala Phe Tyr Leu Leu Pro
 210 215 220

Gly Val Ser Xaa Ala Ser Val Gly Ile Ala Ile Tyr Thr Ser Met Met
 225 230 235 240

Thr Ser Asp Asn Tyr Leu Leu Thr Thr His Ser Ile Leu Gly Asn Ile
 245 250 255

WO 99/26973

PCT/US98/24944

Leu Leu Ala Gly Ser Ala Ala Leu Leu Leu Pro Pro Pro Asp Gln Pro
 260 265 270

Ala Glu Pro Trp Gly Leu Xaa Ala Glu Ile Pro Leu Pro Leu Ser Asp
 275 280 285

Leu Gln Glu Arg Ser Gly Gly Thr Val Arg Ser Asp Val Thr Leu Ala
 290 295 300

Trp Gly Gln Leu Leu Leu
 305 310

<210> 7

<211> 4252

<212> DNA

<213> Homo sapiens

<400> 7

cgaacttggt cggggcgcgagg atccccgagag ggaaagtcac aacaaccgca cgaggggagtt 60
 cgactggcga actggaaggc cagcctcct cccgcctgcc cctcagccc tgtggctggg 120
 ggcagagctc agactgtctt ctgaagattg atgtctatct ccttgagctc ttttaattttg 180
 ttgccaatct ggataaacat ggcacaaatc cagcagggag gtccagatga aaaagaaaag 240
 actaccgcac tgaaagattt attatctagg atagatttgg atgaactaat gaaaaaagat 300
 gaaccgcctc ttgattttcc tgataccctg gaaggatttg aatatgcttt taatgaaaag 360
 ggacagttaa gacacataaa aactggggaa ccatttgctt ttaactaccg ggaagattta 420
 cacagatgga accagaaaag ataccgaggt ctaggagaga tcatcacgaa gtatgtatat 480
 gagctcctgg aaaaggattg taatttgaaa aaagtatcta ttccagtaga tgccactgag 540
 agtgaaccaa agagttttat ctttatgagt gaggatgctt tgacaaatcc acagaaactg 600
 atggttttaa ttcattgtag tgggtgtgtc agggcagggc agtgggctag aagacttatt 660
 ataatgaag atctggacag tggcacacag ataccgttta ttaaaagagc tgtggctgaa 720
 ggatatggag taatagtact aaatcccaat gaaaactata ttgaagtaga aaagccgaag 780
 atacacgtac agtcatcatc tgatagttca gatgaaccag cagaaaaacg ggaaagaaaa 840
 gataaagttt ctaaagaaac aaagaagcga cgtgatttct atgagaagta tcgtaacccc 900
 caaagagaaa aagaaatgat gcaattgtat atcagagaaa atggtttctc tgaagaacat 960
 gcaatctatg tttgggatca tttcatagct caggctgctg ctgagaatgt gtttttcgtt 1020
 gctcacagct atggaggact tgcttttgtt gaactgatga ttcaacgaga agccgatgta 1080
 aaaaataagg taactgctgt ggcattgaca gactctgttc acaatgtgtg gcatcaagaa 1140
 gctggcaaaa cgattcgaga atggatgaga gagaactgtt gtaattgggt ctctagctca 1200
 gaaccattag acacatcagt ggagtcacat ctacctgatt gccccgggt ctcagcaggc 1260
 accgaccgtc acgagctaac ttccctggaag agctttccgt ctattttcaa attctttacc 1320
 gaagcctcag aggccaaagc cagctccctg aagccggctg tgacgcgccg ctcccaccgc 1380
 atcaagcacg aagagctgta agaggagcga gcgcgacggg ggaggccgcc ctggcgccacc 1440
 caccgcacg cctcctcact gcttggtgtc agcggactcc cagccctca ttagattgtt 1500
 ttcttcccag agcccagggt cgtgatata acatctaaat agcgttttgc attatttcta 1560
 gatgagtgca actgtcaaag caatatgggt tcaactggtc tgcttcctgc gggctgagcg 1620
 cgggctgagc gctgccagtc agcgtcaca ttaaggctga cagcgccctg cctggctcgg 1680
 ccggcgaagc tctaattgcc ctgaaggaga ccgcgcgggc gctgcgggtc cggcggcgctc 1740
 ggcgcggtcc tagcgccgcg cgtagcggag ccgctgctgc ttccccctcc ttaatcatgt 1800
 ccatctttcc ccgctctcaa ctggagcaaa cttctattcc agacttcaga tttccatttt 1860
 cactagggtt ttccctgagg gcattctatt acccacctct tttttttttt ttttaaggaa 1920
 gtccacaca cactccaaag ccgatttcaa attcagaacc tgaatgccat gatgtaccat 1980
 gtagtttggg gaatgcaaat tgttctctcc ctgttttcat ttcgggacca gaaaaaaaaa 2040
 caactctgca taaaaatcta taaagtactg aatccgcatt actgctgaaa atccttttgc 2100
 cagctaattg tgagagttaa cacaagtctc tgatttcaga agagactgtt aaaacaaaaa 2160
 caatgatggg cagctctttt aagtgtagggt gtgaaggctc cattttcaat ggaatttcca 2220
 actgttatca ctgggattga ctttactttt taaacacata atgtgtactg tgtggcattg 2280
 taatttagat ataacacact taagttttgc tttttaaatc tctctgtgga gaaaggttgt 2340
 tgttaatect ttccagaatg atctattctg agctttcctg gagttaggcc cttctaggga 2400
 gagaattttt ttattgtcat caggaaacga aacctttgtg ctctgcagcc tttttcttct 2460

WO 99/26973

PCT/US98/24944

```

gaaaggctaa gtggggctaa aattatcctt ttagttttct gctttaacaa gaagagaagg 2520
acttggtgtg aaagaatttc ttctctcagt ccaatggtat aatttttagc actccgcttc 2580
ctctgtrggt ttagccctac agtttgaaca attattttta tccagctaag atgtggccaa 2640
cactgtgaaa tacaggagat gttaagggtt tgctgacttt tagattaaaa tcttaaaatt 2700
tcacattata ttttaattac ttgaaaagtt taattaccta gtaaagattg tttctaatag 2760
atgagaacat aaatttaata gttttcatcc ttttttaaag tgtgtgcaac aattaatatg 2820
cctgccttat ttgaggacat gataaaatgt acccaaatg acttcgaact gtctaatagcc 2880
tcagaaaagt aacttaaaat caaccacttc gtgcttaaatt gtttttatat tatgaaccga 2940
tttcaacaag ttttaaagct gttaatatct cattgctgtg ttgacatac aagtacattc 3000
attggttcta tagtcttaat gatgacaaat taaagatggt ttttcagtgc tcaggatatgc 3060
atatattttc gtgttactta agcaaatca actatatagg aggaaaaatc aaaatggcat 3120
tttattcagc taccagatgg cttaaaatga gtaaacccca acaacatcaa gcacatttgt 3180
ctgtgatatt gacccttttt atccaatcat tactatttta gaagtagtgg tgaactgtgt 3240
aaaataatgg tatcttcagc agtggtccgg aatcttagtt gagggacaaa cattccttcc 3300
agtgagagat tcaagaattg atgtgaattg aatatatttt tcaaggattt ataaattgtg 3360
ttgtgttttc agtataagaa aatgttgaca ggaaacaatt ttatagcatt tataaaaaac 3420
caacacttgt gcaatgctaa attggcgaag cttctgcacc tgaattagag cacaataaat 3480
atgctgttta taaaccaaat cactgctatt ccttctctga aatcatctct cctcttttta 3540
aacctttact tatagctaga ataatcact atttaattgc ctctaatact ttaaaactac 3600
tggtatggtta ggcctggttt aactattttat ggagagctat ttgcaaactt aagttgtgta 3660
aatgtaattt ctacttgtga atctgagctg tagcagccca gagggagcta ggcaaactat 3720
tccagaccac caactgataa gtgatcagat tctttgtaat gtaggatttt ttaacctgtt 3780
gattatgggt ttgttgatat aaatgtaata atgttcacct cgattttcct ggagtaacaa 3840
ccagcgttgg tagtagccca cctgcatgag gacggccagt gttaacaata tttttgttct 3900
gatcttcttc cccatttttg tttcctcaaa caggttttta ggagagtgga gatttaaagt 3960
caggatgtgg cctttttatt ttaattatat acttaattct tagaacaagt agaatgggaa 4020
aggagtgact gataaatcta agattcaaaa tagtcccgtc gaaacttaaa ggccagatta 4080
ttgctttgga gctttctata ggtactagcc atcccgtcgt taaatgtttt catggatatt 4140
tgaaaagaag accatgtacc ttttaataact gttcttttct cgagtttctg cctcgtgctt 4200
tgacctggat tgcattatta ttgtttatgc gaagtaaaaa aaaaaaaaaa aa 4252

```

<210> 8

<211> 416

<212> PRT

<213> Homo sapiens

<400> 8

```

Met Ser Ile Ser Leu Ser Ser Leu Ile Leu Leu Pro Ile Trp Ile Asn
  1             5             10            15

```

```

Met Ala Gln Ile Gln Gln Gly Gly Pro Asp Glu Lys Glu Lys Thr Thr
      20             25             30

```

```

Ala Leu Lys Asp Leu Leu Ser Arg Ile Asp Leu Asp Glu Leu Met Lys
      35             40             45

```

```

Lys Asp Glu Pro Pro Leu Asp Phe Pro Asp Thr Leu Glu Gly Phe Glu
      50             55             60

```

```

Tyr Ala Phe Asn Glu Lys Gly Gln Leu Arg His Ile Lys Thr Gly Glu
      65             70             75             80

```

```

Pro Phe Val Phe Asn Tyr Arg Glu Asp Leu His Arg Trp Asn Gln Lys
      85             90             95

```

```

Arg Tyr Glu Ala Leu Gly Glu Ile Ile Thr Lys Tyr Val Tyr Glu Leu
      100            105            110

```

```

Leu Glu Lys Asp Cys Asn Leu Lys Lys Val Ser Ile Pro Val Asp Ala
      115            120            125

```

WO 99/26973

PCT/US98/24944

Thr Glu Ser Glu Pro Lys Ser Phe Ile Phe Met Ser Glu Asp Ala Leu
 130 135 140
 Thr Asn Pro Gln Lys Leu Met Val Leu Ile His Gly Ser Gly Val Val
 145 150 155 160
 Arg Ala Gly Gln Trp Ala Arg Arg Leu Ile Ile Asn Glu Asp Leu Asp
 165 170 175
 Ser Gly Thr Gln Ile Pro Phe Ile Lys Arg Ala Val Ala Glu Gly Tyr
 180 185 190
 Gly Val Ile Val Leu Asn Pro Asn Glu Asn Tyr Ile Glu Val Glu Lys
 195 200 205
 Pro Lys Ile His Val Gln Ser Ser Ser Asp Ser Ser Asp Glu Pro Ala
 210 215 220
 Glu Lys Arg Glu Arg Lys Asp Lys Val Ser Lys Glu Thr Lys Lys Arg
 225 230 235 240
 Arg Asp Phe Tyr Glu Lys Tyr Arg Asn Pro Gln Arg Glu Lys Glu Met
 245 250 255
 Met Gln Leu Tyr Ile Arg Glu Asn Gly Ser Pro Glu Glu His Ala Ile
 260 265 270
 Tyr Val Trp Asp His Phe Ile Ala Gln Ala Ala Ala Glu Asn Val Phe
 275 280 285
 Phe Val Ala His Ser Tyr Gly Gly Leu Ala Phe Val Glu Leu Met Ile
 290 295 300
 Gln Arg Glu Ala Asp Val Lys Asn Lys Val Thr Ala Val Ala Leu Thr
 305 310 315 320
 Asp Ser Val His Asn Val Trp His Gln Glu Ala Gly Lys Thr Ile Arg
 325 330 335
 Glu Trp Met Arg Glu Asn Cys Cys Asn Trp Val Ser Ser Ser Glu Pro
 340 345 350
 Leu Asp Thr Ser Val Glu Ser Met Leu Pro Asp Cys Pro Arg Val Ser
 355 360 365
 Ala Gly Thr Asp Arg His Glu Leu Thr Ser Trp Lys Ser Phe Pro Ser
 370 375 380
 Ile Phe Lys Phe Phe Thr Glu Ala Ser Glu Ala Lys Thr Ser Ser Leu
 385 390 395 400
 Lys Pro Ala Val Thr Arg Arg Ser His Arg Ile Lys His Glu Glu Leu
 405 410 415

<210> 9

<211> 436

<212> DNA

<213> Homo sapiens

WO 99/26973

PCT/US98/24944

<220>

<221> unsure

<222> (15)

<220>

<221> unsure

<222> (37)

<220>

<221> unsure

<222> (47)

<400> 9

```

gctttttttt ccacnggtgt ccactcccag gtccaantgc agatttngaa ttcggctttc 60
atggcctagc agttaggaaa gtarcgttat gagttgwact gaaaatgttg attctmtaat 120
ctgccagaaa aggamctgtc ttttcatgca gatttcatat tgtctttgtc cttttcattg 180
cttcttgacc ttcttggcag gtgtcgtca gtttcttctt gtttcccttc ctgtcctctc 240
cacacctgct atcccgtecc actcccatct acctcccggg aagccagccc tgcattgctga 300
gtttgtgacc tgcttcattc ccatttcatt tctagagggt ttagagggtga cctggaaccg 360
ttccctttcc ctctcctacc cctcctctg caacaccaag aggcctggag gggcagacag 420
aaagcagcca gccacg                                     436

```

<210> 10

<211> 116

<212> PRT

<213> Homo sapiens

<220>

<221> UNSURE

<222> (3)

<220>

<221> UNSURE

<222> (10)

<220>

<221> UNSURE

<222> (16)

<400> 10

```

Met Ser Xaa Thr Glu Asn Val Asp Ser Xaa Ile Cys Gln Lys Arg Xaa
  1              5              10              15

```

```

Cys Leu Phe Met Gln Ile Ser Tyr Cys Leu Cys Pro Phe His Cys Phe
      20              25              30

```

```

Leu Thr Phe Leu Ala Gly Val Ala Gln Phe Leu Pro Val Ser Leu Pro
      35              40              45

```

```

Val Leu Ser Thr Pro Ala Ile Pro Ser His Ser His Leu Pro Pro Gly
      50              55              60

```

```

Lys Pro Ala Leu His Ala Glu Phe Val Thr Cys Phe Ile Pro Ile Ser
      65              70              75              80

```

```

Phe Leu Glu Gly Leu Glu Val Thr Trp Asn Arg Ser Leu Ser Leu Ser
      85              90              95

```

```

Tyr Pro Leu Leu Cys Asn Thr Lys Arg Pro Gly Gly Ala Asp Arg Lys

```

WO 99/26973

PCT/US98/24944

100

105

110

Gln Pro Ala Thr
115

<210> 11
<211> 318
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (38)

<220>
<221> unsure
<222> (100)

<220>
<221> unsure
<222> (132)

<220>
<221> unsure
<222> (189)

<220>
<221> unsure
<222> (198)

<220>
<221> unsure
<222> (221)

<220>
<221> unsure
<222> (231)..(232)

<220>
<221> unsure
<222> (236)

<220>
<221> unsure
<222> (243)

<220>
<221> unsure
<222> (245)

<220>
<221> unsure
<222> (250)

<400> 11
gtatttttct ggggatagag ggggtggggt tagggatntc cctgtagatt agttccagaa 60
tggggtgtct gtatatactg tattaatagg catgtttgan tttcgtaaag ggacgtagt 120
agctgctgca gntcctgttt ggaaacccca tgaacaattc ccagtttttt gtaagtgtca 180
gtgcgagana catttgantc ttgtgtttgt atctcctttt natgattgct nnaccnacc 240

WO 99/26973

PCT/US98/24944

atntnttttn ggggaggggt gaaaagagat ttgaaataaa aatgtttaga aattaaaaaa 300
 aaacaaaaaa aaaaaaaa 318

<210> 12
 <211> 1055
 <212> DNA
 <213> Homo sapiens

<220>
 <221> unsure
 <222> (28)

<220>
 <221> unsure
 <222> (49)

<220>
 <221> unsure
 <222> (55)

<220>
 <221> unsure
 <222> (146)

<220>
 <221> unsure
 <222> (244)

<220>
 <221> unsure
 <222> (248)

<220>
 <221> unsure
 <222> (322)

<220>
 <221> unsure
 <222> (361)

<220>
 <221> unsure
 <222> (391)

<220>
 <221> unsure
 <222> (427)

<220>
 <221> unsure
 <222> (430)

<400> 12
 gtttagacaca ggacctgctg ggccacanaa aggaggctct gggtagacnc actanattac 60
 tggataaatc acttcaattt cccaatgaat tttatattgt ttatttttat acctggagtt 120
 ttttccttaa aaagtacact ttgaanccta ctattgaagc attgcctaata gtgctacctt 180
 taaatgaaga tgttaataag caggaagaaa agaatagaaga tcatactccc aattatgctc 240
 ctgntaanga gaaaaatggc aattattata aagatataaa acaatatgtg ttcacaacac 300
 aaaatccaaa tggcactgag tntgaaatat ttgtgagagc cacaactgac ctgaattttg 360
 ntttaaaaaa cgataaaaact gtcaatgcaa ntacatatga aaaatccacc attgaagaag 420

WO 99/26973

PCT/US98/24944

```

aaacaantan tagcgaaccc tctcataaaa atattcaaag atcaacccca aacgtgcctg 480
caatttggac aatgttagct aaagctataa atggaacagc agtgggcatg gatgataaag 540
atcaattatt tcacccaatt ccagagtctg atgtgaatgc tacacaggga gaaaatcagc 600
cagatctaga ggatctgaag atcaaaaataa tgctgggaat ctggttgaag accctcctcc 660
tctttgtggg ccttcttggc attctgtagt gctacactgt acaaactgag gcatctgagt 720
tataaaagtt gtgagagtca gtactctgtc aaccagagc tggccacgat gtcttacttt 780
catccatcag aaggtgtttc agatacatcc tttccaaga gtgcagagag cagcacattt 840
ttgggtacca cttcttcaga tatgagaaga tcaggcaca gaacatcaga atctaagata 900
atgacggata tcatttccat aggctcagat aatgagatgc atgaaaacga tgagtcgggt 960
accgggtgaa gaaatcaagg aaccgggtga agaaatctta ttgatgaata aataacttta 1020
attattttgt catcaaaaaa aaaaaaaaaa aaaaaa 1055

```

<210> 13

<211> 66

<212> PRT

<213> Homo sapiens

<400> 13

```

Met Ser Tyr Phe His Pro Ser Glu Gly Val Ser Asp Thr Ser Phe Ser
  1              5              10              15

```

```

Lys Ser Ala Glu Ser Ser Thr Phe Leu Gly Thr Thr Ser Ser Asp Met
          20              25              30

```

```

Arg Arg Ser Gly Thr Arg Thr Ser Glu Ser Lys Ile Met Thr Asp Ile
          35              40              45

```

```

Ile Ser Ile Gly Ser Asp Asn Glu Met His Glu Asn Asp Glu Ser Val
          50              55              60

```

```

Thr Arg
  65

```

<210> 14

<211> 1389

<212> DNA

<213> Homo sapiens

<400> 14

```

gactgcgtcc tcacccccag caaaccttgg cccggagatg cttccccgct atccacgcct 60
acaaggggtgt cctgatgggtg ggcaatgaga cgacctatga ggatgggcat ggctcccgga 120
aaaacatcac agacctgggtg gaaggcgcca agaaagccaa tggagtccta gaggcgcggc 180
aactcgccat gcgcatattt gaagattaca ccgtctcttg gtactggatt atcataggcc 240
tggtcattgc catggcgatg agcctcctgt tcatcatcct gcttcgcttc ctggctggta 300
ttatgggtctg ggtgaatgat catcatgggtg attctgggtg tgggctacgg aatatttcac 360
tgctacatgg agttactccc gactgcgtgg tgaggcggtc tgatgtctct ttggtggact 420
cggcttttcag acggattccg ggtgtactgc acttacggca gactggttgg cttttagtga 480
gtcacagtct cccattcctg cccccacatg aggccttgga gggagtgggg agcccagccg 540
gctcagcctt tgccctttgc agtgatcatt ctgagtatcc ttgaagtcac tatccaaaaa 600
aaaaaaaaag gccctgccc atttactgcg aaaacctgca acccagagac cttcccctcc 660
tccaatgagt cccgccaatg cccaatgcc cgttgccagt tcgccttcta cgggtggtgag 720
tcgggctacc accgggccct gctgggcctg cagatcttca atgccttcat gttcttcttg 780
ttggcccaac ttctgtgctg cgctgggcca aggtcaacgc tggccggggc ctttgettcc 840
taattaactg ggccctgccc aagccggacg acctgccggc cttcccgttc ttcttctgcc 900
tttggccggg cgctcaggta ccacacaggc tcctggcct ttggcgcgct catcctggcc 960
attgtgcaga tcatccgtgt gatactcgag tacctggatc agcggctgaa agctgcagag 1020
aacaagtttg ccaagtgcct catgacctgt ctcaaagtgt gcttctggtg cctggagaag 1080
ttcatcaaat tccttaatag gaatgcctac atcatgattg ccatctacgg caccaatttc 1140
tgcacctcgg ccaggaatgc cttcttctct ctcatgagaa acatcatcag agtggctgtc 1200

```

WO 99/26973

PCT/US98/24944

ctggataaag ttactgactt cctcttcctg ttgggcaaac ttctgatcgt tggtagtgtg 1260
 gggatcctgg ctttcttctt cttcacccac cgtatcagga tcgtgcagga tacagcacca 1320
 cccctcaatt attactgggt tcctatactg acggtgatcg ttggctccta cttgattgcg 1380
 tcgacggcc 1389

<210> 15
 <211> 116
 <212> PRT
 <213> Homo sapiens

<400> 15
 Met Thr Cys Leu Lys Cys Cys Phe Trp Cys Leu Glu Lys Phe Ile Lys
 1 5 10 15
 Phe Leu Asn Arg Asn Ala Tyr Ile Met Ile Ala Ile Tyr Gly Thr Asn
 20 25 30
 Phe Cys Thr Ser Ala Arg Asn Ala Phe Phe Leu Leu Met Arg Asn Ile
 35 40 45
 Ile Arg Val Ala Val Leu Asp Lys Val Thr Asp Phe Leu Phe Leu Leu
 50 55 60
 Gly Lys Leu Leu Ile Val Gly Ser Val Gly Ile Leu Ala Phe Phe Phe
 65 70 75 80
 Phe Thr His Arg Ile Arg Ile Val Gln Asp Thr Ala Pro Pro Leu Asn
 85 90 95
 Tyr Tyr Trp Val Pro Ile Leu Thr Val Ile Val Gly Ser Tyr Leu Ile
 100 105 110
 Ala Ser Thr Ala
 115

<210> 16
 <211> 69
 <212> DNA
 <213> Homo sapiens

<220>
 <221> unsure
 <222> (22)

<400> 16
 aaaaaaaaaa aaaaaaaaaa anaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60
 aaaaaaaaaa 69

<210> 17
 <211> 422
 <212> DNA
 <213> Homo sapiens

<220>
 <221> unsure
 <222> (67)

<220>
 <221> unsure

WO 99/26973

PCT/US98/24944

<222> (148)

<220>

<221> unsure

<222> (206)

<220>

<221> unsure

<222> (230)

<220>

<221> unsure

<222> (334)

<220>

<221> unsure

<222> (354)

<400> 17

```

tttttttttg ctccagcacc agtggtccct aaacacctta ccagcagctt ccatttttggc 60
atggaanagt gttctcggca atggccattt gtcactactg ggaaccagag acacccatcc 120
ctacgccagc ttgagccgtg cactgcanac acaatgctgt atttcttctc ccagtcacct 180
gatgagccag cagtatagac catatngttt cttcactaaa ttgactgcan atgagctgtg 240
gaaagggcgt ttagcagaga ctggtgctgg agcaaaaaaa ggaagaggcc aaagaactaa 300
aaagaagaaa agaaaggatc tgaacagggg tcanatcatt ggtgaagggc gttntggttt 360
tctatggccc ggactgaatg tccctcctta tgaaaaatgg agcagtgcag accattgccc 420
cc                                         422

```

<210> 18

<211> 515

<212> DNA

<213> Homo sapiens

<400> 18

```

gcaaccacaa tgggcagagg caacattctt cccggatttc cacaacatgg aggccttttc 60
ttatcagcca gctgttgatg ggtttcctgt ctggagagcc cacggaagag gccctgggtg 120
aggctgagca tattaatgga cccagagacc ttggcataca tgtctttgat gccaatgagc 180
cggcagatgg tgatgatggc cctgtggcag cggaggccgt aacctttggg ttgtttcttc 240
atcttgatat gcgtcctttt aaatcttaat gaaatatcat ggaatattgt atggtcttca 300
tatcgttcta tataatgcaa atggtgaact gctctgttct ttgctttcct gaaagcatcc 360
atccgatcag tagctttccc aatagaaaaa cctgcagctc cttttccggt ccccacagcc 420
accaagacac ggatcgattt ctttcttccc tctttcgcag tcatagttaa aacgtttctt 480
acctcaagta tcctggtatc aaaatcctca tatgt                                         515

```

<210> 19

<211> 79

<212> PRT

<213> Homo sapiens

<400> 19

```

Met Glu Tyr Cys Met Val Phe Ile Ser Phe Tyr Ile Met Gln Met Val
  1             5             10             15

```

```

Asn Cys Ser Val Leu Cys Phe Pro Glu Ser Ile His Pro Ile Ser Ser
      20             25             30

```

```

Phe Pro Asn Arg Lys Thr Cys Ser Ser Phe Ser Val Pro His Ser His
      35             40             45

```

```

Gln Asp Thr Asp Arg Phe Leu Ser Ser Leu Phe Arg Ser His Ser Glu

```

WO 99/26973

PCT/US98/24944

50 55 60
 Asn Val Ser Tyr Leu Lys Tyr Pro Gly Ile Lys Ile Leu Ile Cys
 65 70 75

<210> 20
 <211> 144
 <212> DNA
 <213> Homo sapiens

<220>
 <221> unsure
 <222> (11)..(12)

<220>
 <221> unsure
 <222> (14)..(15)

<400> 20
 aaaaaaaaaa nntnnttttt ttataaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120
 aaaaaaaaaa aaaaaaaaaa aaaa 144

<210> 21
 <211> 1243
 <212> DNA
 <213> Homo sapiens

<400> 21
 tgcttctctg aagacttgca gcaaggcttg ctgaggctca cagaagatag cccagtggtt 60
 ttggagtggt tttgaatgtg attctgagat cagactgact gagctggaat cctggcttta 120
 tatcttacca gctacacaac cttggagtct tagaaatttt ttcttttcaa taagcagtca 180
 tccttacttt ccttcaagat gacaaacagt tcttcttctt gccagttta taaagatctg 240
 gagccattca cgtatttttt ttatttagtt ttccttggtg gaattattgg aagttgtttt 300
 gcaacctggg cttttataca gaagaatacg aatcacaggt gtgtgagcat ctacttaatt 360
 aatttgctta cagccgattt cctgcttact ctggcattac cagtgaataat tgttggtgac 420
 ttgggtgtgg caccttgga gctgaagata ttccactgcc aagtaacagc ctgcctcatc 480
 tatatcaata tgtatttata aattatcttc ttagcatttg tcagcattga ccgctgtctt 540
 cagctgacac acagctgcaa gatctaccga atacaagaac ccggatttgc caaatgata 600
 tcaaccgttg tgtggctaata ggtccttctt ataattgtgc caaatatgat gattcccatc 660
 aaagacatca aggaaaagtc aaatgtgggt tgtatggagt ttaaaaagga atttggaaga 720
 aattggcatt tgctgacaaa ttccatatgt gtagcaatat ttttaaattt ctcagccatc 780
 attttaatat ccaattgcct tgtaattcga cagctctaca gaaacaaaga taatgaaaat 840
 taccctaatg tgaaaaaggc tctcatcaac atacttttag tgaccacggg ctacatcata 900
 tgctttgttc cttaccacat tgtccgaatc ccgtataccc tcagccagac agaagtcata 960
 actgattgct caaccaggat ttcactcttc aaagccaaag aggctacact gctcctggct 1020
 gtgtcgaacc tgtgctttga tctatctctg tactatcacc tctcaaaagc attccgctca 1080
 aaggctcactg agacttttgc ctcacctaaa gagaccaagg ctcagaaaga aaaattaaga 1140
 tgtgaaaata atgcataaaa gacaggattt tttgtgtctac caattctggc cttactggac 1200
 cataaagtta attatagctt tgaaagataa aaaaaaaaaa aaa 1243

<210> 22
 <211> 319
 <212> PRT
 <213> Homo sapiens

<400> 22
 Met Thr Asn Ser Ser Phe Phe Cys Pro Val Tyr Lys Asp Leu Glu Pro
 1 5 10 15

WO 99/26973

PCT/US98/24944

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

<210> 23

WO 99/26973

PCT/US98/24944

<211> 29
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> oligonucleotide

<220>
 <221> misc_feature
 <222> (2)
 <223> biotinylated phosphoramidite residue

<400> 23
 anaacacgtc ctttcatgcc acggctgag

29

<210> 24
 <211> 29
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> oligonucleotide

<220>
 <221> misc_feature
 <222> (2)
 <223> biotinylated phosphoramidite residue

<400> 24
 gntgctccat ttccttgatc ataatgctc

29

<210> 25
 <211> 31
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> oligonucleotide

<220>
 <221> misc_feature
 <222> (2)
 <223> biotinylated phosphoramidite residue

<400> 25
 anagggtaga acgtggagaa gaacatggtg t

31

<210> 26
 <211> 29
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> oligonucleotide

<220>
 <221> misc_feature
 <222> (2)
 <223> biotinylated phosphoramidite residue

WO 99/26973

PCT/US98/24944

<400> 26
tntgggtcca tctgtgtaaa tcttcccgg 29

<210> 27
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<220>
<221> misc_feature
<222> (2)
<223> biotinylated phosphoramidite residue

<400> 27
gncacaaact cagcatgcag ggctggctt 29

<210> 28
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<220>
<221> misc_feature
<222> (2)
<223> biotinylated phosphoramidite residue

<400> 28
antcacatca gactctggaa ttgggtgaa 29

<210> 29
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<220>
<221> misc_feature
<222> (2)
<223> biotinylated phosphoramidite residue

<220>
<221> unsure
<222> (3)

<400> 29
gnntaaaact tggtctctgc agctttcage cg 32

<210> 30
<211> 29
<212> DNA
<213> Artificial Sequence

WO 99/26973

PCT/US98/24944

<220>

<223> oligonucleotide

<220>

<221> misc_feature

<222> (2)

<223> biotinylated phosphoramidite residue

<400> 30

gncattatat agaacgatat gaagaccat

29

<210> 31

<211> 26

<212> DNA

<213> Artificial Sequence

<220>

<223> oligonucleotide

<400> 31

gctgacacac agctgcaaga tctacc

26

<210> 32

<211> 1405

<212> DNA

<213> Homo sapiens

<400> 32

```

gcagtttagga aagtagcgtt atgagttgta ctgaaaatgt tgattctcta atctgccaga 60
aaaggacctg tcttttcatg cagatttcat attgtctttg tccttttcat tgcttcttga 120
ccttcctggc aggtgtcgct cagtttcttc ctgtttccct tcctgtcctc tccacacctg 180
ctatcccgtc ccactcccat ctacctcccg ggaagccagc cctgcatgct gagtttgtga 240
cctgcttcat tcccatttca tttctagagg gtttagaggt gacctggaac cgttcccttt 300
ccctctccta cccctcctc tgcaacacca agaggcctgg aggggcagac agaaagcagc 360
cagccacggc ggggaagacat gcatgttttg ttgcagctgg actgcgatcg tagttcctcc 420
tgagataga gtgtgaggaa cttaggacac tcttcctcag actctgggat catcacatac 480
cacactgccc cgctcagagt ttcgtcctga gctccctaac cagctcaggt ggagcagaag 540
cctgctctca ctctccatc tctgggtgct ccttgggcgg ggacctgtcc ctactctta 600
ggcccagaac ctgtccaagg gacaggtagg gtccagggtc cactttgggt agctggctgt 660
tggaatgccc aactgggtgc tgcctgtggc atagccactg ctgtacgttt ttggttggtt 720
ttaagaaact cgatgaagag ggggtgtcatt ctgggctcgg ggtggttgcc aatttttcac 780
cagaaaggga gccacccctt gcaaccactt ctgtctccgt tagccccccc tctgccctcc 840
tccaagccaa agcgtggcct ggcttttgtc tccccattta gttttcctct tttacccttc 900
cttttgtgct taatttatta aaatagttgc tgtataattt attttcataa actataaaaa 960
aataactaaat ggttaaaata gacttgcagg ccaatcttaa atgggggtggg aggggtctga 1020
gggtgggatg gggaaaggga aagaggtttt gatataaaca aaacaaatgc actttgggtg 1080
tgtttttgta tttttctggg gatagagggg gtgggggttag ggatgtccct gtagattagt 1140
tccagaatgg ggtgtctgta tatactgtat taataggcat gtttgactct cgtaaaggga 1200
cgttagtagc tgctgcaggt cctgtttgga aaccccatgt acaattccca gttttttgta 1260
agtgtcagtg cgagagacat ttgactcttg tgtttgtatc tcctttttat gattgctgta 1320
cctacccatg tctttttggg gaggggtgaa aagagatttg aaataaaaat gtttagaaat 1380
taaaaaaaaa aaaaaaaaaa aaaaaa

```

1405

<210> 33

<211> 130

<212> PRT

<213> Homo sapiens

<400> 33

Met Ser Cys Thr Glu Asn Val Asp Ser Leu Ile Cys Gln Lys Arg Thr

WO 99/26973

PCT/US98/24944

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

WO 99/26973

PCT/US98/24944

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 54 to nucleotide 1283;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 648 to nucleotide 1283;
 - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 458 to nucleotide 947;
 - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AY421_2 deposited under accession number ATCC 98145;
 - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AY421_2 deposited under accession number ATCC 98145;
 - (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AY421_2 deposited under accession number ATCC 98145;
 - (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AY421_2 deposited under accession number ATCC 98145;
 - (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 at least one expression control sequence.

WO 99/26973

PCT/US98/24944

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 encoded by a composition of claim 2, which process comprises:
 - (a) growing a culture of the host cell of claim 3 in a suitable culture medium; and
 - (b) purifying said protein from the culture.
6. A protein produced according to the process of claim 5.
7. An isolated polynucleotide encoding the protein of claim 6.
8. The polynucleotide of claim 7, wherein the polynucleotide comprises the cDNA insert of clone AY421_2 deposited under accession number ATCC 98145.
9. 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 180 to amino acid 298;
 - (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 AY421_2 deposited under accession number ATCC 98145;the protein being substantially free from other mammalian proteins.
10. The composition of claim 9, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.
11. The composition of claim 9, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 180 to amino acid 298.

WO 99/26973

PCT/US98/24944

12. The composition of claim 9, further comprising a pharmaceutically acceptable carrier.

13. 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 12.

14. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.

15. 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 720 to nucleotide 974;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 715 to nucleotide 947;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BV278_2 deposited under accession number ATCC 98145;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BV278_2 deposited under accession number ATCC 98145;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BV278_2 deposited under accession number ATCC 98145;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BV278_2 deposited under accession number ATCC 98145;

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

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

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

WO 99/26973

PCT/US98/24944

(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).

16. 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 76;

(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 BV278_2 deposited under accession number ATCC 98145;

the protein being substantially free from other mammalian proteins.

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

18. 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 36 to nucleotide 968;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 340 to nucleotide 717;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone C544_1 deposited under accession number ATCC 98145;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone C544_1 deposited under accession number ATCC 98145;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone C544_1 deposited under accession number ATCC 98145;

WO 99/26973

PCT/US98/24944

- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone C544_1 deposited under accession number ATCC 98145;
- (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).

19. 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 103 to amino acid 227;
- (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 C544_1 deposited under accession number ATCC 98145;

the protein being substantially free from other mammalian proteins.

20. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.

21. 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 151 to nucleotide 1398;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 637 to nucleotide 1398;

WO 99/26973

PCT/US98/24944

- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 255 to nucleotide 429;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CC332_33 deposited under accession number ATCC 98145;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CC332_33 deposited under accession number ATCC 98145;
- (g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CC332_33 deposited under accession number ATCC 98145;
- (h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CC332_33 deposited under accession number ATCC 98145;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 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).

22. 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) the amino acid sequence of SEQ ID NO:8 from amino acid 36 to amino acid 93;
- (c) fragments of the amino acid sequence of SEQ ID NO:8; and
- (d) the amino acid sequence encoded by the cDNA insert of clone CC332_33 deposited under accession number ATCC 98145;

the protein being substantially free from other mammalian proteins.

23. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.

WO 99/26973

PCT/US98/24944

24. A composition comprising an isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 21 to nucleotide 410;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 144 to nucleotide 410;
 - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 68 to nucleotide 368;
 - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CC365_40 deposited under accession number ATCC 98145;
 - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145;
 - (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone CC365_40 deposited under accession number ATCC 98145;
 - (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145;
 - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:33;
 - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:33 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:33;
 - (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 that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

WO 99/26973

PCT/US98/24944

25. A process for producing an isolated polynucleotide, wherein the process is selected from the group consisting of:

- (a) a process comprising the steps of:
 - (i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:
 - (aa) SEQ ID NO:32, but excluding the poly(A) tail at the 3' end of SEQ ID NO:32; and
 - (ab) the nucleotide sequence of the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145; and
 - (ii) hybridizing said probe(s) to human DNA; and
 - (iii) isolating the DNA polynucleotide detected with the probe(s);

and

- (b) a process comprising the steps of:
 - (i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:
 - (ba) SEQ ID NO:32, but excluding the poly(A) tail at the 3' end of SEQ ID NO:32; and
 - (bb) the nucleotide sequence of the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145; and
 - (ii) hybridizing said primer(s) to human DNA;
 - (iii) amplifying human DNA sequences; and
 - (iv) isolating the polynucleotide product of step (b)(iii).

26. 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:33;
- (b) the amino acid sequence of SEQ ID NO:33 from amino acid 17 to amino acid 116;
- (c) fragments of the amino acid sequence of SEQ ID NO:33 comprising eight consecutive amino acids of SEQ ID NO:33; and

WO 99/26973

PCT/US98/24944

(d) the amino acid sequence encoded by the cDNA insert of clone CC365_40 deposited under accession number ATCC 98145; the protein being substantially free from other mammalian proteins.

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

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 769 to nucleotide 966;
- (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CG68_4 deposited under accession number ATCC 98145;
- (d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CG68_4 deposited under accession number ATCC 98145;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CG68_4 deposited under accession number ATCC 98145;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CG68_4 deposited under accession number ATCC 98145;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;
- (i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;
- (j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and
- (k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

28. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:12.

WO 99/26973

PCT/US98/24944

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

- (a) the amino acid sequence of SEQ ID NO:13;
- (b) the amino acid sequence of SEQ ID NO:13 from amino acid 18 to amino acid 57;
- (c) fragments of the amino acid sequence of SEQ ID NO:13; and
- (d) the amino acid sequence encoded by the cDNA insert of clone CG68_4 deposited under accession number ATCC 98145;

the protein being substantially free from other mammalian proteins.

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

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14 from nucleotide 1042 to nucleotide 1389;
- (c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone D329_1 deposited under accession number ATCC 98145;
- (d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone D329_1 deposited under accession number ATCC 98145;
- (e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone D329_1 deposited under accession number ATCC 98145;
- (f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone D329_1 deposited under accession number ATCC 98145;
- (g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:15;
- (h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:15 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

WO 99/26973

PCT/US98/24944

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

31. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:14.

32. 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:15;
- (b) fragments of the amino acid sequence of SEQ ID NO:15; and
- (c) the amino acid sequence encoded by the cDNA insert of clone

D329_1 deposited under accession number ATCC 98145;

the protein being substantially free from other mammalian proteins.

33. 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 279 to nucleotide 515;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone H698_3 deposited under accession number ATCC 98145;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone H698_3 deposited under accession number ATCC 98145;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H698_3 deposited under accession number ATCC 98145;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H698_3 deposited under accession number ATCC 98145;

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

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

WO 99/26973

PCT/US98/24944

- (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).

34. An isolated gene corresponding to the cDNA sequences of SEQ ID NO:17 and SEQ ID NO:18.

35. 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 H698_3 deposited under accession number ATCC 98145;
- the protein being substantially free from other mammalian proteins.

36. 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 199 to nucleotide 1155;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 304 to nucleotide 1155;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone H963_20 deposited under accession number ATCC 98145;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone H963_20 deposited under accession number ATCC 98145;
- (f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H963_20 deposited under accession number ATCC 98145;

WO 99/26973

PCT/US98/24944

- (g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H963_20 deposited under accession number ATCC 98145;
- (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).

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

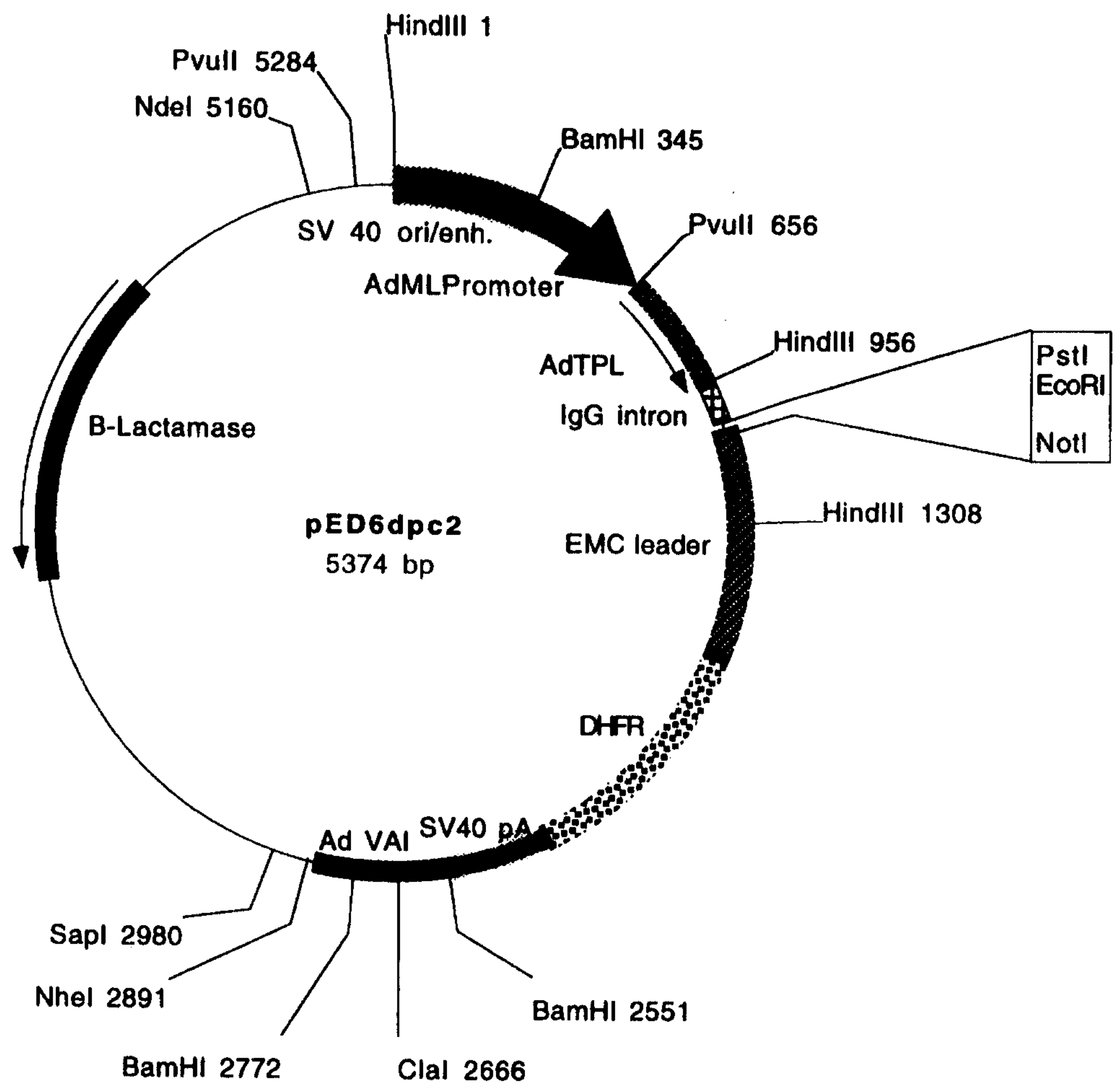
38. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:22;
 - (b) the amino acid sequence of SEQ ID NO:22 from amino acid 19 to amino acid 84;
 - (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 H963_20 deposited under accession number ATCC 98145;
- the protein being substantially free from other mammalian proteins.

WO 99/26973

PCT/US98/24944

FIGURE 1A



Plasmid name: pED6dpc2

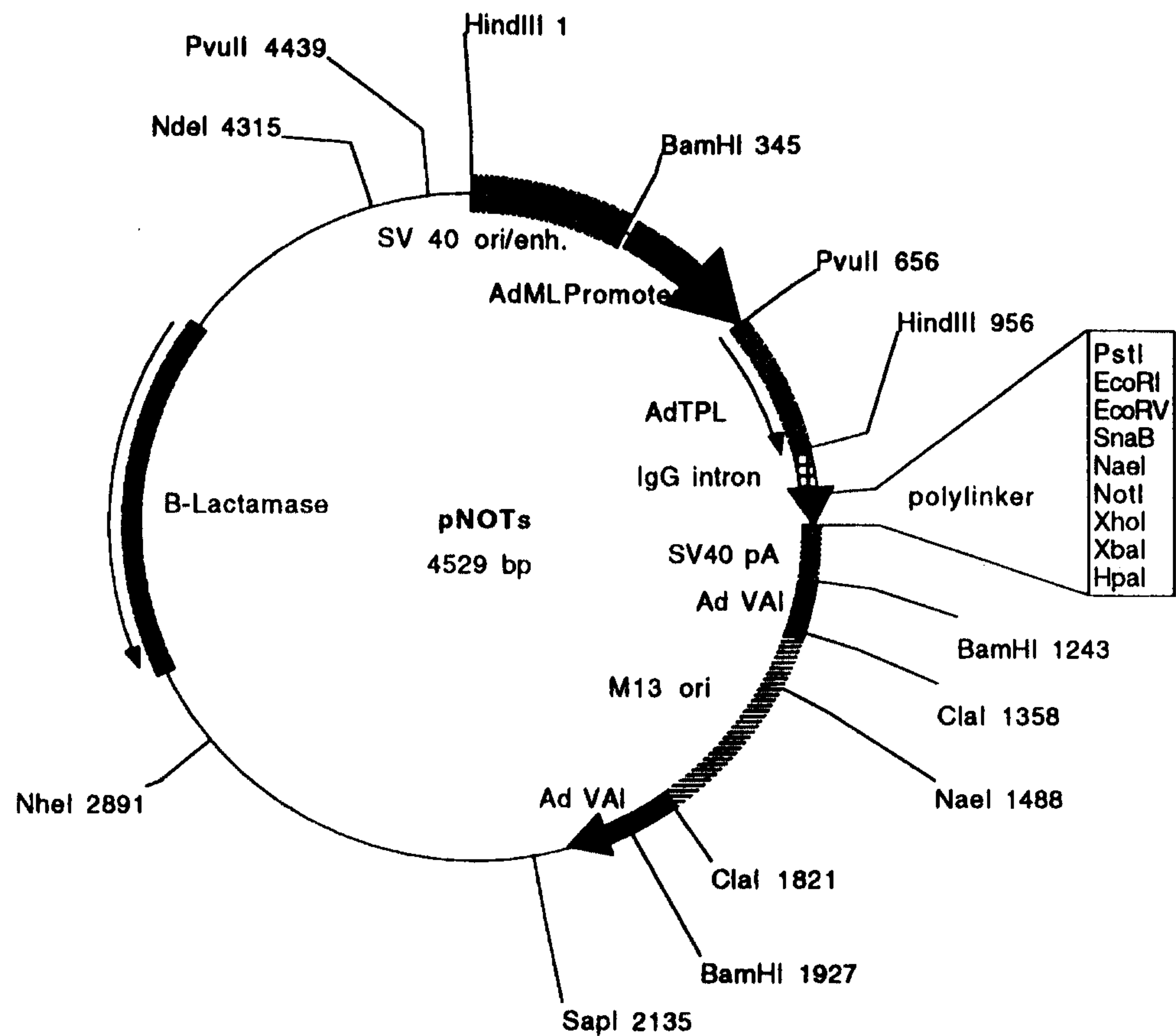
Plasmid size: 5374 bp

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.

WO 99/26973

PCT/US98/24944

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