693767

AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **Cambridge Neuroscience, Inc.,**

of **One Kendall Square, Building 700, Cambridge, Massachusetts 02139, United States of America,**

as applicant/Nominated Person in respect of Application No. 50026/93, state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person derives title to the invention from the inventor/s by virtue of an assignment.

The Nominated Person is entitled to claim priority from the applications listed in the declaration under Article 8 of the PCT because the Nominated Person is the assignee of the applicants in respect of the applications listed in the declaration under Article 8 of the PCT and because those applications were first made in a Convention country in respect of the invention.

The Applicant/Nominated Persons have entitlement by consent from Mark Marchionni, the depositor in respect of the deposit listed hereafter:

Microorganism	International Depository Authority	Accession No.	Date of Deposit
Brain stem factor 1 pGGF2HBS11	American Type Culture Collection	ATCC 75347	16 November 1992

DATED this SIXTEENTH day of AUGUST, 1996.

....

a member of the firm of
DAVIES COLLISON CAVE
for and on behalf of the applicant(s)

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INHIBITORS OF CELL PROLIFERATION, THEIR PREPARATION AND USE

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(57) Claim

6. A method for inhibiting proliferation of a cell, said method comprising contacting said cell with a polypeptide comprising FBA polypeptide segments, FBA' polypeptide segments, EBA polypeptide segments, EBA' polypeptide segments, FEBA polypeptide segments, or FEBA' polypeptide segments having the amino acid sequences corresponding to polypeptide segments shown in Figure 31 (SEQ ID Nos. 136-140, 163) or SEQ ID No. 168, said polypeptide lacking an EGF-like domain.

21. A method for detecting, in a sample, the presence of a molecule capable of binding to a receptor which binds to a polypeptide selected from the group consisting of polypeptides defined by the formula

VYBAZWX

wherein VYBAZWX is composed of the polypeptide segments shown in Figure 31 (SEQ ID Nos. 136-139, 141, 146, 147, 160, 161, and 163); wherein V comprises F, or is absent; wherein Y comprises polypeptide segment E, or is absent; wherein Z comprises polypeptide segment G or is absent; wherein W comprises C or is absent; and wherein X comprises polypeptide segments H, HK, or HKL,

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said method comprising the steps of

i) contacting said sample with said polypeptide together with said receptor, and

ii) detecting competitive inhibition of the binding of said polypeptide to said receptor as an indication of the presence of a receptor binding molecule in said sample.

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(54) Title: INHIBITORS OF CELL PROLIFERATION, THEIR PREPARATION AND USE

(57) Abstract

Disclosed is the characterization and purification of DNA encoding numerous polypeptides factors useful for the inhibition of cell (particularly, Schwann cell) proliferation. These factors are useful for the treatment of neural tumors. Also disclosed are the DNA sequences encoding novel polypeptides which may have use as agents which inhibit cell proliferation. Methods for the synthesis, purification, and testing of both known and novel polypeptides for their use as therapeutic and diagnostic aids in the treatment of diseases are also provided. Methods are also provided for the use of these polypeptides for the preparation of antibody probes. Such probes have diagnostic and therapeutic use in diseases involving neural and glial cells.

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INHIBITORS OF CELL PROLIFERATION, THEIR PREPARATION AND USE

Background of the Invention

5 The invention relates to compounds which are inhibitors of cell proliferation, having antiproliferative activity on a variety of cell types.

Many vertebrate cell types respond to diffusible growth factors as stimuli which regulate proliferation. 10 A number of these growth factors and their cognate receptors have been purified, and the genes encoding them have been cloned and characterized (Sporn and Roberts eds. (1991) Peptide Growth Factors and their Receptors I and II. Springer-Verlaz, New York). Many cancers, which 15 are diseases of cell proliferation, involve genetic modifications which affect the nature of the growth factor-receptor interaction. Such modifications can result in unregulated stimulation of proliferation in the receptor bearing target cell. Additionally, certain 20 tumors of the nervous system involve the regulation of proliferation of cells from both the central and peripheral nervous systems.

The glial cells of vertebrates constitute the specialized connective tissue of the central and 25 peripheral nervous systems. Important glial cells include the peripheral Schwann cells which provide both the metabolic support for neurons and the myelin sheathing around the axons of certain peripheral neurons, thereby forming individual nerve fibers. Schwann cells 30 support neurons and provide a sheath effect by forming concentric layers of membrane around adjacent neuron axons, twisting as they develop around the axons. These myelin sheaths are a susceptible element of many nerve fibers. Damage to Schwann cells, or failure in growth 35 and development, can be associated with significant

demyelination or nerve degeneration characteristic of a number of peripheral nervous system diseases and disorders. In the development of the nervous system, it has become apparent that cells require various factors to regulate their division and growth. Several regulators of Schwann cell proliferation and differentiation have been identified. Such factors play an important role in both the development and the regeneration (following injury) of the peripheral nervous system.

Brockes et al. ((1984) J. Neuroscience 4:75-83) describe a protein growth factor present in extracts from bovine brain and pituitary tissue, termed Glial Growth Factor (GGF). This factor stimulates cultured rat Schwann cells to divide against a background medium containing ten percent fetal calf serum. GGF has been described as having a molecular weight of 31 KD and readily forming dimers. Brockes ((1987) Meth. Enz. 147:217-225) describes a Schwann cell-based assay for 31 kD GGF and purification using reversed phase HPLC.

The J. Neuroscience article of Brockes et al., supra, describes methods of purification of GGF to apparent homogeneity. In brief, one large-scale purification method described involves extraction of the lyophilized bovine anterior lobes and chromatography of material obtained thereby, using NaCl gradient elution from CM cellulose. Gel filtration is then carried out with an Ultrogel column, followed by elution from a phosphocellulose column, and finally, small-scale SDS gel electrophoresis. Alternatively, the CM-cellulose material was applied directly to a phosphocellulose column, fractions from the column were pooled and purified by preparative native gel electrophoresis, followed by a final SDS gel electrophoresis.

Brockes et al. ((1980) J. Biol. Chem. 255:8374-8377) observe that in gel filtration experiments

the major peak of growth factor activity is observed to migrate with a molecular weight of 56 KD, whereas in the first of the above-described procedures activity was predominantly observed at molecular weight 31 KD. They
5 report that the GGF dimer is largely removed as a result of the gradient elution from CM-cellulose in this procedure.

Benveniste et al. ((1985) PNAS 82:3930-3934) describe a T lymphocyte-derived glial growth promoting
10 factor. This factor, under reducing conditions, exhibits a change in apparent molecular weight on SDS gels.

Kimura et al. ((1990) Nature 348:257-260) describe a factor they term Schwannoma-derived growth factor (SDGF) obtained from a sciatic nerve sheath tumor.
15 The authors state that SDGF does not stimulate the incorporation of tritium-labelled TdR into cultured Schwann cells under conditions where, in contrast, partially purified pituitary fraction containing GGF is active. SDGF has an apparent molecular weight between 31
20 KD and 35 KD.

Davis et al. ((1990) J. Cell. Biol. 110:1353-1360) describe the screening of a number of candidate mitogens. The chosen candidate substances being examined for their ability to stimulate DNA
25 synthesis in Rat Schwann cells in the presence of 10% FCS (fetal calf serum), with and without forskolin. One of the factors tested, GGF-carboxymethyl cellulose fraction (GGF-CM), was mitogenic in the presence of FCS, with and without forskolin. It was also observed that in the
30 presence of forskolin platelet derived growth factor (PDGF) is a potent mitogen for Schwann cells. Previous to this finding, PDGF was not thought to have a mitogenic effect on Schwann cells.

Holmes et al. ((1992) Science 256:1205) and Wen et
35 al. ((1992) Cell 69:559) demonstrate that DNA sequences

which encode proteins which bind to a receptor (p185^{erbB2}) are associated with several human tumors.

The p185^{erbB2} protein is a 185 kilodalton membrane spanning protein with tyrosine kinase activity. The protein is encoded by the *erbB2* proto-oncogene (Yarden and Ullrich. (1988) Ann. Rev. Biochem. 57:443). The *erbB2* gene, also referred to as HER-2 (in human cells) and *neu* (in rat cells), is closely related to the receptor for epidermal growth factor (EGF). Recent evidence indicates that proteins which interact with (and activate the kinase of) p185^{erbB2} induce proliferation in the cells bearing p185^{erbB2} (Holmes et al. (1992) Science 256:1205; Dobashi et al. (1991) Proc. Natl. Acad. Sci. 88:8582; and Lupu et al. (1992) Proc. Natl. Acad. Sci. 89:2287).

Although ligands have been identified which stimulate proliferation of cells with certain receptors (e.g., the p185^{erbB2} receptor), there exists a need to identify and isolate factors which act as inhibitors of cell proliferation at these receptor sites. Such inhibitors could be used for the purpose of treating cell proliferative disorders (e.g., neoplasms).

Summary of the Invention

In general, the invention provides methods for inhibiting proliferation of cells, including cells of the nervous system. The antiproliferative factors of the invention are alternative splicing products and fragments thereof of the DNA encoding the GGF/p185^{erbB2} family of proteins.

The invention also provides a DNA sequence encoding a glial growth inhibitory factor; the sequence is included in the clone pGGF2HBS11 (ATCC Deposit No. 75347).

The peptide encoded by this clone is also a part of the invention. The invention further includes a peptide comprising a peptide encoded by the E sequence (SEQ ID Nos. 137 and 163) and at least a portion of the
5 peptides encoded by brain derived DNA sequences flanking the encoding sequences on clone pGGF2HBS11 (ATCC Deposit No. 75347). Preferably, the E encoded polypeptide sequence lacks 48 amino acids on the amino-terminal end and includes between 20 and 100 or, more
10 preferably, between 25 and 70 amino acids of flanking the E encoded polypeptide. In addition, the E encoded polypeptide may be flanked by between 30 and 50, or, more preferably, between 35 and 45 amino acids on the carboxy terminal side of the E encoded segment. The sequences
15 flanking the E encoded polypeptide are encoded by the DNA sequences flanking the E sequence present in clone pGGF2HBS11 (ATCC Deposit No. 75347).

Specifically, the invention also provides a method for inhibiting cell proliferation *in vitro* or *in vivo*
20 comprising contacting the cell with

a) a polypeptide defined by the formula

VYBAZWX

wherein VYBAZWX is composed of the polypeptide segments shown in Figure 31 (SEQ ID Nos. 136-139, 141-
25 147, 160, 161); wherein V comprises F, or is absent; wherein Y comprises polypeptide segment E, or is absent; wherein Z comprises polypeptide segment G or is absent; wherein W comprises C or is absent; and wherein X comprises polypeptide segments C/D HKL, C/D H, C/D HL,
30 C/D D, C/D′ HL, C/D′ HKL, C/D′ H, C/D′ D, C/D C/D′ HKL, C/D C/D′ H, C/D C/D′ HL, C/D C/D′ D, C/D D′ H, C/D D′ HL, C/D D′ HKL, C/D′ D′ H, C/D′ D′ HL, C/D′ D′ HKL, C/D C/D′ D′ H, C/D C/D′ D′ HL, H, HK, HKL, or C/D C/D′ D′ HKL;

b) a polypeptide comprising FBA polypeptide segments having the amino acid sequences shown in Figure 31 (SEQ ID Nos. 136, 138, 139);

c) a polypeptide comprising FBA′ polypeptide segments having the amino acid sequences shown in Figure 31 (SEQ ID Nos. 136, 138, 140, 168);

d) a polypeptide comprising FEBA polypeptide segments having the amino acid sequences shown in Figure 31 (SEQ ID Nos. 136-139); or

e) a polypeptide comprising FEBA′ polypeptide segments having the amino acid sequences corresponding to polypeptide segments shown in Figure 31 (SEQ ID Nos. 136-138, 140, 168);

f) a polypeptide comprising EBA′ polypeptide segments having the amino acid sequences corresponding to polypeptide segments shown in Figure 31 (SEQ ID Nos. 136, 138, 140, 168); or

g) a polypeptide comprising a portion of the E sequence (SEQ ID Nos. 137 and 163) and flanked by new sequence not contained in F, B, A, C/D, C/D′, D, D′, HK or L and contained in clone pGGF2HBS11, ATCC Deposit No. 75347; or to glial cells (i.e., astrocytes and microglial cells of the central and peripheral nervous system and Schwann cells of the peripheral nervous system).

The invention also provides a method of inhibiting proliferation of cells, including cells of the nervous system, by a method which consists of contacting the cells with a compound which specifically binds the $p185^{erbB2}$ receptor of the cell type.

Also included is the method comprising the administration of any of the above mentioned peptides when the peptides are administered in the treatment or prophylaxis of a nervous disease or disorder. Further included in the invention is the method of administering any of the above mentioned peptides when the cell is

present in a mammal and the contacting of the cell is carried out by the administration of the peptide to the mammal for the prophylaxis or treatment of a pathophysiological condition in the mammal which involves
5 the stated cell. Also included is the use of the method, as stated above, wherein the condition involves a disease of cell proliferation, such as a tumor, and more specifically, where the condition involves peripheral nerve

damage caused by a tumor of the nervous system. Also a part of the invention is the administration of the inhibitory factors for the purpose of increasing myelination of existing or regenerated neural tissue.

5 Further included as a part of the invention are methods comprising administration of any of the above mentioned polypeptides to a cell when the cell is present in a mammal and the contacting of the cell is carried out by administering the peptide to the mammal for the 10 prophylaxis or treatment of a condition which involves one of the following conditions: a tumor of the Schwann cells, for example, neurofibromatosis, malignant Schwannomas or neurofibrosarcomas; a meningioma; a bilateral acoustic neuroma; an astrocytoma; a 15 retinoblastoma; a neuroglioma; a neuroblastoma; an adenocarcinoma; or a glioma, by the method comprising administering to the mammal an effective amount of a polypeptide, as defined above.

The invention also includes a method for producing 20 an antibody specific for a polypeptide, consisting of immunizing a mammal with a polypeptide selected from the above listed polypeptides, or a fragment thereof, and purifying the antibody from the tissue of the animal, or from a hybridoma made using the tissue.

25 Furthermore, the invention provides a method for detecting, in a sample, the presence of a molecule capable of binding to a receptor which binds to a polypeptide selected from the above mentioned polypeptides, and contacting the sample with the 30 polypeptide together with the receptor, and detecting inhibition of the binding of the polypeptide to the receptor as an indication of the presence of a receptor binding molecule in the sample. The invention also provides methods for determining whether such a

competitive inhibitor is an antagonist or agonist of receptor function.

Thus, factors useful in the methods of the invention are:-

5 (a) basic polypeptide factors having antiproliferative activity when contacted with cells, including cells of the nervous system and specifically Schwann cells, and containing within their amino acid sequences one or more of the following peptide sequences:

10 F K G D A H T E (SEQ ID NO: 1)
A S L A D E Y E Y M X K (SEQ ID NO: 2)
T E T S S S G L X L K (SEQ ID NO: 3)
A S L A D E Y E Y M R K (SEQ ID NO: 7)
A G Y F A E X A R (SEQ ID NO: 11)
15 T T E M A S E Q G A (SEQ ID NO: 13)
A K E A L A A L K (SEQ ID NO: 14)
F V L Q A K K (SEQ ID NO: 15)
E T Q P D P G Q I L K K V P M V I G A Y T (SEQ ID NO: 169)
20 E Y K C L K F K W F K K A T V M (SEQ ID NO: 17)
E X K F Y V P (SEQ ID NO: 19)
K L E F L X A K (SEQ ID NO: 32); and

(b) basic polypeptide factors capable of inhibiting the division of cells, including cells of the
25 nervous system and particularly Schwann cells, and containing within their amino acid sequences, respectively, one or more of the following peptide sequences:

V H Q V W A A K (SEQ ID NO: 45)
30 Y I F F M E P E A X S S G (SEQ ID NO: 46)
L G A W G P A F P V X Y (SEQ ID NO: 35)
W F V V I E G K (SEQ ID NO: 48)
A S P V S V G S V Q E L Q R (SEQ ID NO: 37)
V C L L T V A A L P P T (SEQ ID NO: 38)
35 K V H Q V W A A K (SEQ ID NO: 51)

K A S L A D S G E Y M X K (SEQ ID NO: 52)

D L L L X V (SEQ ID NO: 39)

The peptide sequences set out above, derived from lower and higher molecular weight polypeptide factors described in detail below, are also aspects of this invention in their own right. These sequences are potentially useful as therapeutics, probes for large polypeptide factors, for investigating, isolating or preparing such factors (or corresponding gene sequences) from a range of different species, or preparing such factors by recombinant technology, and in the generation of antibodies (preferably monoclonal), by conventional technologies, which are themselves useful as investigative tools and potential medicaments. Such antibodies are included within this invention. The invention also includes inhibitors of cell proliferation encoded by gene sequences obtainable using the peptide sequences of the invention.

The invention further includes methods for use of a polypeptide factor having cell, including cells of the nervous system, antiproliferative activity and including an amino acid sequence encoded by:

(a) a DNA sequence shown in any one of Figures 28a, 28b or 28c (SEQ ID Nos. 133-135 respectively);

(b) a DNA sequence shown in Figure 22 (SEQ ID No. 89);

(c) the DNA sequence represented by nucleotides 281-557 of the sequence shown in Figure 28a (SEQ ID No. 133); or

(d) a DNA sequence hybridizable to any one of the DNA sequences according to (a), (b) or (c).

While the present invention is not limited to a particular set of hybridization conditions, the following

protocol gives general guidance which may, if desired, be followed:

Thus, DNA probes may be labelled to high specific activity (approximately 10^8 to 10^9 dpm ^{32}P per μg) by nick-translation or by PCR reactions according to Schowalter and Sommer ((1989) Anal. Biochem. 177:90-94) and purified by desalting on G-150 Sephadex columns. Probes may be denatured (10 minutes in boiling water followed by immersion into ice water), then added to hybridization solutions of 80% buffer B (2g polyvinylpyrolidine, 2g Ficoll-400, 2g bovine serum albumin, 50μl 1M Tris HCL (pH 7.5), 58g NaCl, 1g sodium pyrophosphate, 10g sodium dodecyl sulfate, 950μl H_2O) containing 10% dextran sulfate at 10^6 dpm ^{32}P per μl and incubated overnight (say, 16 hours) at 60°C. The filters may then be washed at 60°C, first in buffer B for 15 minutes followed by three 20-minute washes in 2X SSC, 0.1% SDS then one for 20 minutes in 1x SSC, 0.1% SDS.

The methods of the invention take advantage of the fact that a Glial Growth Factor and the p185^{erbB2} ligand protein are encoded by the same gene. A variety of messenger RNA splicing variants (and their resultant proteins) are derived from this gene, and many of these products exhibit p185^{erbB2} binding. This binding may result in either cell proliferation or cessation of cell division. At least two of the gene products (GGFI and GGFII) have been used to induce Schwann cell mitogenic activity. This invention employs some of the known products of the GGF/p185^{erbB2} ligand gene (described in the references listed above) as inhibitors of cell proliferation and, more specifically, as inhibitors of glial cell proliferation.

This invention also relates to other, not yet naturally isolated splicing variants of the Glial Growth Factor gene. Figure 30 shows the known patterns of

splicing derived from polymerase chain reaction experiments (on reverse transcribed RNA) and analysis of cDNA clones (as presented within) and derived from what has been published as sequences encoding p185^{erbB2} ligands (Peles et al. (1992) Cell 69:205 and Wen et al. (1992) Cell 69:559). These patterns, as well as additional patterns disclosed herein, represent probable existing splicing variants.

Thus other aspects of the invention are :

Methods for the use of a series of human and bovine polypeptide factors having cell antiproliferative activity, including the inhibition of the division of cells of the nervous system, such as Schwann cells. Such peptide sequences are shown in Figure 31-34, (SEQ ID Nos. 136-137), respectively.

The human peptide sequences described above and presented in Figures 31-34, SEQ ID Nos. 136-137 respectively, represent a series of splicing variants which can be isolated as full length complementary DNA's (cDNA's) from natural sources (cDNA libraries prepared from the appropriate tissues) or assembled as DNA constructs with individual exons (e.g., derived as separate exons) by one skilled in the art.

Other compounds, in particular, peptides, which bind specifically to the p185^{erbB2} receptor can also be used according to the invention as inhibitors of glial cell proliferation. A candidate compound can be routinely screened for p185^{erbB2} binding, and, if it binds, can be screened for inhibition of cell proliferation using the methods described herein.

The invention includes the use of any modifications or equivalents of the above polypeptide factors which do not exhibit a significant reduction in the stated inhibitory activity. For example, modifications in which amino acid content or sequence is

altered without substantially adversely affecting inhibitory activity are included. By way of illustration, in EP-A 109748 muteins of native proteins are disclosed in which the possibility of unwanted
5 disulfide binding is avoided by replacing any cysteine in the native sequence which is not necessary for biological activity with a neutral amino acid. The statements of effect and use contained herein are therefore to be construed accordingly, with such uses and effects
10 employing modified or equivalent factors as aforesaid being part of the invention.

The peptides useful in the invention can be made recombinantly using DNA constructs comprising DNA sequences, as defined above, in operable reading frame
15 position in vectors under the control of control sequences so as to permit expression of the sequences in suitable host cells after transformation thereof by said constructs (preferably the control sequence includes a regulatable promoter, e.g. Trp) - it will be appreciated
20 that the selection of a promoter and regulatory sequences (if any) are matters of choice for those of ordinary skill in the art.

The factors of the invention can be formulated for pharmaceutical or veterinary use by combination with an
25 acceptable diluent, carrier or excipient and/or in unit dosage form. In using the factors of the invention, conventional pharmaceutical or veterinary practice may be employed to provide suitable formulations or compositions.

30 Thus, the formulations of this invention can be applied to parenteral administration, for example, intravenous, subcutaneous, intramuscular, intraorbital, ophthalmic, intraventricular, intracranial, intracapsular, intraspinal, intracisternal,
35 intraperitoneal, topical, intranasal, aerosol,

scarification, and also oral, buccal, rectal or vaginal administration.

The formulations of the invention may also be administered by the transplantation into the patient of host cells expressing the DNA of the instant invention or by the use of surgical implants which release the formulations of the invention.

Parenteral formulations may be in the form of liquid solutions or suspensions; for oral administration, formulations may be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

Methods well known in the art for making formulations are to be found in, for example, "Remington's Pharmaceutical Sciences." Formulations for parenteral administration may, for example, contain as excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes, biocompatible, biodegradable lactide polymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the present factors. Other potentially useful parenteral delivery systems for the factors include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain as excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Formulations for parenteral administration may also include glycocholate for buccal administration, methoxysalicylate for rectal

administration, or citric acid for vaginal administration.

The present factors can be used as the sole active agents or can be used in combination with other active ingredients.

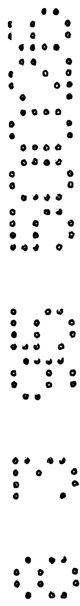
The concentration of the present factors in the formulations of the invention will vary depending upon a number of issues, including the dosage to be administered, and the route of administration.

In general terms, the factors of this invention may be provided in an aqueous physiological buffer solution containing about 0.1 to 10% w/v compound for parenteral administration. General dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day; a preferred dose range is from about 0.01 mg/kg to 100 mg/kg of body weight per day. The preferred dosage to be administered is likely to depend upon the type and extent of progression of the pathophysiological condition being addressed, the overall health of the patient, the make up of the formulation, and the route of administration.

As indicated above, cell proliferation, particularly that of Schwann cells (the glial cells of the peripheral nervous system) and other cells of the nervous system is inhibited in the presence of the factors of the invention. There are a variety of tumors of glial cells, the most common of which is probably neurofibromatosis, which is a patchy small tumor created by overgrowth of glial cells. Also, it has been found that an activity very much like GGF can be found in some Schwann cell tumors (Brockes et al., Ann. Neurol. 20:317 (1986)). Therefore inhibitors of GGF action on their receptors provides a therapy of a glial tumor. This therapy comprises administering an effective amount of a substance which inhibits the binding of a stimulatory factor as defined above to its receptor.

Additionally, given the association of GGF receptor amplification with human adenocarcinomas (Kraus et al., (1987) EMBO J. 6:605; Slamon et al. (1987) Science 235:177; Varley et al. (1987) Oncogene 1:423; and van de Vijver et al. (1987) Mol Cell Biol 7:2019) and tumors of the breast and ovary (Slamon et al. supra; Varley et al. supra: Venter et al. (1987) Lancet ii:67; Zhou et al. (1987) Cancer Res. 47:6123; Berger et al. (1988) Cancer Res. 48:1238; Tsuda et al. (1989) Cancer Res. 49:3104; Slamon et al. (1989) Science 244:707), a similar therapeutic approach may be taken with adenocarcinomas and tumors of breast and ovarian tissues.

In general, the invention includes the use of present polypeptide factors in the prophylaxis or treatment of any pathophysiological condition in which a



factor-sensitive or factor-responsive cell type is involved.

The polypeptide factors of the invention can also be used as immunogens for making antibodies, such as monoclonal antibodies, following standard techniques. Such antibodies are included within the present invention. These antibodies can be used for therapeutic or diagnostic purposes. Thus, conditions associated with abnormal levels of the factor may be tracked by using such antibodies. In vitro techniques can be used, employing assays on isolated samples using standard methods. Imaging methods can also be employed in which the antibodies are, for example, tagged with radioactive isotopes which can be remotely imaged from outside the body using techniques employed in the art of, for example, tumour imaging.

Such antibodies, as described above, may also be used for therapeutic purposes. Anti-idiotypic antibodies raised against the polypeptide factors of the invention or idiotypic antibodies raised against their cognate receptor can be used as antagonists of GGF/*erbB2* ligand induced proliferation of $p185^{erbB2}$ bearing cells.

The invention also includes the general use of the present factors as inhibitors of cell proliferation in vivo or in vitro, and the methods for such use. One embodiment is thus a method for producing a tumor cell antiproliferative effect in a vertebrate by administering an effective amount of a factor of the invention. An example of such a method is the treatment or prophylaxis of nervous system tumors or tumors of other tissues.

A further general aspect of the invention is the use of a factor of the invention in the manufacture of a medicament, preferably for the treatment of a nervous disease or disorder.

Also included in the invention are the use of the factors of the invention in competitive assays to identify or quantify molecules having receptor binding characteristics corresponding to those of said polypeptides. The polypeptides may be labelled, optionally with a radioisotope and these labelled products may be used to determine if receptor binding exists. A competition assay can identify both antagonists and agonists of the relevant receptor. Any competition for receptor binding between a known agonist and an antagonist (shown to bind the receptor) in a bioassay would be reflected by a decrease in biological activity with in an increase in concentration of antagonist.

In another aspect, the invention provides the use of the factors in an affinity isolation process, e.g., affinity chromatography, for the separation of a respective corresponding receptor. Such processes for the isolation of receptors corresponding to particular proteins are known in the art, and a number of techniques are available and can be applied to the factors of the present invention. For example, in relation to IL-6 and IFN-gamma, the reader is referred to Novick et al. ((1990) J. Chromatogr. 510:331-7), in relation to gonadotropin releasing hormone, reference is made to Hazum ((1990) J. Chromatogr. 510:233-8), in relation to G-CSF, reference is made to Fukunaga et al. ((1990) J. Biol. Chem. 265:13386-13390), in relation to IL-2, reference is made to Smart et al. ((1990) J. Invest. Dermatol. 94:158S-163S), and in relation to human IFN-gamma, reference is made to Stefanos et al. ((1989) J. Interferon Res. 9:719-30)

The following examples are not intended to limit the invention, but are intended to usefully illustrate the same, and provide specific guidance for effective

preparative techniques. Examples 1-4 teach the purification and consequent cloning of bovine DNA sequences encoding GGF Examples 5 and 7 demonstrate the isolation of human DNA sequences encoding GGF. Examples 8 and 9 demonstrate the isolation of splicing variants. Examples 10 and 11 show specific antiproliferative variants and examples of their function. Examples 12 and 13 demonstrate the production and testing of antiproliferative molecules.

Brief Description of the Drawings

The drawings will first be described.

Drawings

Figures 1 to 8 relate to Example 1 hereinafter, and are briefly described below:

Figure 1 is the profile for product from carboxymethyl cellulose chromatography;

Figure 2 is the profile for product from hydroxylapatite HPLC;

Figure 3 is the profile for product from Mono S FPLC;

Figure 4 is the profile for product from Gel filtration FPLC;

Figures 5 and 6 depict the profiles for the two partially purified polypeptide products from reversed-phase HPLC; and

Figures 7 and 8 depict dose response curves for the GGF-I and GGF-II fractions from reversed-phase HPLC using either a fetal calf serum or a fetal calf plasma background;

Figures 9 to 12 depict peptides derived from GGF-I and GGF-II, (SEQ ID Nos. 1-53, 164-166 and 169) (see Example 2, hereinafter), Figures 10 and 12 specifically depict novel sequences:

In Figure 10, Panel A, the sequences of GGF-I peptides used to design degenerate oligonucleotide probes and degenerate PCR primers are listed (SEQ ID Nos. 20-30). Some of those sequences in Panel A were also used to design synthetic peptides. Panel B shows the novel peptides that were too short (less than 6 amino acids) for the design of degenerate probes or degenerate PCR primers (SEQ ID Nos. 19 and 32);

In Figure 12, Panel A, the sequences of GGF-II peptides used to design degenerate oligonucleotide probes and degenerate PCR primers are listed (SEQ ID Nos. 45-52). Some of these sequences in Panel A were also used to design synthetic peptides. Panel B shows the novel peptides that were too short (less than 6 amino acids) for the design of degenerate probes or degenerate PCR primers (SEQ ID No. 53);

Figures 13 to 20 relate to Example 3 hereinafter, and show various aspects of the mitogenic activity of factors related to the invention;

Figures 21 to 28 (a, b and c) relate to Example 4 hereinafter, and are briefly described below:

Figure 21 lists the degenerate oligonucleotide probes (SEQ ID Nos. 54-88) designed from the novel peptide sequences listed in Figure 10, Panel A and Figure 12, Panel A;

Figure 22 (SEQ ID No. 89) depicts a stretch of the putative bovine GGF-II gene sequence from the recombinant bovine genomic phage GGF2BG1, which contains the binding site of degenerate oligonucleotide probes 609 and 650 (see Figure 21, SEQ ID Nos. 69 and 72, respectively).

Shown are the coding strand of the DNA sequence and the deduced amino acid sequence in the third reading frame. The sequence of peptide 12 from GGF-2 (shown in bold) is part of a 66 amino acid open reading frame (nucleotides 75272);

Figure 23A lists the degenerate PCR primers (SEQ ID No. 90-108) and unique PCR primers Figure 23B (SEQ ID Nos. 109-119) used in experiments to isolate segments of the bovine GGF-II coding sequences present in RNA from
5 posterior pituitary;

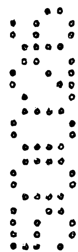
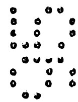
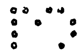
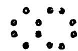





Figure 24 summarizes the nine distinct contiguous bovine GGF-II cDNA structures and sequences that were obtained in PCR amplification experiments using the list of primers in Figure 7, Panels A and B, on RNA from
5 posterior pituitary. The top line of the Figure shows a schematic of the exon sequences which contribute to the cDNA structures that were characterized;

Figure 25 is a physical map of bovine recombinant phage GGF2BG1. The bovine DNA fragment is roughly 20 kb
10 in length and contains two exons (bold) of the bovine GGFII gene. Restriction sites for the enzymes Xbal, Spe I, Ndel, EcoRI, Kpnl, and SstI have been placed on this physical map. Shaded portions correspond to fragments which were subcloned for sequencing;

15 Figure 26 shows schematically the structure of three alternative gene products of the putative bovine GGF-II gene. Exons are listed A through E in the order of their discovery. The alternative splicing patterns 1, 2 and 3 generate three overlapping deduced protein
20 structures (GGF2BPP1, 2, and 3), which are displayed in the various Figures 28;

Figure 27 compares the GGF-I and GGF-II sequences identified in the deduced protein sequences (SEQ ID Nos. 120-132) shown in Figures 28A, 28B, 28B′ and 28C with the
25 novel peptide sequences listed in Figures 10 and 12. The Figure shows that six of the nine novel GGF-II peptide sequences are accounted for in these deduced protein sequences. Two peptide sequences similar to GGF-I sequences are also found;

30 Figure 28A shows the coding strand DNA sequence and deduced amino acid sequence of the cDNA (SEQ ID No. 133) obtained from splicing pattern number 1 shown in Figure 26. This partial cDNA of the putative bovine GGF-II gene encodes a protein of 206 amino acids in
35 length. Peptides shown in bold were those identified

from the lists presented in Figures 10 and 12. Potential glycosylation sites are underlined (along with polyadenylation signal AATAAA);

Figure 28B, 28B′ show the coding strand DNA sequence and deduced amino acid sequence of the cDNA (SEQ ID No. 134) obtained from splicing pattern number 2 shown in Figure 26. This partial cDNA of the putative bovine GGF-II gene encodes a protein of 281 amino acids in length. Peptides shown in bold were those identified from the lists presented in Figures 10 and 12. Potential glycosylation sites are underlined (along with polyadenylation signal AATAAA);

Figure 28C shows the coding strand DNA sequence and deduced amino acid sequence of the cDNA (SEQ ID No. 135) obtained from splicing pattern number 3 shown in Figure 26. This partial cDNA of the putative bovine GGF-II gene encodes a protein of 257 amino acids in length. Peptides shown in bold were those identified from the lists presented in Figures 10 and 12. Potential glycosylation sites are underlined (along with polyadenylation signal AATAAA); and the DNA sequences shown in Figures 28a, 28b and 28c are themselves further aspects of this invention; and the invention further includes polypeptides encoded by said sequences;

Figure 29 relates to Example 7, hereinafter, and shows an autoradiogram of a cross hybridization analysis of putative bovine GGF-II gene sequences to a variety of mammalian DNAs on a Southern blot. The filter contains lanes of Eco RI-digested DNA (5 Mg per lane) from the species listed in the Figure. The probe detects a single strong band in each DNA sample, including a four kb fragment in the bovine DNA as anticipated by the physical map in Figure 25. Bands of relatively minor intensity are observed as well, which could represent related DNA sequences. The strong hybridizing band from each of the

other mammalian DNA samples presumably represents the GGF-II homologue of those species.

In Example 1 hereinafter, unless otherwise indicated, all operations were conducted at 40°C, and, with reference to Figures 1 to 6, activity at each stage was determined using the Brockes (Meth. Enz., supra) techniques with the following modifications. Thus, in preparing Schwann cells, 5μM forskolin was added in addition to DMEM (Dulbecco's modified Eagle's medium), FCS and GGF. Cells used in the assay were fibroblast-free Schwann cells at passage number less than 10, and these cells were removed from flasks with trypsin and plated into flat-bottomed 96-well plates at 3.3 thousand cells per microwell.

^{125}IIUdR was added for the final 24 hours after the test solution addition. The background (unstimulated) incorporation to each assay was less than 100 cpm, and maximal incorporation was 20 to 200 fold over background depending on Schwann cell batch and passage number.

In the case of the GGF-I and GGF-II fractions from reversed-phase HPLC as described below in Example 1, two dose response curves were also produced for each factor, using exactly the above method for one of the curves for each factor, and the above method modified in the assay procedure only by substituting fetal calf plasma for fetal calf serum to obtain the other curve for each factor. The results are in Figures 7 and 8.

Figure 30 is a schematic diagram of representative splicing variants. The coding segments are represented by F, E, B, A, G, C, C/D, C/D', D, D', H, K and L. The location of the peptide sequences derived from purified protein are indicated by "o".

Figure 31A through 31O (SEQ ID No. 136-147, 173-182, 160, 161 and 163) (is a listing of the DNA sequences

and predicted peptide sequences of the coding segments of GGF. Line 1 represents the predicted amino acid sequence of bovine GGF, line 2 represents the nucleotide sequence of bovine GGF, line 3 represents the nucleotide sequence
5 of human GGF (heregulin) (nucleotide base matches are indicated with a vertical line) and line 4 represents the predicted amino acid sequence of human GGF/heregulin where it differs from the predicted bovine sequence. Coding segment K represents only the bovine sequence.
10 The human and bovine coding segments for both E and A' are provided. Coding segment D' represents only the human (heregulin) sequence.

Figure 32A and 32B is the predicted GGF2 amino acid sequence and nucleotide sequence of BPP5 (SEQ ID No.
15 148). The upper line represents the nucleotide sequence and the lower line represents the predicted amino acid sequence.

Figure 33A and 33B is the predicted amino acid sequence and nucleotide sequence of GGF2BPP2 (SEQ ID No.
20 149). The upper line represents the nucleotide sequence and the lower line represents the predicted amino acid sequence.

Figure 34A through Figure 34C is the predicted amino acid sequence and nucleotide sequence of GGF2BPP4
25 (SEQ ID NO: 150). The upper line represents the nucleotide sequence and the lower line represents the predicted amino acid sequence.

Figure 35 (SEQ ID Nos. 151-152) depicts the alignment of two GGF peptide sequences (GGF2bpp4 and
30 GGF2bpp5) with the human EGF (hEGF) peptides sequences. Asterisks indicate positions of conserved cysteines.

Figure 36 depicts the level of GGF activity (Schwann cell mitogenic assay) and tyrosine phosphorylation of a ca. 200kD protein (intensity of a
35 200 kD band on an autoradiogram of a Western blot

developed with an antiphosphotyrosine polyclonal antibody) in response to increasing amounts of GGF.

Figure 37A and Figure 37B is a list of splicing variants derived from the sequences shown in Figure 31.

5 Figure 38 is a scale coding segment map of the clone. T3 refers to the bacteriophage promoter used to produce mRNA from the clone. R = flanking EcoRI restriction enzyme sites. 5′ UT refers to the 5′ untranslated region. E, B, A, C, C/D′, and D refer to 10 the coding segments. O = the translation start site. Λ = the 5′ limit of the region homologous to the bovine E segment (see example 6) and 3′ UT refers to the 3′ untranslated region.

Figure 39 is the predicted amino acid sequence, 15 bottom, and nucleic sequence, top, of EGFL1 (SEQ ID No. 154).

Figure 40 is the predicted amino acid sequence, bottom, and nucleic sequence, top, of EGFL2 (SEQ ID No. 155).

20 Figure 41 is the predicted amino acid sequence, bottom, and nucleic sequence, top, of EGFL3 (SEQ ID No. 156).

Figure 42 is the predicted amino acid sequence, bottom, and nucleic sequence, top, of EGFL4 (SEQ ID No. 25 157).

Figure 43 is the predicted amino acid sequence, bottom, and nucleic sequence, top, of EGFL5 (SEQ ID No. 158).

Figure 44 is the predicted amino acid sequence, 30 bottom, and nucleic sequence, top, of EGFL6 (SEQ ID No. 159).

Figure 45A through Figure 45D is the predicted amino acid sequence (middle) and nucleic sequence (top) of GGF2HBS5 (SEQ ID No. 121). The bottom (intermittent

sequence represents peptide sequences derived from GGFII preparations (see Figures 11, 12).

Detailed Description

The invention pertains to methods for the use of novel factors which are inhibitors of cell, particularly neural and glial cell proliferation, and the use of DNA sequences encoding these factors. Disclosed are several gene splicing variants of these factors which may encode inhibitors of cell division.

Holmes et al. ((1992) Science 256:1205) and Wen et al. ((1992) Cell 69:559) demonstrate that DNA sequences encoding proteins which bind to a receptor associated with several human tumors ($p185^{erbB2}$) share a great deal of homology with GGF DNA sequences. This provides evidence to indicate that the bovine GGFs and the human and rat $p185^{erbB2}$ ligands are encoded by the same (homologous) gene and that ligand groups both interact with the same receptor ($p185^{erbB2}$).

The $p185^{erbB2}$ protein is a 185 kilodalton membrane spanning protein with tyrosine kinase activity. The protein is encoded by the *erbB2* proto-oncogene (Yarden and Ullrich. (1988) Ann. Rev. Biochem. 57:443). The *erbB2* gene, also referred to as HER-2 (in human cells) and *neu* (in rat cells), is closely related to the receptor for epidermal growth factor (EGF). Recent evidence indicates that proteins which interact with (and activate the kinase of) $p185^{erbB2}$ induce proliferation in the cells bearing $p185^{erbB2}$ (Holmes et al. (1992) Science 256:1205; Dobashi et al. (1991) Proc. Natl. Acad. Sci. 88:8582; Lupu et al. (1992) Proc. Natl. Acad. Sci. 89:2287). This evidence supports the conclusion that the gene encoding GGF's and the $p185^{erbB2}$ binding proteins are responsible for the production of a family of growth factors which have pleiotropic effects in that they

target both neural cells, particularly Schwann cells, and cells which give rise to human adenocarcinoma and other carcinomas.

Furthermore, it is evident that the gene encoding 5 GGF and $p185^{erbB2}$ binding proteins produces a number of variably-sized, differentially-spliced RNA transcripts that give rise to a series of proteins, which are of different lengths and contain some common peptide sequences and some unique peptide sequences. This is 10 supported by the evidence that differentially spliced sequences are recoverable from bovine posterior pituitary RNA (as presented herein), and human breast cancer cell line (MDA-MB-231) RNA (Holmes et al. (1992) Science 256:1205). Further support for this "one gene: multiple 15 product" conclusion derives from the wide size range of proteins which act as both mitogens for Schwann cells (as disclosed herein) and ligands for the $p185^{erbB2}$ receptor (see below).

Further evidence to support the fact that the 20 genes encoding GGF and $p185^{erbB2}$ receptor ligands are homologous comes from nucleotide sequence comparison. Holmes et al. ((1992) Science, 256:1205-1210) demonstrate the purification of a 45-kilodalton human protein (heregulin) which specifically interacts with the 25 $p185^{erbB2}$ receptor. The predicted sequences of the polypeptides encoded by these human DNA sequences match very closely with the sequences predicted from the Glial Growth Factor sequences. Peles et al. ((1992) Cell 69:205) and Wen et al ((1992) Cell 69:559) describe a 30 complementary DNA isolated from rat cells encoding a protein called *neu* differentiation factor (NDF), which shares homology with the heregulin sequences described by Holmes et al. In addition, the translation product of the NDF cDNA has $p185^{erbB2}$ binding activity. Several 35 other groups have reported the purification of proteins

of various molecular weights with *erbB2* binding activity. These groups include Lupu et al. ((1992) Proc. Natl. Acad. Sci. USA 89:2287), Yarden and Peles ((1991) Biochemistry 30:3543), Lupu et al ((1990) Science 249:1552), and Dobashi et al. ((1991) Biochem Biophys. Res. Comm. 179:1536).

It has been established that the p185^{erbB2} oncogene and, by inference, its cognate ligands play a significant role in the development and maintenance of several types of tumors. Amplification and overexpression of *erbB2* has been associated with human adenocarcinomas from several tissues (Kraus et al. (1987) EMBO J. 6:605; Slamon et al. (1987) Science 235:177; Varley et al. (1987) Oncogene 1:423; and van de Vijver et al. (1987) Mol Cell Biol 7:2019). An association has also been reported with breast and ovarian cancer (Slamon et al. supra; Varley et al. supra: Venter et al. (1987) Lancet ii:67; Zhou et al. (1987) Cancer Res. 47:6123; Berger et al. (1988) Cancer Res. 48:1238; Tsuda et al. (1989) Cancer Res. 49:3104; Slamon et al. (1989) Science 244:707).

There is also evidence that the *erbB2* gene plays a role in oncogenesis of cells of the Schwann cell lineage (Perantoni et al. (1987) Proc. Nat. Acad. Sci. 84:6317; Nikitin et al. (1991) Proc. Nat. Acad. Sci. 88:9939). Several tumor types are a result of abnormal proliferation of Schwann cells and these include neurofibromas, and malignant schwannomas and neurofibrosarcomas.

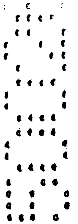
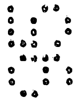
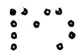
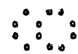
As candidate ligands for the *erbB2* receptor, the GGFs could play a significant role in the development of the tumors described above.

As outlined above, the gene encoding the GGFs and the p185^{erbB2} ligands gives rise to a number of variant transcripts which encode a variety of proteins. Several of these variant proteins bind to the p185^{erbB2} receptor

on neural cells, including Schwann cells (described above and disclosed herein), as well as to the same receptor on tumor cell lines as described above. Some of these variant proteins activate cell proliferation in Schwann cells and in tumor cell lines (described above and disclosed herein). Other variants may possibly interfere with the activity of the ligands which stimulate proliferation by competing with those ligands for binding sites on the $p185^{erbB2}$ receptor. Chan et al. ((1991) Science 254:1382) showed that a naturally occurring hepatocyte growth factor (HGF) variant was derived from a smaller transcript encoded by the same gene as the full length molecule. The truncated protein encoded by the variant transcript specifically inhibits HGF induced mitogenesis and was demonstrated to compete with HGF for binding to the HGF receptor. The HGF receptor has been identified as the *c-met* proto-oncogene product. Thus, these variant versions of growth factor proteins may play a significant regulatory role in the control of cell proliferation. GGF-related factors which inhibit glial proliferation will be therapeutically useful as anti-proliferative compounds for the treatment of tumors of the neural system.

It has been shown that myelination by Schwann cells and oligodendrocytes is regulated by the proliferative state (Jessen et al., 1991 *Ann NY Acad Science* 633:78-89). When the cell withdraws from the proliferative cycle the myelination process appears to begin. Factors of the invention which induce Schwann cells and oligodendrocytes to exit the proliferative cell cycle and enter the quiescent state may be administered to increase myelination of existing or newly regenerated neural tissue in a mammal suffering from diseases or disorders of demyelination. Examples of diseases and disorders which may be treated using an inhibitor of

mutagenesis include Charot-Marie-Tooth disease (particularly type I and type III), peroneal muscular atrophy, Dejérine-Sottos disease (type III hereditary motor and sensory neuropathy), multiple sclerosis,
5 chronic inflammatory demyelinating polyradiculoneuropathy, chronic liver disease, diphtheritic polyneuritis, Guillain-Barré syndrome, hypothyroid polyneuropathy, metachromatic leukodystrophy, type I hereditary motor and sensory neuropathy, type III
10 hereditary motor and sensory neuropathy, and vasculitic neuropathy.

EXAMPLE 1

I. Preparation of Factor-CM Fraction

4,000 frozen whole bovine pituitaries (c.a. 12 kg) were thawed overnight, washed briefly with water and then
5 homogenized in an equal volume of 0.15 M ammonium sulphate in batches in a Waring Blender. The homogenate was taken to pH 4.5 with 1.0 M HCl and centrifuged at 4,900g for 80 minutes. Any fatty material in the supernatant was removed by passing it through glass wool.
10 After taking the pH of the supernatant to 6.5 using 1.0 M NaOH, solid ammonium sulphate was added to give a 36% saturated solution. After several hours stirring, the suspension was centrifuged at 4,900 g for 80 minutes and the precipitate discarded. After filtration through
15 glass wool, further solid ammonium sulphate was added to the supernatant to give a 75% saturated solution which was once again centrifuged at 4,900 g for 80 minutes after several hours stirring. The pellet was resuspended in c.a. 2 L of 0.1 M sodium phosphate pH 6.0 and dialyzed
20 3 x 40 L of the same buffer. After confirming that the conductivity of the dialysate was below 20.0 μSiemens, it was loaded onto a Bioprocess column (120 x 113 mm, Pharmacia) packed with carboxymethyl cellulose (CM-52, Whatman) at a flow rate of 2 $\mu l.min^{-1}$ The column was
25 washed with 2 volumes of 0.1 M sodium phosphate pH 6.0, followed by 2 volumes of 50 mM NaCl, and finally 2 volumes of 0.2 M NaCl both in the same buffer. During the final step, 10 μL (5 minute) fractions were collected. Fractions 73 to 118 inclusive were pooled,
30 dialyzed against the 10 volumes of 10 mM sodium phosphate pH 6.0 twice and clarified by centrifugation at 100,000 g for 60 minutes.

II. Hydroxylapatite HPLC

Hydroxylapatite HPLC is not a technique hitherto used in isolating glial growth factors, but proved particularly efficacious in this invention.
The material obtained from the above CM-cellulose chromatography was filtered through a 0.22 μm filter (Nalgene), loaded at room temperature on to a high performance hydroxylapatite column (50 x 50 mm, Biorad) equipped with a guard column (15 x 25 mm, Biorad) and equilibrated with 10 mM potassium phosphate pH 6.0. Elution at room temperature was carried out at a flow rate of 2 μl.minute^{-1} using the following programmed linear gradient:

time (min)	%B
0.0	0
5.0	0
7.0	20
70.0	20
150.0	100
180.0	100
185.0	0

Solvent A : 10 mM potassium phosphate pH 6.0
Solvent B : 1.0 M potassium phosphate pH 6.0

6.0 μL (3 minutes) fractions were collected during the gradient elution. Fractions 39-45 were pooled and dialyzed against 10 volumes of 50 mM sodium phosphate pH 6.0.

III. Mono S FPLC

Mono S FPLC enabled a more concentrated material to be prepared for subsequent gel filtration.

Any particulate material in the pooled material from the hydroxylapatite column was removed by a clarifying spin at 100,000 g for 60 minutes prior to loading on to a preparative HR10/10 Mono S cation

exchange column (100 x 10 mm, Pharmacia) which was then re-equilibrated to 50 MM sodium phosphate pH 6.0 at room temperature with a flow rate of 1.0 μL.minute^{-1}. Under these conditions, bound protein was eluted using the following programmed linear gradient:

time (min)	%B
0.0	0
70.0	30
240.0	100
250.0	100
260.0	0

Solvent A : 50 mM potassium phosphate pH 6. 0

Solvent B : 1.2 M sodium chloride, 50 mm sodium phosphate pH 6.0

1 μL (1 minute) fractions were collected throughout this gradient program. Fractions 99 to 115 inclusive were pooled.

IV. Gel Filtration FPLC

This step commenced the separation of the two factors of the invention prior to final purification, producing enriched fractions.

For the purposes of this step, a preparative Superose 12 FPLC column (510 x 20 mm, Pharmacia) was packed according to the manufacturers' instructions. In order to standardize this column, a theoretical plates measurement was made according to the manufacturers' instructions, giving a value of 9,700 theoretical plates.

The pool of Mono S eluted material was applied at room temperature in 2.5 μL aliquots to this column in 50 MM sodium phosphate, 0.75 NaCl pH 6.0 (previously passed through a C18 reversed phase column (Sep-pak, Millipore) at a flow rate of 1.0 $\mu L.minute^{-1}$. 1 μL (0.5 minute) fractions were collected from 35 minutes after each sample was applied to the column. Fractions 27 to 41 (GGF-II) and 42 to 57 (GGF-I) inclusive from each run were pooled.

V. Reversed-Phase HPLC

The GGF-I and GGF-II pools from the above Superose 12 runs were each divided into three equal aliquots. Each aliquot was loaded on to a C8 reversed-phase column (Aquapore RP-300 7 μ C8 220 x 4.6 mm, Applied Biosystems) protected by a guard cartridge (RP-8, 15 x 3.2 mm, Applied Biosystems) and equilibrated to 4°C at 0.5 μL.minute. Protein was eluted under these conditions using the following programmed linear gradient:

time (min)	%B
0	
60	66.6
62.0	100
72.0	100
75.0	0

Solvent A : 0.1% trifluoroacetic acid (TFA)

Solvent B : 90% acetonitrile, 0.1% TFA

200 μL (0.4 minute) fractions were collected in siliconized tubes (Multilube tubes, Bioquote) from 15.2 minutes after the Beginning of the programmed gradient.

VI. SDS-Polyacrylamide Gel Electrophoresis

In this step, protein molecular weight standards, low range, catalogue no. 161-0304, from Bio-Rad Laboratories Limited, Watford, England were employed. The actual proteins used, and their molecular weight standards, have been listed hereinbefore.

Fractions 47 to 53 (GGF-I) and fractions 61 to 67 (GGF-II) from the reversed-phase runs were individually pooled. 7 μL of the pooled material was boiled in an equal volume of 0.0125 M Tris-Cl, 4% SDS, 20% glycerol, and 10% β-mercaptoethanol for GGF-I, for 5 minutes and loaded on to an 11% polyacrylamide Leammli gel with a 4%

stacking gel and run at a constant voltage of 50 V for 16 hours. This gel was then fixed and stained using a silver staining kit (Amersham). Under these conditions, the factors are each seen as a somewhat diffuse band at
5 relative molecular weights 30,000 to 36,000 Daltons (GGF-I) and 55,000 to 63,000 Daltons (GGF-II), as defined by molecular weight markers. From the gel staining, it is apparent that there are a small number of other protein species present at equivalent levels to the GGF-I
10 and GGF-II species in the material pooled from the reversed-phase runs.

VII. Stability in Trifluoroacetic Acid

Stability data were obtained for the present Factors in the presence of trifluoroacetic acid, as
15 follows:

GGF-I

Material from the reversed-phase HPLC, in the presence of 0.1% TFA and acetonitrile, was assayed within 12 hours of the completion of the column run and then
20 after 10 weeks incubation at 40°C. Following incubation, the GGF-I had at least 50% of the activity of that material assayed directly off the column.

GGF-II

Material from the reversed-phase HPLC, in the
25 presence of 0.1% TFA and acetonitrile, and stored at -20°C, was assayed after thawing and then after 4 days incubation at 40°C. Following incubation, the GGF-II had at least 50% of the activity of that material freshly thawed.

30 It will be appreciated that the trifluoroacetic acid concentration used in the above studies is that most commonly used for reversed-phase chromatography.

EXAMPLE 2

Amino acid sequences purified GGF-I and GGF-II

Amino acid sequence analysis studies were performed using highly purified bovine pituitary GGF-I and GGF-II. The conventional single letter code was used 5 to describe the sequences. Peptides were obtained by lysyl endopeptidase and protease V8 digests, carried out on reduced and carboxymethylated samples, with the lysyl endopeptidase digest of GGF-II carried out on material eluted from the 55-65 RD region of a 11% SDS-PAGE (MW 10 relative to the above-quoted markers).

A total of 21 peptide sequences (see Figure 9) were obtained for GGF-I, of which 12 peptides (see Figure 10) are not present in current protein databases and therefore represent unique-sequences. A total of 12 15 peptide sequences (see Figure 11) were obtained for GGF-II, of which 10 peptides (see Figure 12) are not present in current protein databases and therefore represent unique sequences (an exception is peptide GGF-II 06 (SEQ ID No. 38) which shows identical sequences in many 20 proteins which are probably of no significance given the small number of residues). These novel sequences are extremely likely to correspond to portions of the true amino acid sequences of GGFs I and II.

Particular attention can be drawn to the sequences 25 of GGF-I 07 (SEQ ID No. 39) and GGF-II 12 (SEQ ID No. 44), which are clearly highly related. The similarities indicate that the sequences of these peptides are almost certainly those of the assigned GGF species, and are most unlikely to be derived from contaminant proteins.

30 In addition, in peptide GGF-II 02 (SEQ ID No. 34), the sequence X S S is consistent with the presence of an N linked carbohydrate moiety on an asparagine at the position denoted by X.

In general, in Figures 9 and 11, X represents an 35 unknown residue denoting a sequencing cycle where a

single position could not be called with certainty either because there was more than one signal of equal size in the cycle or because no signal was present. As asterisk denotes those peptides where the last amino acid called
5 corresponds to the last amino acid present in that peptide. In the remaining peptides, the signal strength after the last amino acid called was insufficient to continue sequence calling to the end of that peptide. The right hand column indicates the results of a computer
10 database search using the GCG package FASTA and TFASTA programs to analyze the NBRF and EMBL sequence databases. The name of a protein in this column denotes identity of a portion of its sequence with the peptide amino acid sequence called allowing a maximum of two mismatches. A
15 question mark denotes three mismatches allowed. The abbreviations used are as follows:

HMG-1 High Mobility Group protein-1
HMG-2 High Mobility Group protein-2
LH-alpha Luteinizing hormone alpha subunit
20 LH-beta Luteinizing hormone beta subunit

EXAMPLE 3

Mitogenic activity of purified GGF-I and GGF-II

The mitogenic activity of a highly purified sample containing both GGFs I and II was studied using a
25 quantitative method, which allows a single microculture to be examined for DNA synthesis, cell morphology, cell number and expression of cell antigens. This technique has been modified from a method previously reported by Muir et al. ((1990) Analytical Biochemistry 185:377-382).
30 The main modifications are: 1) the use of uncoated microtiter plates, 2) the cell number per well, 3) the use of 5% Fetal Bovine Plasma (FBP) instead of 10% Fetal Calf Serum (FCS), and 4) the time of incubation in presence of mitogens and bromodeoxyuridine (BrdU), added

simultaneously to the cultures. In addition the cell monolayer was not washed before fixation to avoid loss of cells, and the incubation time of monoclonal mouse anti-BrdU antibody and peroxidase conjugated goat
5 anti-mouse immunoglobulin (IgG) antibody were doubled to increase the sensitivity of the assay. The assay, optimized for rat sciatic nerve Schwann cells, has also been used for several cell lines, after appropriate modifications to the cell culture conditions.

10 I. Methods of Mitogenesis Testing

On day 1, purified Schwann cells were plated onto uncoated 96 well plates in 5% FBP/Dulbecco's Modified Eagle Medium (DMEM) (5,000 cells/well). On day 2, GGFs or other test factors were added to the cultures, as well
15 as BrdU at a final concentration of 10mm. After 48 hours (day 4) BrdU incorporation was terminated by aspirating the medium and cells were fixed with 200 μl/well of 70% ethanol for 20 min at room temperature. Next, the cells were washed with water and the DNA denatured by
20 incubation with 100 μl 2N HCl for 10 min at 37°C. Following aspiration, residual acid was neutralized by filling the wells with 0.1M borate buffer, pH 9.0, and the cells were washed with phosphate buffered saline (PBS). Cells were then treated with 50 μl of blocking
25 buffer (PBS containing 0.1% Triton X 100 and 2% normal goat serum) for 15 min at 37°C. After aspiration, monoclonal mouse anti-BrdU antibody (Dako Corp., Santa Barbara, CA) (50 μl/well, 1.4 mg/ml diluted in blocking buffer) was added and incubated for two hours at 37°C.
30 Unbound antibodies were removed by three washes in PBS containing 0.1% Triton X-100 and peroxidase-conjugated goat ant-mouse IgG antibody (Dako Corp., Santa Barbara, CA) (50 μl/well, 2 mg/ml diluted in blocking buffer) was added and incubated for one hour at 37°C. After three

washes in PBS/Triton and a final rinse in PBS, wells received 100 μl/well of 50 mM phosphate/citrate buffer, pH 5.0, containing 0.05% of the soluble chromogen o-phenylenediamine (OPD) and 0.02% H_2O_2. The reaction was terminated after 5-20 min at room temperature, by pipetting 80 μl from each well to a clean plate containing 40 μl/well of 2N sulfuric acid. The absorbance was recorded at 490nm using a plate reader (Dynatech Labs). The assay plates containing the cell monolayers were washed twice with PBS and immunocytochemically stained for BrdU-DNA by adding 100 μl/well of the substrate diaminobenzidine (DAB) and 0.02% H_2O_2 to generate an insoluble product. After 10-20 min the staining reaction was stopped by washing with water, and BrdU-positive nuclei observed and counted using an inverted microscope. Occasionally, negative nuclei were counterstained with 0-001% Toluidine blue and counted as before.

II. Cell Lines used for Mitogenesis Assays

Swiss 3T3 Fibroblasts

Cells, from Flow Labs, were maintained in DMEM supplemented with 10% FCS, penicillin and streptomycin, at 37°C in a humidified atmosphere of 10% CO_2 in air. Cells were fed or subcultured every two days. For mitogenic assay, cells were plated at a density of 5,000 cells/well in complete medium and incubated for a week until cells were confluent and quiescent. The serum containing medium was removed and the cell monolayer washed twice with serum free-medium. 100 μl of serum free medium containing mitogens and 10μM BrdU were added to each well and incubated for 48 hours. Dose responses to GGFs and serum or PDGF (as a positive control) were performed.

BHK (Baby Hamster Kidney) 21 C13 Fibroblasts

Cells from European Collection of Animal Cell Cultures (ECACC), were maintained in Glasgow Modified Eagle Medium (GMEM) supplemented with 5% tryptose phosphate broth, 5% FCS, penicillin and streptomycin, at 37°C in a humidified atmosphere of 5% CO_2 in air. Cells were fed or subcultured every two to three days. For mitogenic assay, cells were plated at a density of 2,000 cell/well in complete medium for 24 hours. The serum containing medium was then removed and after washing with serum free medium, replaced with 100 µl of 0.1% FCS containing GMEM or GMEM alone. GGFs and FCS or BFGF as positive controls were added, coincident with 10µM BrdU, and incubated for 48 hours. Cell cultures were then processed as described for Schwann cells.

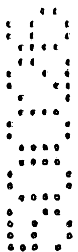
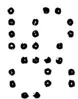
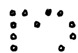
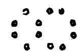
C6 Rat Glioma Cell Line

Cells, obtained at passage 39, were maintained in DMEM containing 5% FCS, 5% Horse serum (HS), penicillin and streptomycin, at 37°C in a humidified atmosphere of 10% CO_2 in air. Cells were fed or subcultured every three days. For mitogenic assay, cells were plated at a density of 2,000 cells/well in complete medium and incubated for 24 hours. Then medium was replaced with a mixture of 1:1 DMEM and F12 medium containing 0.1% FCS, after washing in serum free medium. Dose responses to GGFs, FCS and AFGF were then performed and cells were processed through the ELISA as previously described for the other cell types.

PC12 (Rat Adrenal Pheochromocytoma Cells)

Cells from ECACC, were maintained in RPMI 1640 supplemented with 10% HS, 5% FCS, penicillin and streptomycin, in collagen coated flasks, at 37°C in a humidified atmosphere of 5% CO_2 in air. Cells were fed

every three days by replacing 80% of the medium. For mitogenic assay, cells were plated at a density of 3,000 cells/well in complete medium, on collagen coated plates (50 μl/well collagen, Vitrogen Collagen Corp., diluted 1 : 50, 30 min at 37°C) and incubated for 24 hours. The medium was then placed with fresh RPMI either alone or containing 1 mM insulin or 1% FCS. Dose responses to FCS/HS (1:2) as positive control and to GGFs were performed as before. After 48 hours cells were fixed and the ELISA performed as previously described.

III. Results of Mitogenesis Assays

All the experiments presented in this Example were performed using a highly purified sample from a Superose 12 chromatography purification step (see Example 1, section D) containing a mixture of GGF-I and GGF-II (GGFs).

Firstly, the results obtained with the BrdU incorporation assay were compared with the classical mitogenic assay for Schwann cells based on ^{125}I-UdR incorporation into DNA of dividing cells, described by J.P.Brockes ((1987) Methods Enzymol. 147:217).

Figure 13 shows the comparison of data obtained with the two assays, performed in the same cell culture conditions (5,000 cells/well, in 5% FBP/DMEM, incubated in presence of GGFs for 48hrs). As clearly shown, the results are comparable, but BrdU incorporation assay appears to be slightly more sensitive, as suggested by the shift of the curve to the left of the graph, i.e. to lower concentrations of GGFS.

As described under the section "Methods", after the immunoreactive BrdU-DNA has been quantitated by reading the intensity of the soluble product of the OPD peroxidase reaction, the original assay plates containing cell monolayers can undergo the second reaction resulting in the insoluble DAB product, which stains the BrdU positive nuclei. The microcultures can then be examined under an inverted microscope, and cell morphology and the numbers of BrdU-positive and negative nuclei can be observed.

In Figure 14a and Figure 14b the BrdU-DNA immunoreactivity, evaluated by reading absorbance at 490 nm, is compared to the number of BrdU-positive nuclei and to the percentage of BrdU-positive nuclei on the total number of cells per well, counted in the same cultures. Standard deviations were less than 10%. The two

evaluation methods show a very good correlation and the discrepancy between the values at the highest dose of GGFs can be explained by the different extent of DNA synthesis in cells detected as BrdU-positive.

5 The BrdU incorporation assay can therefore provide additional useful information about the biological activity of GGFs on Schwann cells when compared to the ^{125}I-UdR incorporation assay. For example, the data reported in Figure 15 show that GGFs can act on Schwann 10 cells to induce DNA synthesis, but at lower doses to increase the number of negative cells present in the microculture after 48 hours.

The BrdU incorporation assay has been used on several cell lines of different origin. In Figure 16 the 15 mitogenic responses of Schwann cells and Swiss 3T3 fibroblasts to GGFs are compared; despite the weak response obtained in 3T3 fibroblasts, some clearly BrdU-positive nuclei were detected in these cultures. Control cultures were run in parallel in presence of 20 several doses of FCS or human recombinant PDGF, showing that the cells could respond to appropriate stimuli (not shown).

The ability of fibroblasts to respond to GGFs was further investigated using the BHK 21 C13 cell line. 25 These fibroblasts, derived from kidney, do not exhibit contact inhibition or reach a quiescent state when confluent. Therefore the experimental conditions were designed to have a very low background proliferation without comprising the cell viability. GGFs have a 30 significant mitogenic activity on BHK21 C13 cells as shown by Figure 17 and Figure 18. Figure 17 shows the Brdu incorporation into DNA by BHK 21 C13 cells stimulated by GGFS in the presence of 0.1% FCS. The good mitogenic response to FCS indicates that cell culture 35 conditions were not limiting. In Figure 18 the mitogenic

effect of GGFs is expressed as the number of BrdU-positive and BrdU-negative cells and as the total number of cells counted per well. Data are representative of two experiments run in duplicates; at least three fields per well were counted. As observed for Schwann cells in addition to a proliferative effect at low doses, GGFs also increase the numbers of nonresponding cells surviving. The percentage of BrdU positive cells is proportional to the increasing amounts of GGFs added to the cultures. The total number of cells after 48 hours in presence of higher doses of GGFs is at least doubled, confirming that GGFs induce DNA synthesis and proliferation in BHK21 C13 cells. Under the same conditions, cells maintained for 48 hours in the presence of 2% FCS showed an increase of about six fold (not shown).

C6 glioma cells have provided a useful model to study glial cell properties. The phenotype expressed seems to be dependent on the cell passage, the cells more closely resembling an astrocyte phenotype at an early stage, and an oligodendrocyte phenotype at later stages (beyond passage 70). C6 cells used in these experiments were from passage 39 to passage 52. C6 cells are a highly proliferating population, therefore the experimental conditions were optimized to have a very low background of BrdU incorporation. The presence of 0.1% serum was necessary to maintain cell viability without significantly affecting the mitogenic responses, as shown by the dose response to FCS (Figure 19).

In Figure 20 the mitogenic responses to aFGF (acidic Fibroblast growth factor) and GGFs are expressed as the percentages of maximal BrdU incorporation obtained in the presence of FCS (8%). Values are averages of two experiments, run in duplicates. The effect of GGFs was comparable to that of a pure preparation of aFGF. aFGF

has been described as a specific growth factor for C6 cells (Lim R. et al. (1990) Cell Regulation 1:741-746) and for that reason it was used as a positive control. The direct counting of BrdU positive and negative cells
5 was not possible because of the high cell density in the microcultures. In contrast to the cell lines so far reported, PC12 cells did not show any evident responsiveness to GGFS, when treated under culture conditions in which PC12 could respond to sera (mixture
10 of FCS and HS as used routinely for cell maintenance). Nevertheless the number of cells plated per well seems to affect the behavior of PC12 cells, and therefore further experiments are required.

EXAMPLE 4

15 **Isolation and cloning of nucleotide sequences encoding proteins containing GGF-I and GGF-II peptides**

Isolation and cloning of the GGF-II nucleotide sequences was performed as outlined herein, using peptide sequence information and library screening, and was
20 performed as set out below. It will be appreciated that the peptides of Figures 4 and 5 can be used as the starting point for isolation and cloning of GGF-I sequences by following the techniques described herein. Indeed, Figure 21, (SEQ ID No. 54-88) shows possible
25 degenerate oligonucleotide probes for this purpose, and Figure 23, (SEQ ID Nos. 90-119), lists possible PCR primers. DNA sequence and polypeptide sequence should be obtainable by this means as with GGF-II, and also DNA constructs and expression vectors incorporating such DNA
30 sequence, host cells genetically altered by incorporating such constructs/vectors, and protein obtainable by cultivating such host cells. The invention envisages such subject matter.

I. Design and Synthesis of oligonucleotide Probes and Primers

Degenerate DNA oligomer probes were designed by backtranslating the amino acid sequences (derived from
5 the peptides generated from purified GGF protein) into nucleotide sequences. Oligomers represented either the coding strand or the non-coding strand of the DNA sequence. When serine, arginine or leucine were included in the oligomer design, then two separate syntheses were
10 prepared to avoid ambiguities. For example, serine was encoded by either TCN or AGY as in 537 and 538 or 609 and 610. Similar codon splitting was done for arginine or leucine (e.g. 544, 545). DNA oligomers were synthesized on a Biosearch 8750 4-column DNA synthesizer using ß
15 cyanoethyl chemistry operated at 0.2 micromole scale synthesis. Oligomers were cleaved off the column (500 angstrom CpG resins) and deprotected in concentrated ammonium hydroxide for 6-24 hours at 55-60'C. Deprotected oligomers were dried under vacuum (Speedvac)
20 and purified by electrophoresis in gels of 15% acrylamide (20 mono : 1 bis), 50 mM Tris-borate-EDTA buffer containing 7M urea. Full length oligomers were detected in the gels by UV shadowing, then the bands were excised and DNA oligomers eluted into 1.5 μls H20 for 4-16 hours
25 with shaking. The eluate was dried, redissolved in 0.1 μl H_2O and absorbance measurements were taken at 260nm.

Concentrations were determined according to the following formula:

(A 260 x units/μl) (60.6/length) = x μM

30 All oligomers were adjusted to 50 μM concentration by addition of H_2O.

Degenerate probes designed as above are shown in Figure 21, (SEQ ID Nos. 54-88).

PCR primers were prepared by essentially the same
35 procedures that were used for probes with the following modifications. Linkers of thirteen nucleotides

containing restriction sites were included at the 5′ ends of the degenerate oligomers for use in cloning into vectors. DNA synthesis was performed at 1 micromole scale using 1,000 angstrom CpG resins and inosine was
5 used at positions where all four nucleotides were incorporated normally into degenerate probes. Purifications of PCR primers included an ethanol precipitation following the gel electrophoresis purification.

10 II. Library Construction and Screening

A bovine genomic DNA library was purchased from Stratagene (Catalogue Number: 945701). The library contained 2 x 10^6 15-20kb Sau3A1 partial bovine DNA fragments cloned into the vector lambda DashII. A bovine
15 total brain CDNA library was purchased from Clonetech (Catalogue Number: BL 10139). Complementary DNA libraries were constructed (In Vitrogen; Stratagene) from mRNA prepared from bovine total brain, from bovine pituitary and from bovine posterior pituitary. In
20 Vitrogen prepared two cDNA libraries: one library was in the vector lambda g10, the other in vector pcDNAI (a plasmid library). The Stratagene libraries were prepared in the vector lambda unizap. Collectively, the cDNA libraries contained 14 million primary recombinant phage.
25 The bovine genomic library was plated on *E. coli* K12 host strain LE392 on 23 x 23 cm plates (Nunc) at 150,000 to 200,000 phage plaques per plate. Each plate represented approximately one bovine genome equivalent. Following an overnight incubation at 37°c, the plates
30 were chilled and replicate filters were prepared according to procedures of Grunstein and Hogness ((1975) PNAS (USA) 72:3961). Four plaque lifts were prepared from each plate onto uncharged nylon membranes (Pall Biodyne A or MSI Nitropure). The DNA was immobilized

onto the membranes by cross-linking under UV light for 5 minutes or, by baking at 80°C under vacuum for two hours. DNA probes were labelled using T4 polynucleotide kinase (New England Biolabs) with gamma ^{32}P ATP (New England
5 Nuclear; 6500 Ci/mmol) according to the specifications of the suppliers. Briefly, 50 pmols of degenerate DNA oligomer were incubated in the presence of 600 μCi gamma ^{32}P-ATP and 5 units T4 polynucleotide kinase for 30 minutes at 37°C. Reactions were terminated, gel
10 electrophoresis loading buffer was added and then radiolabelled probes were purified by electrophoresis. ^{32}P labelled probes were excised from gel slices and eluted into water. Alternatively, DNA probes were labelled via PCR amplification by incorporation of $\alpha^{32}P$-dATP or $\alpha^{32}P$
15 dCTP according to the protocol of Schowalter and Sommer ((1989) Anal. Biochem 177:90-94). Probes labelled in PCR reactions were purified by desalting on Sephadex G-150 columns.

Prehybridization and hybridization were performed
20 in GMC buffer (0.52M NaPi, 7% SDS, 1% BSA, 1.5mM EDTA, 0.1MNaCl 10μg/μl TRNA). Washing was performed in buffer A oligowash (160μl 1M $Na2HPO_4$, 200 μl 20% SDS, 8.0 μl 0.5m EDTA, 100 μl 5M NaCl, 3632 μl H20). Typically, 20 filters (400 sq. centimetres each) representing replicate
25 copies of ten bovine genome equivalents were incubated in 200 μl hybridization solution with 100 pmols of degenerate oligonucleotide probe (128-512 fold degenerate). Hybridization was allowed to occur overnight at 5°C below the minimum melting temperature
30 calculated for the degenerate probe. The calculation of minimum melting temperature assumes 2°C for an AT pair and 4°C for a GC pair.

Filters were washed in repeated changes of oligowash at the hybridization temperatures for four to
35 five hours and finally, in 3.2M tetramethylammonium

chloride, 1% SDS twice for 30 min at a temperature dependent on the DNA probe length. For 20mers, the final wash temperature was 60°C. Filters were mounted, then exposed to X-ray film (Kodak XAR5) using intensifying screens (Dupont Cronex Lightening Plus). Usually, a three to five day film exposure at minus 80°C was sufficient to detect duplicate signals in these library screens. Following analysis of the results, filters could be stripped and reprobed. Filters were stripped by incubating through two successive cycles of fifteen minutes in a microwave oven at full power in a solution of 1% SDS containing 10mM EDTA pH8. Filters were taken through at least three to four cycles of stripping and reprobing with various probes.

III. Recombinant Phage Isolation, Growth and DNA Preparation

These procedures followed standard protocol as described in Recombinant DNA (Maniatis et al. Recombinant DNA 2:60-62:81).

IV. Analysis of Isolated Clones Using DNA Digestion and Southern Blots

Recombinant Phage DNA samples (2 micrograms) were digested according to conditions recommended by the restriction endonuclease supplier (New England Biolabs). Following a four hour incubation at 37°C, the reactions products were precipitated in the presence of 0.1M sodium acetate and three volumes of ethanol. Precipitated DNA was collected by centrifugation, rinsed in 75% ethanol and dried. All resuspended samples were loaded onto agarose gels (typically 1% in TAE buffer; 0.04M Tris acetate, 0. 002M EDTA). Gel runs were at 1 volt per centimetre from 4 to 20 hours. Markers included lambda Hind III DNA fragments and/or ØX174HaeIII DNA fragments (New England Biolabs). The gels were stained with 0.5

micrograms/μl of ethidium bromide and photographed. For southern blotting, DNA was first depurinated in the gel by treatment with 0.125 N HCl, denatured in 0.5 N NaOH and transferred in 20x SSC (3M sodium chloride, 0.03 M
5 sodium citrate) to uncharged nylon membranes. Blotting was done for 6 hours up to 24 hours, then the filters were neutralized in 0.5M Tris HCl pH 7.5, 0.15 M sodium chloride, then rinsed briefly in 50 mM Tris-borate EDTA.

For cross-linking, the filters were wrapped first
10 in transparent plastic wrap, then the DNA side exposed for five minutes to an ultraviolet light. Hybridization and washing was performed as described for library screening (see section 2 of this Example). For hybridization analysis to determine whether similar genes
15 exist in other species slight modifications were made. The DNA filter was purchased from Clonetech (Catalogue Number 7753-1) and contains 5 micrograms of EcoRI digested DNA from various species per lane. The probe was labelled by PCR amplification reactions as described
20 in section 2 above, and hybridizations were done in 80% buffer B(2g polyvinylpyrrolidine, 2g Ficoll-400, 2g bovine serum albumin, 50μl 1M Tris-HCl(pH 7.5) 58g NaCl, 1g sodium pyrophosphate, log sodium dodecyl sulfate, 950μl H_2O) containing 10% dextran sulfate. The probes
25 were denatured by boiling for ten minutes then rapidly cooling in ice water. The probe was added to the hybridization buffer at 10^6 dpm ^{32}P per μl and incubated overnight at 60°C. The filters were washed at 60°C first in buffer B followed by 2X SSC, 0.1% SDS then in 1x SSC,
30 0.1% SDS. For high stringency, experiments, final washes were done in 0.1 x SSC, 1% SDS and the temperature raised to 65°C.

Southern blot data were used to prepare a restriction map of the genomic clone and to indicate

which subfragments hybridized to the GGF probes (candidates for subcloning).

V. Subcloning of Pieces of DNA Homologous to Hybridization
5 Probes

DNA digests (e.g. 5 micrograms) were loaded onto 1% agarose gels then appropriate fragments excised from the gels following staining. The DNA was purified by adsorption onto glass beads followed by elution using the
10 protocol described by the supplier (Bio 101). Recovered DNA fragments -(100-200 ng) were ligated into linearized dephosphorylated vectors, e.g. pT3T7 (Ambion), which is a derivative of pUC18, using T4 ligase (New England Biolabs). This vector carries the E. coli ß lactamase
15 gene, hence, transformants can be selected on plates containing ampicillin. The vector also supplies ß-galactosidase complementation to the host cell, therefore non-recombinants (blue) can be detected using isopropylthiogaloctoside and Bluogal (Bethesda Research
20 Labs). A portion of the ligation reactions was used to transform E. coli K12 XL1 blue competent cells (Stratagene Catalogue Number: 200236) and then the transformants were selected on LB plates containing 50 micrograms per μl ampicillin. White colonies were
25 selected and plasmid mini preps were prepared for DNA digestion and for DNA sequence analysis. Selected clones were retested to determine if their insert DNA hybridized with the GGF probes.

VI. DNA Sequencing
30 Double stranded plasmid DNA templates were prepared from double stranded plasmids isolated from 5μl cultures according to standard protocols. Sequencing was by the dideoxy chain termination method using Sequenase 2.0 and a dideoxynucleotide sequencing kit (US

Biochemical) according to the manufacturers protocol (a modification of Sanger et al. (1977) PNAS (USA) 74:5463). Alternatively, sequencing was done in a DNA thermal cycler (Perkin Elmer, model 4800) using a cycle
5 sequencing kit (New England Biolabs; Bethesda Research Laboratories) and was performed according to manufacturers instructions using a 5'-end labelled primer. Sequence primers were either those supplied with the sequencing kits or were synthesized according to
10 sequence determined from the clones. Sequencing reactions were loaded on and resolved on 0.4mm thick sequencing gels of 6% polyacylamide. Gels were dried and exposed to X-Ray film. Typically, 35S was incorporated when standard sequencing kits were used and
15 a ^{32}P end labelled primer was used for cycle sequencing reactions. Sequences were read into a DNA sequence editor from the bottom of the gel to the top (5' direction to 3') and data were analyzed using programs supplied by Genetics Computer Group (GCG, University of
20 Wisconsin).

VII. RNA Preparation and PCR Amplification

Open reading frames detected in the genomic DNA and which contained sequence encoding GGF peptides were extended via PCR amplification of pituitary RNA. RNA was
25 prepared from frozen bovine tissue (Pelfreeze) according to the guanidine neutral-CsCl chloride procedure (Chirgwin et. al. (1979) Biochemistry 18:5294). Polyadenylated RNA was selected by oligo-dT cellulose column chromatography (Aviv and Leder. (1972) PNAS (USA)
30 69:1408).

Specific target nucleotide sequences were amplified beginning with either total RNA or polyadenylated RNA samples that had been converted to cDNA using the Perkin Elmer PCR/RNA Kit Number:
35 N808-0017. First strand reverse transcription reactions

used 1 μg template RNA and either primers of oligo dT with restriction enzyme recognition site linkers attached or specific antisense primers determined from cloned sequences with restriction sites attached. To produce
5 the second strand, the primers either were plus strand unique sequences as used in 3′ RACE reactions (Frohman et. al. (1988) PNAS (USA) 85:8998) or were oligo dT primers with restriction sites attached if the second target site had been added by terminal transferase
10 tailing first strand reaction products with dATP (e.g. 5′ race reactions, Frohman et. al., ibid). Alternatively, as in anchored PCR reactions the second strand primers were degenerate, hence, representing particular peptide sequences.

15 The amplification profiles followed the following general scheme: 1) five minutes soak file at 95°C; 2) thermal cycle file of 1 minute, 95°C; 1 minute ramped down to an annealing temperature of 45°C, 50°C or 55°C; maintain the annealing temperature for one minute; ramp
20 up to 72°C over one minute; extend at 72°C for one minute or for one minute plus a 10 second auto extension; 3) extension cycle at 72°C, five minutes, and; 4) soak file 40°C for infinite time. Thermal cycle files (#2) usually were run for 30 cycles. Sixteen μl of each 100 μl
25 amplification reaction was analyzed by electrophoresis in 2% Nusieve 1% agarose gels run in TAE buffer at 4 volts per centimetre for three hours. The gels were stained, then blotted to uncharged nylon membranes which were probed with labelled DNA probes that were internal to the
30 primers.

Specific sets of DNA amplification products could be identified in the blotting experiments and their positions used as a guide to purification and reamplification. When appropriate, the remaining
35 portions of selected samples were loade onto preparative

gels, then following electrophoresis four to five slices of 0.5 mm thickness (bracketing the expected position of the specific product) were taken from the gel. The agarose was crushed, then soaked in 0.5 μl of electrophoresis buffer from 2-16 hours at 40°C. The crushed agarose was centrifuged for two minutes and the supernate was transferred to fresh tubes.

Reamplification was done on five microlitres (roughly 1% of the product) of the eluted material using the same sets of primers and the reaction profiles as in the original reactions. When the reamplification reactions were completed, samples were extracted with chloroform and transferred to fresh tubes. Concentrated restriction enzyme buffers and enzymes were added to the reactions in order to cleave at the restriction sites present in the linkers. The digested PCR products were purified by gel electrophoresis, then subcloned into vectors as described in the subcloning section above. DNA sequencing was done described as above.

VII. DNA Sequence Analysis

DNA sequences were assembled using a fragment assembly program and the amino acid sequences deduced by the GCG programs GelAssemble, Map and Translate. The deduced protein sequences were used as a query sequence to search protein sequence databases using WordSearch. Analysis was done on a VAX Station 3100 workstation operating under VMS 5.1. The database search was done on SwissProt release number 21 using GCG Version 7.0.

VII. Results

As indicated, to identify the DNA sequence encoding bovine GGF-II degenerate oligonucleotide probes were designed from GGF-II peptide sequences. GGF-II 12 (SEQ ID No. 44), a peptide generated via lysyl

endopeptidase digestion of a purified GGF-II preparation (see Figures 11 and 12) showed strong amino acid sequence homology with GGF-I 07 (SEQ ID No. 39), a tryptic peptide generated from a purified GGF-I preparation. GGF-II 12 was thus used to create ten degenerate oligonucleotide probes (see oligos 609, 610 and 649 to 656 in Figure 21, SEQ ID Nos. 69-71 and 79, respectively). A duplicate set of filters were probed with two sets (set 1=609, 610; set 2=649-656) of probes encoding two overlapping portions of GGF-II 12. Hybridization signals were observed, however, only one clone hybridized to both probe sets. The clone (designated GGF2BG1) was purified.

Southern blot analysis of DNA from the phage clone GGF2BG1 confirmed that both sets of probes hybridized with that bovine DNA sequence, and showed further that both probes reacted with the same set of DNA fragments within the clone. Based on those experiments a 4 kb Eco RI sub-fragment of the original clone was identified, subcloned and partially sequenced. Figure 22 shows the nucleotide sequence and the deduced amino acid sequence (SEQ ID No. 89) of the initial DNA sequence readings that included the hybridization sites of probes 609 and 650, and confirmed that a portion of this bovine genomic DNA encoded peptide 12 (KASLADSGEYM).

Further sequence analysis demonstrated that GGF-II 12 resided on a 66 amino acid open reading frame (see below) which has become the starting point for the isolation of overlapping sequences representing a putative bovine GGF-II gene and a cDNA.

Several PCR procedures were used to obtain additional coding sequences for the putative bovine GGF-II gene. Total RNA and oligo dT-selected (poly A containing) RNA samples were prepared from bovine total pituitary, anterior pituitary, posterior pituitary, and hypothalamus. Using primers from the list shown in

Figure 23 (SEQ ID No. 109-119) one-sided PCR reactions (RACE) were used to amplify cDNA ends in both the 3′ and 5′ directions, and anchored PCR reactions were performed with degenerate oligonucleotide primers representing additional GGF-II peptides. Figure 24 summarizes the contiguous DNA structures and sequences obtained in those experiments. From the 3′ RACE reactions, three alternatively spliced CDNA sequences were produced, which have been cloned and sequenced. A 5′ RACE reaction led to the discovery of an additional exon containing coding sequence for at least 52 amino acids. Analysis of that deduced amino acid sequence revealed peptides GGF-II-6 and a sequence similar to GGF-I-18 (see below). The anchored PCR reactions led to the identification of (cDNA) coding sequences of peptides GGF-II-1, 2, 3 and 10 contained within an additional cDNA segment of 300 bp. The 5′ limit of this segment (i.e. segment E, see Fig. 31) is defined by the oligonucleotide which encodes peptide GGF-II-1 and which is used in the PCR reaction. (Additional 5′ sequence data exists as described for the human clone in Example 6.) Thus this clone contains nucleotide sequences encoding six out of the existing total of nine novel GGF-II peptide sequences.

The cloned gene was characterized first by constructing a physical map of GGF2BG1 that allowed positioning the coding sequences as they were found (see below, Figure 25). DNA probes from the coding sequences described above have been used to identify further DNA fragments containing the exons on this phage clone and to identify clones that overlap in both directions. The putative bovine GGF-II gene is divided into at least 5 coding segments, but only coding segments A and B have been defined as exons and sequenced and mapped thus far. The summary of the contiguous coding sequences identified

is shown in Figure 26. The exons are listed (alphabetically) in the order of their discovery. It is apparent from the intron/exon boundaries that exon B may be included in cDNAs that connect coding segment E and
5 coding segment A. That is, exon B cannot be spliced out without compromising the reading frame. Therefore, we suggest that three alternative splicing patterns can produce putative bovine GGF-II cDNA sequences 1, 2 and 3. The coding sequences of these, designated GGF2BPP1.CDS,
10 GGF2BPP2.CDS and GGF2BPP3.CDS, respectively, are given in Figures 28a (SEQ ID No. 133), 28b (SEQ ID No. 134) and 28c (SEQ ID No. 135), respectively. The deduced amino acid sequence of the three cDNAs is also given in Figures 28a, 28b and 28c (SEQ ID Nos. 133-135, respectively).
15 The three deduced structures encode proteins of lengths 206, 281 and 257 amino acids. The first 183 residues of the deduced protein sequence are identical in all three gene products. At position 184 the clones differ significantly. A codon for glycine GGT in
20 GGF2BPP1 also serves as a splice donor for GGF2BPP2 and GGF2BPP3, which alternatively add on exons C, C/D, C/D′ and D or C, C/D and D, respectively shown in Figure 33 (SEQ ID No. 149). GGF2BPP1 is a truncated gene product which is generated by reading past the coding segment a
25 splice junction into the following intervening sequence (intron). This represents coding segment A′ in Figure 31 (SEQ ID Nos. 140, 168). The transcript ends adjacent to a canonical AATAAA polyadenylation sequence, and we suggest that this truncated gene product represents a
30 bona fide mature transcript. The other two longer gene products share the same 3′ untranslated sequence and polyadenylation site.

All three of these molecules contain six of the nine novel GGF-II peptide sequences (see Figure 12) and
35 another peptide is highly homologous to GGF-I-18 (see

Figure 27). This finding gives a high probability that this recombinant molecule encodes at least a portion of bovine GGF-II. Furthermore, the calculated isoelectric points for the three peptides are consistent with the
5 physical properties of GGF-I and II. Since the molecular size of GGF-2 is roughly 60 kd, the longest of the three cDNAs should encode a protein with nearly one-half of the predicted number of amino acids.

A probe encompassing the B and A exons was
10 labelled via PCR amplification and used to screen a cDNA library made from RNA isolated from bovine posterior pituitary. One clone (GGF2BPP5) showed the pattern indicated in Figure 30 and contained an additional DNA coding segment (G) between coding segments A and C. The
15 entire nucleic acid sequence is shown in Figure 32 (SEQ ID No. 148). The predicted translation product from the longest open reading frame is 241 amino acids. A portion of a second cDNA (GGF2BPP4) was also isolated from the bovine posterior pituitary library using the probe
20 described above. This clone showed the pattern indicated in Figure 30. This clone is incomplete at the 5′ end, but is a splicing variant in the sense that it lacks coding segments G and D. BPP4 also displays a novel 3′ end with regions H, K and L beyond region C/D. The
25 sequence of BPP4 is shown in Figure 34 (SEQ ID no. 150).

EXAMPLE 5

GGF Sequences in Various Species

Computer database searching has not revealed any meaningful similarities between any predicted GGF
30 translation products and known protein sequences. This suggests that GGF-II is the first member of a new family or superfamily of proteins. In high stringency cross hybridization studies (DNA blotting experiments) with other mammalian DNAs we have shown clearly that DNA

probes from this bovine recombinant molecule can readily detect specific sequences in a variety of samples tested. A highly homologous sequence is also detected in human genomic DNA. The autoradiogram is shown in Figure 29. 5 The signals in the lanes containing rat and human DNA represent the rat and human equivalents of GGF, the sequences of which have been recently reported by Holmes et al. ((1992) Science 256:1205) and Wen et al. ((1992) Cell 69:559).

10

EXAMPLE 6

Isolation of a Human Sequence Encoding Human GGF2

Several human clones containing sequences homologous to the bovine GGFII coding segment E were isolated by screening a human cDNA library prepared from 15 brain stem (Stratagene catalog #935206). This strategy was pursued based upon the strong link between most of the GGF2 peptides (unique to GGF2) and the predicted peptide sequence from clones containing the bovine E segment. This library was screened as described in 20 Example 4, Section II using the oligonucleotide probes 914-919 listed below.

914 TCGGGCTCCATGAAGAAGATGTA
915 TCCATGAAGAAGATGTACCTGCT
916 ATGTACCTGCTGTCCTCCTTGA
25 917 TTGAAGAAGGACTCGCTGCTCA
918 AAAGCCGGGGGCTTGAAGAA
919 ATGARGTGTGGGCGGCGAAA

Clones detected with these probes were further analyzed by hybridization. A probe derived from coding 30 segment A (see Figure 21), which was produced by labeling a polymerase chain reaction (PCR) product from segment A, was also used to screen the primary library. Several clones that hybridized with both A and E derived probes were selected and one particular clone, GGF2HBS5, was

selected for further analysis. This clone is represented by the pattern of coding segments (EBACC/D'D as shown in Figure 31). The E segment in this clone is the human equivalent of the truncated bovine version of E shown in
5 Figure 37. GGF2HBS5 is the most likely candidate to encode GGFII of all the "putative" GGFII candidates described. The length of coding sequence segment E is 786 nucleotides plus 264 bases of untranslated sequence. The predicted size of the protein encoded by GGF2HBS5 is
10 approximately 423 amino acids (approximately 45 kilodaltons), which is similar to the size of the deglycosylated form of GGF (see Example 15). Additionally, seven of the GGFII peptides listed in Figure 27 have equivalent sequences which fall within the
15 protein sequence predicted from region E. Peptides II-6 and II-12 are exceptions, which fall in coding segment B and coding segment A, respectively. RNA encoding the GGF2HBS5 protein was produced in an in vitro transcription system driven by the bacteriophage T7
20 promoter resident in the vector (Bluescript SK [Stratagene Inc.] see Figure 44) containing the GGF2HBS5 insert. This RNA can be translated in a cell free (rabbit reticulocyte) translation system and the size of the protein product was 45 Kd. Additionally, the cell-
25 free product has been assayed in a Schwann cell mitogenic assay to confirm biological activity. Schwann cells treated with conditioned medium show both increased proliferation as measured by incorporation of ^{125}-Uridine and phosphorylation on tyrosine of a protein in the 185
30 kilodalton range.

Thus the size of the product encoded by GGF2HBS5 and the presence of DNA sequences which encode human peptides highly homologous to the bovine peptides shown in Figure 12 confirm that GGF2HBS5 encodes the human
35 equivalent of bovine GGF2. The fact that conditioned

media prepared from cells transformed with this clone elicits Schwann cell mitogenic activity confirms that the GGFIIHBS5 gene product (unlike the BPP5 gene product) is secreted. Additionally the GGFBPP5 gene product seems to mediate the Schwann cell proliferation response via a receptor tyrosine kinase such as p185^{erbB2} or a closely related receptor (see Example 13).

EXAMPLE 7

Isolation of Human Sequences Related to Bovine GGF

The result in Example 5 indicates that GGF related sequences from human sources can also be easily isolated by using DNA probes derived from bovine GGF sequences. Alternatively, the procedure described by Holmes et al. ((1992) Science 256:1205) can be used. In this example a human protein (heregulin α) which binds to and activates the p185^{erbB2} receptor (and is related to GGF) is purified from a tumor cell line and the derived peptide sequence is used to produce oligonucleotide probes which were utilized to clone the cDNAs encoding heregulin. This is a similar approach to that used in examples 1-4 for the cloning of GGF sequences from pituitary cDNAs. The heregulin protein and complementary DNAs were isolated according to the following procedures. Heregulin was purified from medium conditioned by MDA-MB-231 breast cancer cells (ATCC #HTB 26) grown on Percell Biolytica microcarrier beads (Hyclone Labs). The medium (10 liters) was concentrated ~25-fold by filtration through a membrane (10-kD cutoff) (Millipore) and clarified by centrifugation and filtration through a filter (0.22 μm). The filtrate was applied to a heparin Sepharose column (Pharmacia) and the proteins were eluted with steps of 0.3, 0.6, and 0.9 M NaCl in phosphate-buffered saline. Activity in the various chromatographic fractions was measured by quantifying the increase in tyrosine

phosphorylation of $p185^{erbB2}$ in MCF-7 breast tumor cells (ATCC # HTB 22). MCF-7 cells were plated in 24-well Costar plates in F12 (50%) Dulbecco's minimum essential medium (50%) containing serum (10%) (10^5 cells per well),
5 and allowed to attach for at least 24 hours. Prior to assay, cells were transferred into medium without serum for a minimum of 1 hour. Column fractions (10 to 100 μl) were incubated for 30 min. at 37°. Supernatants were then aspirated and the reaction was stopped by the
10 addition of SDS-PAGE sample buffer 100 μl). Samples were heated for 5 min. at 100°C, and portions (10 to 15 μl) were applied to a tris-glycine gel (4 to 20%) (Novex). After electrophoresis, proteins were electroblotted onto a polyvinylidenedifluoride (PVDF) membrane and then
15 blocked with bovine serum albumin (5%) in tris-buffered saline containing Tween-20 (0.05%) (TBST). Blots were probed with a monoclonal antibody (1:1000 dilution) to phosphotyrosine (Upstate Biotechnology) for a minimum of 1 hour at room temperature. Blots were washed with TBST,
20 probed with an antibody to mouse immunoglobulin G conjugated to alkaline phosphatase (Promega) (diluted 1:7500) for a minimum of 30 min. at room temperature. Reactive bands were visualized with 5-bromo-4-chloro-3-indoyl-1-phosphate and nitro-blue
25 tetrazolium. Immunoblots were scanned with a Scan Jet Plus (Hewlett-Packard) densitometer. Signal intensities for unstimulated MCF-7 cells were 20 to 30 units. Fully stimulated $p185^{erbB2}$ yielded signals of 180 to 200 units. The 0.6 M NaCl pool, which contained most of the
30 activity, was applied to a polyaspartic acid (PolyLC) column equilibrated in 17 mM sodium phosphate (pH 6.8) containing ethanol (30%). A linear gradient from 0.3 M to 0.6 M NaCl in the equilibration buffer was used to elute bound proteins. A peak of activity (at ~0.45 M
35 NaCl) was further fractionated on a C4 reversed-phase

column (SynChropak RP-4) equilibrated in buffer containing TFA (0.1%) and acetonitrile (15%). Proteins were eluted from this column with an acetonitrile gradient from 25 to 40% over 60 min. Fractions (1 μl) 5 were collected, assayed for activity, and analyzed by SDS-PAGE on tris-glycine gels (4-20%, Novex).

HPLC-purified HRG-α was digested with lysine C in SDS (0.1%), 10 mM dithiothreitol, 0.1 M NH_4HCO_3 (pH 8.0) for 20 hours at 37°C and the resultant fragments were 10 resolved on a Synchrom C4 column (4000Å, 0.2 by 10 cm). The column was equilibrated in 0.1% TFA and eluted with a 1-propanol gradient in 0.1% TFA (Henzel et al. (1989) J. Biol. Chem. 264:15905). Peaks from the chromatographic run were dried under vacuum and sequenced. One of the 15 peptides (eluting at ~24% 1-propanol) gave the sequence [A]AEKEKTF[C]VNGGEXFMVKDLXNP (SEQ ID Nos 162). Residues in brackets were uncertain and an X represents a cycle in which it was not possible to identify the amino acid. The initial yield was 8.5 pmol and the sequence did not 20 correspond to any known protein. Residues 1, 9, 15, and 22 were later identified in the cDNA sequence as cysteine. Direct sequencing of the ~45-kD band from a gel that had been overloaded and blotted onto a PVDF membrane revealed a low abundance sequence 25 XEXKE[G][R]GK[G]K[G]KKKEXGXG[K] (SEQ ID No. 169) with a very low initial yield (0.2 pmol). This corresponded to amino acid residues 2 to 22 of heregulin-α (Fig. 31), suggesting that serine 2 is the NH_2-terminus of proHRG-α. Although the NH_2 terminus was blocked, it was observed 30 that occasionally a small amount of a normally blocked protein may not be post-translationally modified. The NH_2 terminal assignment was confirmed by mass spectrometry of the protein after digestion with cyanogen bromide. The COOH-terminus of the isolated protein has 35 not been definitely identified; however, by mixture

sequencing of proteolytic digests, the mature sequence does not appear to extend past residue 241. Abbreviations for amino residues are: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T. Thr; V, Val; W, Trp; and Y, Tyr.

As a source of cDNA clones, an oligo(dT)-primed λgt10 (Hurn et al. (1984) λgt10 and λgt11 DNA Cloning Techniques: A Practical Approach) cDNA library was constructed (Gubler and Hoffman. (1983) Gene 25:263) with mRNA purified (Chirwin et al. (1979) Biochemistry 18:5294) from MDA-MB-231 cells. The following eightfold degenerate antisense deoxyoligonucleotide encoding the 13-amino acid sequence AEKEKTFCVNGGE (SEQ ID No. 164) was designed on the basis of human codon frequency optima (Lathe. (1985) J. Mol. Biol. 183:1) and chemically synthesized:

5′-CTCGCC (G OR T) CC (A OR G) TTCAC (A OR G) CAGAAGGTCTTCTCCTTCTCAGC-3′ (SEQ ID No. 165). For the purpose of probe design a cysteine was assigned to an unknown residue in the amino acid sequence. The probe was labeled by phosphorylation and hybridized under low-stringency conditions to the cDNA library. The proHRG-α protein was identified in this library. HRB-β1 cDNA was identified by probing a second oligo(dT)-primed λgt10 library made from MDA-MB-231 cell mRNA with sequences derived from both the 5′ and 3′ ends of proHRG. Clone 13 (Fig. 2A) was a product of screening a primed (5′-CCTCGCTCCTTCTTCTTGCCCTTC-3′ primer; proHRG-α antisense nucleotides 33 to 56) MDA-MB-231 λgt10 library with 5′ HRG sequence. A sequence corresponding to the 5′ end of clone 13 as the probe was used to identify proHRGβ2 and proHRGβ3 in a third oligo(dT)-primed λgt10 library derived from MDA-MB-231 cell mRNA. Two cDNA clones encoding each of the four HRGs were sequenced

(Sanger et al. (1977) PNAS (USA) 74:5463). Another cDNA designated clone 84 has an amino acid sequence identical to proHRGß2 through amino acid 420. A stop codon at position 421 is followed by a different 3'-untranslated
5 sequence.

EXAMPLE 8

Isolation of a Further Splicing Variant

The methods in Example 7 produced four closely related sequences (heregulin α, ß1, ß2, ß3) which arise
10 as a result of splicing variation. Peles et al. ((1992) Cell 69:205) and Wen et al. ((1992) Cell 69:559) have isolated another splicing variant (from rat) using a similar purification and cloning approach to that described in Examples 1-4 and 7 involving a protein which
15 binds to $p185^{erbB2}$. The cDNA clone was obtained as follows (via the purification and sequencing of a $p185^{erbB2}$ binding protein from a transformed rat fibroblast cell line).

A $p185^{erbB2}$ binding protein was purified from
20 conditioned medium as follows. Pooled conditioned medium from three harvests of 500 roller bottles (120 liters total) was cleared by filtration through 0.2 μ filters and concentrated 31-fold with a Pelicon ultrafiltration system using membranes with a 20kd molecular size cutoff.
25 All the purification steps were performed by using a Pharmacia fast protein liquid chromatography system. The concentrated material was directly loaded on a column of heparin-Sepharose (150 μl, preequilibrated with phosphate-buffered saline (PBS)). The column was washed
30 with PBS containing 0.2 M NaCl until no absorbance at 280 nm wavelength could be detected. Bound proteins were then eluted with a continuous gradient (250 μl) of NaCl (from 0.2 M to 1.0 M), and 5 μl fractions were collected. Samples (0.01 μl of the collected fractions) were used

for the quantitative assay of the kinase stimulatory activity. Active fractions from three column runs (total volume = 360 μl) were pooled, concentrated to 25 μl by using a YM10 ultrafiltration membrane (Amicon, Danvers, MA), and ammonium sulfate was added to reach a concentration of 1.7 M. After clearance by centrifugation (10,000 x g, 15 min.), the pooled material was loaded on a phenyl-Superose column (HR10/10, Pharmacia). The column was developed with a 45 μl gradient of $(NH_4)_2SO_4$ (from 1.7 M to no salt) in 0.1 M Na_2PO_4 (pH 7.4), and 2 μl fractions were collected and assayed (0.002 μl per sample) for kinase stimulation (as described in Example 7). The major peak of activity was pooled and dialyzed against 50 mM sodium phosphate buffer (pH 7.3). A Mono-S cation-exchange column (HR5/5, Pharmacia) was preequilibrated with 50 mM sodium phosphate. After loading the active material (0.884 mg of protein; 35 μl), the column was washed with the starting buffer and then developed at a rate of 1 μl/min. with a gradient of NaCl. The kinase stimulatory activity was recovered at 0.45-0.55 M salt and was spread over four fractions of 2 μl each. These were pooled and loaded directly on a Cu^{+2} chelating columns (1.6 μl, HR2/5 chelating Superose, Pharmacia). Most of the proteins adsorbed to the resin, but they gradually eluted with a 30 μl linear gradient of ammonium chloride (0-1 M). The activity eluted in a single peak of protein at the range of 0.05 to 0.2 M NH_4Cl. Samples from various steps of purification were analyzed by gel electrophoresis followed by silver staining using a kit from ICN (Costa Mesa, CA), and their protein contents were determined with a Coomassie blue dye binding assay using a kit from Bio-Rad (Richmond, CA).

The p44 protein (10 μg) was reconstituted in 200 μl of 0.1 M ammonium bicarbonate buffer (pH 7.8).

Digestion was conducted with L-1-tosyl-amide 2-phenylethyl chloromethyl ketone-treated trypsin (Serva) at 37°C for 18 hr. at an enzyme-to-substrate ratio of 1:10. The resulting peptide mixture was separated by
5 reverse phase HPLC and monitored at 215 nm using a Vydac C4 micro column (2.1 mm i.d. x 15 cm, 300) and an HP 1090 liquid chromatographic system equipped with a diode-array detector and a workstation. The column was equilibrated with 0.1% trifluoroacetic acid (mobile phase A), and
10 elution was effected with a linear gradient from 0%-55% mobile phase B (90% acetonitrile in 0.1% trifluoroacetic acid) over 70 min. The flow rate was 0.2 μl/min. and the column temperature was controlled at 25°C. One-third aliquots of the peptide peaks collected manually from the
15 HPLC system were characterized by N-terminal sequence analysis by Edman degradation. The fraction eluted after 27.7 min. (T27.7) contained mixed amino acid sequences and was further rechromatographed after reduction as follows: A 70% aliquot of the peptide fraction was dried
20 in vacuo and reconstituted in 100 μl of 0.2 M ammonium bicarbonate buffer (pH 7.8). DTT (final concentration 2 mM) was added to the solution, which was then incubated at 37°C for 30 min. The reduced peptide mixture was then separated by reverse-phase HPLC using a Vydac column (2.1
25 mm i.d. x 15 cm). Elution conditions and flow rat´were identical to those described above. Amino acid sequence analysis of the peptide was performed with a Model 477 protein sequencer (Applied Biosystems, Inc., Foster City, CA) equipped with an on-line phenylthiohydantoin (PTH)
30 amino acid analyzer and a Model 900 data analysis system (Hunkapiller et al. (1986)). The protein was loaded onto a trifluoroacetic acid-treated glass fiber disc precycled with polybrene and NaCl. The PTH-amino acid analysis was performed with a micro liquid chromatography system
35 (Model 120) using dual syringe pumps and reverse-phase

(C-18) narrow bore columns (Applied Biosystems, 2.1 mm x 250 mm).

RNA was isolated from Rat1-EJ cells by standard procedures (Maniatis et al. (1982) Molecular Cloning: A Laboratory Manual) and poly $(A)^+$ was selected using an mRNA Separator kit (Clontech Lab, Inc., Palo, Alto, CA). cDNA was synthesized with the Superscript kit (from BRL Life Technologies, Inc., Bethesda, MS). Column-fractionated double-strand cDNA was ligated into an SalI- and NacI-digested pJT-2 plasmid vector, a derivative of the pCD-X vector (Okayama and Berg (1983) Mol. Cell Biol. 3:280) and transformed into DH10B *E. coli* cells by electroporation (Dower et al. (1988) Nucl. Acids Res. 16:6127). Approximately 5 x 10^5 primary transformants were screened with two oligonucleotide probes that were derived from the protein sequences of the N-terminus of NDF (residues 5-24) and the T40.4 tryptic peptide (residues 7-12). Their respective sequences were as follows (N indicates all 4 nt):

```
(1)   5'-ATA GGG AAG GGC GGG GGA AGG GTC NCC CTC NGC
                                         A       T
                AGG GCC GGG CTT GCC TCT GGA GCC TCT-3'

(2)   5'-TTT ACA CAT ATA TTC NCC-3'
          C   G       G   C
```

(1: SEQ ID No. 167; 2: SEQ ID No. 168)

The synthetic oligonucleotides were end-labeled with [γ-^{32}P]ATP with T4 polynucleotide kinase and used to screen replicate sets of nitrocellulose filters. The hybridization solution contained 6 x SSC, 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 2 x Denhardt's solution, 50 μg/ml salmon sperm DNA, and 20% formamide (for probe 1) or no formamide (for probe 2). The filters were washed at either 50°C with 0.5 x SSC, 0.2% SDS, 2 mM EDTA (for probe 1) or at 37°C with 2 x

SSC, 0.2% SDS, 2 mM EDTA (for probe 2). Autoradiography of the filters gave ten clones that hybridized with both probes. These clones were purified by replating and probe hybridization as described above.

5 The cDNA clones were sequenced using an Applied Biosystems 373A automated DNA sequencer and Applied Biosystems Taq DyeDeoxy™ Terminator cycle sequencing kits following the manufacture's instructions. In some instances, sequences were obtained using [^{35}S]dATP 10 (Amersham) and Sequenase™ kits from U.S. Biochemicals following the manufacturer's instructions. Both strands of the cDNA clone 44 were sequenced by using synthetic oligonucleotides as primers. The sequence of the most 5' 350 nt was determined in seven independent cDNA clones. 15 The resultant clone demonstrated the pattern shown in Figure 30 (NDF).

EXAMPLE 9

Other Possible Splicing Variants

Alignment of the deduced amino acid sequences of 20 the cDNA clones and PCR products of the bovine, and the published human (Fig. 31) and rat sequences show a high level of similarity, indicating that these sequences are derived from homologous genes within the three species. The variable number of messenger RNA transcripts 25 detectable at the cDNA/PCR product level is probably due to extensive tissue-specific splicing. The patterns obtained and shown in Figure 30 suggests that other splicing variants exist. A list of probable splicing variants is indicated as followed. Many of these 30 variants can be obtained by coding segment specific probing of cDNA libraries derived from different tissues. Alternatively, the variants can be assembled from specific (excised from) cDNA clones, PCR products or genomic DNA regions via cutting and splicing techniques

known to one skilled in the art. These variant sequences can be expressed in recombinant systems and the recombinant products can be assayed to determine their level of Schwann cell mitogenic activity as well as their ability to bind and activate the $p185^{erbB2}$ receptor.

EXAMPLE 10

Functional elements of GGF

The deduced structures of family of GGF sequences indicate that the longest forms (as represented by GGF2BPP4) encode transmembrane proteins where the extracellular part contains a domain which resembles epidermal growth factor (see Carpenter and Wahl in Peptide Growth Factors and Their Receptors I pp. 69-133, Springer-Verlag, NY 1991). The positions of the cysteine residues in coding segments C and C/D or C/D' peptide sequence are conserved with respect to the analogous residues in the epidermal growth factor (EGF) peptide sequence. This suggests that the extracellular domain functions as a receptor recognition and biological activation sites. Several of the variant forms lack the H, K, and L coding segments and thus may be expressed as secreted, diffusible biologically active proteins. Likely structures are shown in Figure 35.

Membrane bound versions of this protein may induce Schwann cell proliferation if expressed on the surface of neurons during embryogenesis or during nerve regeneration (where the surfaces of neurons are intimately associated with the surfaces of proliferating Schwann cells).

Secreted (non membrane bound) GGF's may act as classically diffusible factors which can interact with Schwann cells at some distance from their point of secretion. An example of a secreted GGF is the protein encoded by GGF2HBS5 (see example 6)

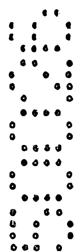
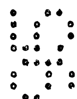
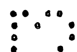
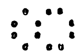
Other GGFs such as that encoded by GGF2BPP5 seem to be non-secreted (see example 6). These GGFs may be injury response forms which are released as a consequence of tissue damage.

5

EXAMPLE 11

Splicing variants with antiproliferative action

One particular splicing variant (GGF2BPP1) is described in Example 4. GGF2BPP1 is a truncated gene product which is generated by reading past the coding 10 segment A splice junction into the adjoining genomic sequence. This represents coding segment A′ in Figure 31. The transcript ends near to a canonical AATAAA polyadenylation sequence. This splicing variant contains regions F, E, B and A′. Other possible variants of this 15 may lack region E (F, B, A′). As described in Example 10 regions C, C/D, or C/D′ are homologous to EGF and are most likely to be the sites which are responsible for biological activity. GGF2BPP1 could retain receptor binding activity yet lack the ability to activate the 20 receptor. Such a ligand would function as an antagonist since it would compete with active GGF/p185 *erbB2* ligands (eg. GGF2BPP5) for receptor binding. Other splicing variants such as those containing region E may also function as antagonists as described above. The presence 25 of an extra domain such as that which is encoded by region E may result in structural differences which would interfere with biological activity following receptor binding. GGF2BPP2 may also be an inhibitor molecule. The presence of region C/D′ in addition to region C/D in 30 GGF2BPP2 adds sequence to the EGF related region which could potentially result in a protein which lacks biological activity. GGF2HBS11 is another potential inhibitor molecule. This clone was isolated from a human brainstem library using the same methods and probes as

described in Example 6 for the isolation of GGF2HBS5. The GGF2HBS11 clone contains a portion of region E which is flanked by new sequence which is not contained in any other known region. The lack of region C, C/D or C/D' suggests that GGF2HBS11 would also lack biological activity.

EXAMPLE 12

Purification of antiproliferative factors from Recombinant Cells

In order to obtain antiproliferative factors to assay for biological activity, the proteins can be overproduced using cloned DNA. Several approaches can be used. A recombinant *E. coli* cell containing the sequences described in example 11 can be constructed. Expression systems such as pNH8a (Stratagene, Inc.) can be used for this purpose by following manufacturers procedures. Alternatively, these sequences can be inserted in a mammalian expression vector and an overproducing cell line can be constructed. As an example, for this purpose DNA encoding GGF2BPP1 can be expressed in COS cells or can be expressed in Chinese hamster ovary cells using the pMSXND expression vector (Lee and Nathans, J. Biol. Chem. 263, 3521-3527, (1981)). This vector containing GGF DNA sequences can be transfected into host cells using established procedures.

Transient expression can be examined or G418-resistant clones can be grown in the presence of methotrexate to select for cells that amplify the DHFR gene (contained on the pMSXND vector) and, in the process, co-amplify the adjacent protein encoding sequence. Because CHO cells can be maintained in a totally protein-free medium (Hamilton and Ham, in Vitro 13, 537-547 (1977)), the desired protein can be purified from the medium. Western analysis using the antisera

produced in Example 9 can be used to detect the presence of the desired protein in the conditioned medium of the overproducing cells.

The desired protein can be purified from the E. coli lysate or the CHO cell conditioned medium using the types of procedures described in Example 1. The protein may be assayed at various points in the procedure using a Western blot assay.

EXAMPLE 13

Design and assay of antiproliferative factors

As indicated above and in Figs. 35 and 39-45, the GGF coding segments include regions with EGF-like homology. These EGF-like domains can be required for the activation of mitogenesis in the binding reaction between GGF ligands containing such domains and the erbB2 receptor. Comparisons of naturally occurring products of the GGF coding sequences which confer mitogenic activity versus those which confer antiproliferative activity, as disclosed above, provide additional support for this. Consequently, preferred antiproliferative factors are those which lack these EGF-like domains. Antiproliferative factors designed in this manner will lack all or part of the C, C/D, or C/D′ coding segments. Examples of such factors likely to have antiproliferative activity using this design strategy are shown in Fig. 37 and described in the summary of the invention.

The recombinant proteins produced in Example 12 using the criterion described above may be assayed as described hereafter. The Schwann cell mitogenic assay described herein may be used to assay the expressed product of the full length clone or any biologically active portions thereof. Any member of the family of splicing variant complementary DNA's derived from the GGF gene (including the Heregulins) can be expressed in this

manner and assayed in the Schwann cell proliferation assay by one skilled in the art. Antiproliferative activity in the GGF assay can be examined by a competition assay (Chan et al., Science 254:1383 (1991)). Varying concentrations of recombinant antiproliferative GGF variants (such as GGF2BPP1) can be added to Schwann cell cultures in the presence of GGF. The extent of antiproliferative activity can be measured by comparing mitogenic activity of the cultures to controls treated only with GGF. This will provide a measure of dose dependent inhibition. The specificity of the response can be measured by examining the effect of varying concentrations of antiproliferative factor on the mitogenic activity of other growth factors and their target cells (e.g. EGF). Antiproliferative activity of recombinant GGF variants can also be examined in breast tumour cells. Cell lines such as SK-BR-3 which proliferate in response to GGF's/$p185^{erbB2}$ ligands can be assayed in a similar manner to that described above for Schwann cells.

Crosslinking studies can be performed to determine whether I^{125} labelled GGF variants, which show antiproliferative activity (as described above), bind to the erbB2 receptor (Chan et al., Science 254:1383 (1991)). Binding can be demonstrated by immunoprecipitation of the cross-linked protein with an antibody to the erbB2 receptor.

(1) GENERAL INFORMATION:

(i) APPLICANTS: Gwynne, David I.; Marchionni, Mark; McBurney, Robert N.

(ii) TITLE OF INVENTION: INHIBITORS OF CELL PROLIFERATION, THEIR PREPARATION AND USE

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(B) COMPUTER: IBM
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(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

```
Phe Lys Gly Asp Ala His Thr Glu
  1               5
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine; Xaa in position 12 is unknown.

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

```
Xaa Ala Ser Leu Ala Asp Glu Tyr Glu Tyr Met Xaa Lys
  1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine; Xaa in position 10 is unknown.

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

```
Xaa Thr Glu Thr Ser Ser Ser Gly Leu Xaa Leu Lys
  1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Lys Leu Gly Glu Met Trp Ala Glu
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Leu Gly Glu Lys Arg Ala
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Ile Lys Ser Glu His Ala Gly Leu Ser Ile Gly Asp Thr Ala Lys
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Ala Ser Leu Ala Asp Glu Tyr Glu Tyr Met Arg Lys
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Ile Lys Gly Glu His Pro Gly Leu Ser Ile Gly Asp Val Ala Lys
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine and Xaa in position 12 is unknown.

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

Xaa Met Ser Glu Tyr Ala Phe Phe Val Gln Thr Xaa Arg
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Ser Glu His Pro Gly Leu Ser Ile Gly Asp Thr Ala Lys
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine; Xaa in position 8 is unknown.

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

Xaa Ala Gly Tyr Phe Ala Glu Xaa Ala Arg
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine; Xaa in position 7 is unknown.

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

Xaa Lys Leu Glu Phe Leu Xaa Ala Lys
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Thr Thr Glu Met Ala Ser Glu Gln Gly Ala
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Ala Lys Glu Ala Leu Ala Ala Leu Lys
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Phe Val Leu Gln Ala Lys Lys
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Leu Gly Glu Met Trp
  1   5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

Glu Tyr Lys Cys Leu Lys Phe Lys Trp Phe Lys Lys Ala Thr Val Met
 1   5   10   15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 8 is unknown.

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

Glu Ala Lys Tyr Phe Ser Lys Xaa Asp Ala
  1   5   10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 2 is unknown.

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

Glu Xaa Lys Phe Tyr Val Pro
  1   5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

```
Glu Leu Ser Phe Ala Ser Val Arg Leu Pro Gly Cys Pro Pro Gly Val
  1               5                  10                  15

Asp Pro Met Val Ser Phe Pro Val Ala Leu
             20                  25
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2003
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N in positions 31 and 32 could be either A or G.

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

```
GGAATTCCTT TTTTTTTTTT TTTTTTTCTT NNTTTTTTTT TGCCCTTATA CCTCTTCGCC        60

TTTCTGTGGT TCCATCCACT TCTTCCCCCT CCTCCTCCCA TAAACAACTC TCCTACCCCT       120

GCACCCCCAA TAAATAAATA AAAGGAGGAG GGCAAGGGGG GAGGAGGAGG AGTGGTGCTG       180

CGAGGGGAAG GAAAAGGGAG GCAGCGCGAG AAGAGCCGGG CAGAGTCCGA ACCGACAGCC       240

AGAAGCCCGC ACGCACCTCG CACC ATG AGA TGG CGA CGC GCC CCG CGC CGC          291
                           Met Arg Trp Arg Arg Ala Pro Arg Arg
                            1               5

TCC GGG CGT CCC GGC CCC CGG GCC CAG CGC CCC GGC TCC GCC GCC CGC         339
Ser Gly Arg Pro Gly Pro Arg Ala Gln Arg Pro Gly Ser Ala Ala Arg
 10                  15                  20                  25

TCG TCG CCG CCG CTG CCG CTG CTG CCA CTA CTG CTG CTG CTG GGG ACC         387
Ser Ser Pro Pro Leu Pro Leu Leu Pro Leu Leu Leu Leu Leu Gly Thr
                 30                  35                  40

GCG GCC CTG GCG CCG GGG GCG GCG GCC GGC AAC GAG GCG GCT CCC GCG         435
Ala Ala Leu Ala Pro Gly Ala Ala Ala Gly Asn Glu Ala Ala Pro Ala
             45                  50                  55

GGG GCC TCG GTG TGC TAC TCG TCC CCG CCC AGC GTG GGA TCG GTG CAG         483
Gly Ala Ser Val Cys Tyr Ser Ser Pro Pro Ser Val Gly Ser Val Gln
         60                  65                  70

GAG CTA GCT CAG CGC GCC GCG GTG GTG ATC GAG GGA AAG GTG CAC CCG         531
Glu Leu Ala Gln Arg Ala Ala Val Val Ile Glu Gly Lys Val His Pro
     75                  80                  85

CAG CGG CGG CAG CAG GGG GCA CTC GAC AGG AAG GCG GCG GCG GCG GCG         579
```

```
Gln Arg Arg Gln Gln Gly Ala Leu Asp Arg Lys Ala Ala Ala Ala Ala
 90                  95                 100                 105

GGC GAG GCA GGG GCG TGG GGC GGC GAT CGC GAG CCG CCA GCC GCG GGC         627
Gly Glu Ala Gly Ala Trp Gly Gly Asp Arg Glu Pro Pro Ala Ala Gly
                110                 115                 120

CCA CGG GCG CTG GGG CCG CCC GCC GAG GAG CCG CTG CTC GCC GCC AAC         675
Pro Arg Ala Leu Gly Pro Pro Ala Glu Glu Pro Leu Leu Ala Ala Asn
        125                 130                 135

GGG ACC GTG CCC TCT TGG CCC ACC GCC CCG GTG CCC AGC GCC GGC GAG         723
Gly Thr Val Pro Ser Trp Pro Thr Ala Pro Val Pro Ser Ala Gly Glu
        140                 145                 150

CCC GGG GAG GAG GCG CCC TAT CTG GTG AAG GTG CAC CAG GTG TGG GCG         771
Pro Gly Glu Glu Ala Pro Tyr Leu Val Lys Val His Gln Val Trp Ala
    155                 160                 165

GTG AAA GCC GGG GGC TTG AAG AAG GAC TCG CTG CTC ACC GTG CGC CTG         819
Val Lys Ala Gly Gly Leu Lys Lys Asp Ser Leu Leu Thr Val Arg Leu
170                 175                 180                 185

GGG ACC TGG GGC CAC CCC GCC TTC CCC TCC TGC GGG AGG CTC AAG GAG         867
Gly Thr Trp Gly His Pro Ala Phe Pro Ser Cys Gly Arg Leu Lys Glu
                190                 195                 200

GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC GAC GCC AAC AGC ACC AGC         915
Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro Asp Ala Asn Ser Thr Ser
            205                 210                 215

CGC GCG CCG GCC GCC TTC CGA GCC TCT TTC CCC CCT CTG GAG ACG GGC         963
Arg Ala Pro Ala Ala Phe Arg Ala Ser Phe Pro Pro Leu Glu Thr Gly
        220                 225                 230

CGG AAC CTC AAG AAG GAG GTC AGC CGG GTG CTG TGC AAG CGG TGC GCC        1011
Arg Asn Leu Lys Lys Glu Val Ser Arg Val Leu Cys Lys Arg Cys Ala
    235                 240                 245

TTG CCT CCC CAA TTG AAA GAG ATG AAA AGC CAG GAA TCG GCT GCA GGT        1059
Leu Pro Pro Gln Leu Lys Glu Met Lys Ser Gln Glu Ser Ala Ala Gly
250                 255                 260                 265

TCC AAA CTA GTC CTT CGG TGT GAA ACC AGT TCT GAA TAC TCC TCT CTC        1107
Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser Ser Leu
                270                 175                 180

AGA TTC AAG TGG TTC AAG AAT GGG AAT GAA TTG AAT CGA AAA AAC AAA        1155
Arg Phe Lys Trp Phe Lys Asn Gly Asn Glu Leu Asn Arg Lys Asn Lys
            185                 190                 195

CCA CAA AAT ATC AAG ATA CAA AAA AAG CCA GGG AAG TCA GAA CTT CGC        1203
Pro Gln Asn Ile Lys Ile Gln Lys Lys Pro Gly Lys Ser Glu Leu Arg
        200                 205                 210

ATT AAC AAA GCA TCA CTG GCT GAT TCT GGA GAG TAT ATG TGC AAA GTG        1251
Ile Asn Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys Lys Val
    215                 220                 225

ATC AGC AAA TTA GGA AAT GAC AGT GCC TCT GCC AAT ATC ACC ATC GTG        1299
Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr Ile Val
230                 235                 240                 245

GAA TCA AAC GCT ACA TCT ACA TCC ACC ACT GGG ACA AGC CAT CTT GTA        1347
Glu Ser Asn Ala Thr Ser Thr Ser Thr Thr Gly Thr Ser His Leu Val
                250                 255                 260
```

```
AAA TGT GCG GAG AAG GAG AAA ACT TTC TGT GTG AAT GGA GGG GAG TGC        1395
Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Cys
            265                 270                 275

TTC ATG GTG AAA GAC CTT TCA AAC CCC TCG AGA TAC TTG TGC AAG TGC        1443
Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr Leu Cys Lys Cys
        280                 285                 290

CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC GTA ATG GCC AGC        1491
Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser
    295                 300                 305

TTC TAC AGT ACG TCC ACT CCC TTT CTG TCT CTG CCT GAA                    1530
Phe Tyr Ser Thr Ser Thr Pro Phe Leu Ser Leu Pro Glu
400                 405                 410

TAGGAGCATG CTCAGTTGGT GCTGCTTTCT TGTTGCTGCA TCTCCCCTCA GATTCCACCT      1590

AGAGCTAGAT GTGTCTTACC AGATCTAATA TTGACTGCCT CTGCCTGTCG CATGAGAACA      1650

TTAACAAAAG CAATTGTATT ACTTCCTCTG TTCGCGACTA GTTGGCTCTG AGATACTAAT      1710

AGGTGTGTGA GGCTCCGGAT GTTTCTGGAA TTGATATTGA ATGATGTGAT ACAAATTGAT      1770

AGTCAATATC AAGCAGTGAA ATATGATAAT AAAGGCATTT CAAAGTCTCA CTTTTATTGA      1830

TAAAATAAAA ATCATTCTAC TGAACAGTCC ATCTTCTTTA TACAATGACC ACATCCTGAA      1890

AAGGGTGTTG CTAAGCTGTA ACCGATATGC ACTTGAAATG ATGGTAAGTT AATTTTGATT      1950

CAGAATGTGT TATTTGTCAC AAATAAACAT AATAAAAGGA AAAAAAAAAA AAA             2003
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 22:

val cys leu leu thr val ala ala

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 11 is unknown.

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

```
Ala Ser Leu Ala Asp Glu Tyr Glu Tyr Met Xaa Lys
  1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 9 is unknown.

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

Thr Glu Thr Ser Ser Ser Gly Leu Xaa Leu Lys
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

Ala Ser Leu Ala Asp Glu Tyr Glu Tyr Met Arg Lys
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 7 is unknown.

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

Ala Gly Tyr Phe Ala Glu Xaa Ala Arg
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

Thr Thr Glu Met Ala Ser Glu Gln Gly Ala
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

```
Ala Lys Glu Ala Leu Ala Ala Leu Lys
  1               5
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

```
Phe Val Leu Gln Ala Lys Lys
  1               5
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

```
Glu Thr Gln Pro Asp Pro Gly Gln Ile Leu Lys Lys Val Pro Met Val
  1               5                  10                  15

Ile Gly Ala Tyr Thr
             20
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in positions 1, 3, 17 and 19 is unknown.

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

Xaa Glu Xaa Lys Glu Gly Arg Gly Lys Gly Lys Gly Lys Lys Lys Glu
1 5 10 15

Xaa Gly Xaa Gly Lys
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

Ala Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 6 is unknown.

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

Lys Leu Glu Phe Leu Xaa Ala Lys
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Val His Gln Val Trp Ala Ala Lys
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine, Xaa in position 11 is unknown.

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

```
Xaa Tyr Ile Phe Phe Met Glu Pro Glu Ala Xaa Ser Ser Gly
  1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine, Xaa in position 13 is unknown.

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

```
Xaa Leu Gly Ala Trp Gly Pro Pro Ala Phe Pro Val Xaa Tyr
  1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

```
Xaa Trp Phe Val Val Ile Glu Gly Lys
  1               5
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Ala Ser Pro Val Ser Val Gly Ser Val Gln Glu Leu Val Gln Arg
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine.

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

Xaa Val Cys Leu Leu Thr Val Ala Ala Leu Pro Pro Thr
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is Lysine or Arginine; Xaa in position 6 is unknown.

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

Xaa Asp Leu Leu Leu Xaa Val
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

```
Cys Thr Cys Gly Cys Cys Lys Cys Cys Arg Thr Thr Cys Ala Cys Arg
 1               5                  10                  15

Cys Ala Gly Ala Ala Gly Gly Thr Cys Thr Thr Cys Thr Cys Cys Thr
            20                  25                  30

Thr Cys Thr Cys Ala Gly Cys
        35
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

```
Cys Cys Thr Cys Gly Cys Thr Cys Cys Thr Thr Cys Thr Thr Cys Thr
 1               5                  10                  15

Thr Gly Cys Cys Cys Thr Thr Cys
            20
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

```
TCGGGCTCCA TGAAGAAGAT GTA
23
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

TCCATGAAGA AGATGTACCT GCT
23

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

ATGTACCTGC TGTCCTCCTT GA
22

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 45:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

Val His Gln Val Trp Ala Ala Lys
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 10 is unknown.

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

Tyr Ile Phe Phe Met Glu Pro Glu Ala Xaa Ser Ser Gly
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 12 is unknown.

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

Leu Gly Ala Trp Gly Pro Pro Ala Phe Pro Val Xaa Tyr
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 48:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

Trp Phe Val Val Ile Glu Gly Lys
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 49:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Ala Ser Pro Val Ser Val Gly Ser Val Gln Glu Leu Val Gln Arg
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

Val Cys Leu Leu Thr Val Ala Ala Leu Pro Pro Thr
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

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

Lys Val His Gln Val Trp Ala Ala Lys
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 12 is unknown.

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

Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Xaa Lys
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 5 is unknown.

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

Asp Leu Leu Leu Xaa Val
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 54:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid

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

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

TTYAARGGNG AYGCNCAYAC 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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

CATRTAYTCR TAYTCRTCNG C 21

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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

TGYTCNGANG CCATYTCNGT 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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

TGYTCRCTNG CCATYTCNGT 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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

CCDATNACCA TNGGNACYTT 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 59:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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

GCNGCCCANA CYTGRTGNAC 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 60:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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

GCYTCNGGYT CCATRAARAA 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 61:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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

CCYTCDATNA CNACRAACCA 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 62:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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

TCNGCRAART ANCCNGC 17

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 63:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

GCNGCNAGNG CYTCYTTNGC 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 64:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

GCNGCYAANG CYTCYTTNGC 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 65:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

TTYTTNGCYT GNAGNACRAA 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 66:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

TTYTTNGCYT GYAANACRAA 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 67:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

TGNACNAGYT CYTGNAC 17

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 68:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

TGNACYAAYT CYTGNAC 17

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 69:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

CATRTAYTCN CCNGARTCNG C 21

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 70:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

CATRTAYTCN CCRCTRTCNG C 21

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 71:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

NGARTCNGCY AANGANGCYT T 21

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

NGARTCNGCN AGNGANGCYT T 21

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 73:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

RCTRTCNGCY AANGANGCYT T 21

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 74:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

RCTRTCNGCN AGNGANGCYT T 21

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 75:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21

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

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

NGARTCNGCY AARCTNGCYT T 21

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 76:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

NGARTCNGCN AGRCTNGCYT T 21

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 77:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

TTGAAGAAGG ACTCGCTGCT CA
22

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 78:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

RCTRTCNGCY AARCTNGCYT T 21

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 79:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

RCTRCTNGCN AGRCTNGCYT T 21

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 80:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

ACNACNGARA TGGCTCNNGA 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 81:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

ACNACNGARA TGGCAGYNGA 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 82:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

CAYCARGTNT GGGCNGCNAA 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 83:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

TTYGTNGTNA THGARGGNAA 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 84:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

AARGGNGAYG CNCAYACNGA 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 85:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

GARGCNYTNG CNGCNYTNAA 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 86:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

GTNGGNTCNG TNCARGARYT 20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 87:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

```
GTNGGNAGYG TNCARGARYT                  20
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 88:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

```
NACYTTYTTN ARDATYTGNC C                21
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 89:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 417
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in positions 14, 23, 90, 100, 126, and 135 is a stop codon.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

```
TCTAA AAC TAC AGA GAC TGT ATT TTC ATG ATC ATC ATA GTT CTG TGA AAT ATA     53
      Asn Tyr Arg Asp Cys Ile Phe Met Ile Ile Ile Val Leu Xaa Asn Ile
        1               5                  10                  15

CTT AAA CCG CTT TGG TCC TGA TCT TGT AGG AAG TCA GAA CTT CGC ATT          101
Leu Lys Pro Leu Trp Ser Xaa Ser Cys Arg Lys Ser Glu Leu Arg Ile
            20                  25                  30

AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA TAT ATG TGC AAA GTG ATC          149
Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Ser Met Cys Lys Val Ile
        35                  40                  45

AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC AAC ATC ACC ATT GTG GAG          197
Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Arg Ile Val Glu
    50                  55                  60

TCA AAC GGT AAG AGA TGC CTA CTG CGT GCT ATT TCT CAG TCT CTA AGA          245
Ser Asn Gly Lys Arg Cys Leu Leu Arg Ala Ile Ser Gln Ser Leu Arg
65                  70                  75                  80

GGA GTG ATC AAG GTA TGT GGT CAC ACT TGA ATC ACG CAG GTG TGT GAA          293
Gly Val Ile Lys Val Cys Gly His Thr Xaa Ile Thr Gln Val Cys Glu
                85                  90                  95

ATC TCA TTG TGA ACA AAT AAA AAT CAT GAA AGG AAA ACT CTA TGT TTG          341
Ile Ser Cys Xaa Thr Asn Lys Asn His Glu Arg Lys Thr Leu Cys Leu
            100                 105                 110

AAA TAT CTT ATG GGT CCT CCT GTA AAG CTC TTC ACT CCA TAA GGT GAA          389
Lys Tyr Leu Met Gly Pro Pro Val Lys Leu Phe Thr Pro Xaa Gly Glu
```

```
        115                 120                 125

ATA GAC CTG AAA TAT ATA TAG ATT ATT T                                   417
Ile Asp Leu Lys Tyr Ile Xaa Ile Ile
    130                 135
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 90:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 19, 25, and 31 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

CCGAATTCTG CAGGARACNC ARCCNGAYCC NGG 33

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 91:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 37
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 14, 20, 23, 29, and 35 is Inosine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

AAGGATCCTG CAGNGTRTAN GCNCCDATNA CCATNGG 37

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 92:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 34
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 16, 21, and 24 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

CCGAATTCTG CAGGCNGAYT CNGGNGARTA YATG 34

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 93:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 34
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 16 and 25 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

CCGAATTCTG CAGGCNGAYA GYGGNGARTA YAT 33

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 94:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 34
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 14, 15, 16, 26, and 29 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

AAGGATCCTG CAGNNNCATR TAYTCNCCNG ARTC 34

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 95:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 34
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 14, 15, 16, and 26 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

AAGGATCCTG CAGNNNCATR TAYTCNCCRC TRTC 34

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 96:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 21, 28, and 31 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

CCGAATTCTG CAGCAYCARG TNTGGGCNGC NAA 33

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 97:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 35
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at position 31 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

CCGAATTCTG CAGATHTTYT TYATGGARCC NGARG 35

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 98:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 35
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 18, 21, 24, 27, and 33 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

CCGAATTCTG CAGGGGGNCC NCCNGCNTTY CCNGT 35

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 99:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 21 and 24 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

CCGAATTCTG CAGTGGTTYG TNGTNATHGA RGG 33

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 100:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 34
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 17, 20, and 26 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

AAGGATCCTG CAGYTTNGCUN GCCCANACYT GRTG 34

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 101:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at position 19 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

AAGGATCCTG CAGGCYTCNG GYTCCATRAA RAA 33

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 102:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 16, 22, 25, 28, and 31 is Inosine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

AAGGATCCTG CAGACNGGRA ANGCNGGNGG NCC 33

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 103:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 35
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at positions 17, 26, and 29 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

AAGGATCCTG CAGYTTNCCY TCDATNACNA CRAAC 35

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 104:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at position 18 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

CATRTAYTCR TAYTCTCNGC AAGGATCCTG CAG 33

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 105:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at position 19, 25, and 31 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

CCGAATTCTG CAGAARGGNG AYGCNCAYAC NGA 33

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 106:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at position 3 and 18 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

GCNGCYAANG CYTCYTTNGC AAGGATCCTG CAG 33

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 107:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N at position 3, 6, 9, and 18 is Inosine. Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:

GCNGCNAGNG CYTCYTTNGC AAGGATCCTG CAG 33

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 108:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30

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

(ix) FEATURE:

(D) OTHER INFORMATION: N at position 3, 12, and 15 is Inosine.Y can be cytidine or thymidine.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:

TCNGCRAART ANCCNGCAAG GATCCTGCAG 30

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 109:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 38
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109:

CATCGATCTG CAGGCTGATT CTGGAGAATA TATGTGCA 38

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 110:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 37
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110:

AAGGATCCTG CAGCCACATC TCGAGTCGAC ATCGATT 37

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 111:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 37
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:

CCGAATTCTG CAGTGATCAG CAAACTAGGA AATGACA 37

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 112:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 37
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:

CATCGATCTG CAGCCTAGTT TGCTGATCAC TTTGCAC 37

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 113:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 37
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:

AAGGATCCTG CAGTATATTC TCCAGAATCA GCCAGTG 37

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 114:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 34
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:

AAGGATCCTG CAGGCACGCA GTAGGCATCT CTTA 34

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 115:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 35
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

CCGAATTCTG CAGCAGAACT TCGCATTAGC AAAGC 35

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 116:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33

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

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

CATCCCGGGA TGAAGAGTCA GGAGTCTGTG GCA 33

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 117:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

ATACCCGGGC TGCAGACAAT GAGATTTCAC ACACCTGCG 39

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 118:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 36
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118:

AAGGATCCTG CAGTTTGGAA CCTGCCACAG ACTCCT 36

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 119:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:

ATACCCGGGC TGCAGATGAG ATTTCACACA CCTGCGTGA 39

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 120:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120:

```
His Gln Val Trp Ala Ala Lys Ala Ala Gly Leu Lys
  1               5                   10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 121:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:

```
Gly Gly Leu Lys Lys Asp Ser Leu Leu Thr Val Arg Leu Gly Ala Asn
  1               5                   10                  15
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 122:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 12 is unknown.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:

```
Leu Gly Ala Trp Gly Pro Pro Ala Phe Pro Val Xaa Tyr
  1               5                   10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 123:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:

```
Leu Leu Thr Val Arg Leu Gly Ala Trp Gly His Pro Ala Phe Pro Ser
  1               5                   10                  15

Cys Gly Arg Leu Lys Glu Asp
             20
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 124:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 10 is unknown.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

```
Tyr Ile Phe Phe Met Glu Pro Glu Ala Xaa Ser Ser Gly
  1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 125:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 125:

```
Lys Glu Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro Glu Ala Asn Ser
  1               5                  10                  15

Ser Gly Gly Pro Gly Arg Leu
             20
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 126:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126:

```
Val Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser
  1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 127:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:

Glu Tyr Lys Cys Leu Lys Phe Lys Trp Phe Lys Lys Ala Thr Val Met
1 5 10 15

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 128:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:

Cys Glu Thr Ser Ser Glu Tyr Ser Ser Leu Lys Phe Lys Trp Phe Lys
1 5 10 15

Asn Gly Ser Glu Leu Ser Arg Lys Asn Lys
20 25

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 129:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 12 is unknown.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:

Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Xaa Lys
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 130:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:

Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met
1 5 10 15

Cys Lys Val Ile Ser Lys Leu
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 131:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131:

```
Ala Ser Leu Ala Asp Glu Tyr Glu Tyr Met Arg Lys
  1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 132:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 132:

```
Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys
  1               5                  10                  15

Lys Val Ile Ser Lys Leu
            20
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 133:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 744
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133:

```
CCTGCAG CAT CAA GTG TGG GCG GCG AAA GCC GGG GGC TTG AAG AAG GAC TCG CTG
55
        His Gln Val Trp Ala Ala Lys Ala Gly Gly Leu Lys Lys Asp Ser Leu
          1               5                  10                  15

CTC ACC GTG CGC CTG GGC GCC TGG GGC CAC CCC GCC TTC CCC TCC TGC
103
Leu Thr Val Arg Leu Gly Ala Trp Gly His Pro Ala Phe Pro Ser Cys
            20                  25                  30

GGG CGC CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC GAG
151
Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro Glu
        35                  40                  45

GCC AAC AGC AGC GGC GGG CCC GGC CGC CTT CCG AGC CTC CTT CCC CCC          199
Ala Asn Ser Ser Gly Gly Pro Gly Arg Leu Pro Ser Leu Leu Pro Pro
    50                  55                  60
```

```
TCT CGA GAC GGG CCG GAA CCT CAA GAA GGA GGT CAG CCG GGT GCT GTG
247
Ser Arg Asp Gly Pro Glu Pro Gln Glu Gly Gly Gln Pro Gly Ala Val
65                  70                  75                  80

CAA CGG TGC GCC TTG CCT CCC CGC TTG AAA GAG ATG AAG AGT CAG GAG
295
Gln Arg Cys Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu
                85                  90                  95

TCT GTG GCA GGT TCC AAA CTA GTG CTT CGG TGC GAG ACC AGT TCT GAA
343
Ser Val Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu
            100                 105                 110

TAC TCC TCT CTC AAG TTC AAG TGG TTC AAG AAT GGG AGT GAA TTA AGC
391
Tyr Ser Ser Leu Lys Phe Lys Trp Phe Lys Asn Gly Ser Glu Leu Ser
        115                 120                 125

CGA AAG AAC AAA CCA GAA AAC ATC AAG ATA CAG AAA AGG CCG GGG AAG
439
Arg Lys Asn Lys Pro Glu Asn Ile Lys Ile Gln Lys Arg Pro Gly Lys
    130                 135                 140

TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA TAT
487
Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr
145                 150                 155                 160

ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC AAC
535
Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn
                165                 170                 175

ATC ACC ATT GTG GAG TCA AAC GGT AAG AGA TGC CTA CTG CGT GCT ATT
583
Ile Thr Ile Val Glu Ser Asn Gly Lys Arg Cys Leu Leu Arg Ala Ile
            180                 185                 190

TCT CAG TCT CTA AGA GGA GTG ATC AAG GTA TGT GGT CAC ACT
625
Ser Gln Ser Leu Arg Gly Val Ile Lys Val Cys Gly His Thr
        195                 200                 205

TGAATCACGC AGGTGTGTGA AATCTCATTG TGAACAAATA AAAATCATGA AGGAAAAAA
685

AAAAAAAAAA AATCGATGTC GACTCGAGAT GTGGCTGCAG GTCGACTCTA GAGGATCCC
744
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 134:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1193
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134:

CCTGCAG CAT CAA GTG TGG GCG GCG AAA GCC GGG GGC TTG AAG AAG GAC TCG CTG
55
His Gln Val Trp Ala Ala Lys Ala Gly Gly Leu Lys Lys Asp Ser Leu
1 5 10 15

CTC ACC GTG CGC CTG GGC GCC TGG GGC CAC CCC GCC TTC CCC TCC TGC
103
Leu Thr Val Arg Leu Gly Ala Trp Gly His Pro Ala Phe Pro Ser Cys
20 25 30

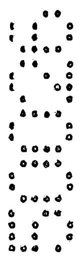
GGG CGC CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC GAG
151
Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro Glu
35 40 45

GCC AAC AGC AGC GGC GGG CCC GGC CGC CTT CCG AGC CTC CTT CCC CCC
199
Ala Lys Ser Ser Gly Gly Pro Gly Arg Leu Pro Ser Leu Leu Pro Pro
50 55 60

TCT CGA GAC GGG CCG GAA CCT CAA GAA GGA GGT CAG CCG GGT GCT GTG
247
Ser Arg Asp Gly Pro Glu Pro Gln Glu Gly Gly Gln Pro Gly Ala Val
65 70 75 80

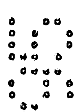
CAA CGG TGC GCC TTG CCT CCC CGC TTG AAA GAG ATG AAG AGT CAG GAG
295
Gln Arg Cys Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu
85 90 95

TCT GTG GCA GGT TCC AAA CTA GTG CTT CGG TGC GAG ACC AGT TCT GAA
343
Ser Val Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu
100 105 110

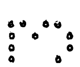


TAC TCC TCT CTC AAG TTC AAG TGG TTC AAG AAT GGG AGT GAA TTA AGC
391
Tyr Ser Ser Leu Lys Phe Lys Trp Phe Lys Asn Gly Ser Glu Leu Ser
115 120 125

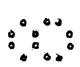
CGA AAG AAC AAA CCA GAA AAC ATC AAG ATA CAG AAA AGG CCG GGG AAG
439
Arg Lys Asn Lys Gly Gly Asn Ile Lys Ile Gln Lys Arg Pro Gly Lys
130 135 140



TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA TAT
487
Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr
145 150 155 160



ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC AAC
535
Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn
165 170 175



ATC ACC ATT GTG GAG TCA AAC GCC ACA TCC ACA TCT ACA GCT GGG ACA
583
Ile Thr Ile Val Glu Ser Asn Ala Thr Ser Thr Ser Thr Ala Gly Thr
180 185 190

AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT
631
Ser His Leu Val Lys Ser Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
195 200 205

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC
679
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
210 215 220

TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT
727
Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn
225 230 235 240

GTG CCC ATG AAA GTC CAA ACC CAA GAA AGT GCC CAA ATG AGT TTA CTG
775
Val Pro Met Lys Val Gln Thr Gln Glu Ser Ala Gln Met Ser Leu Leu
245 250 255

GTG ATC GCT GCC AAA ACT ACG TAATGGCCAG CTTCTACAGT ACGTCCACTC
826
Val Ile Ala Ala Lys Thr Thr
260

CCTTTCTGTC TCTGCCTGAA TAGCGCATCT CAGTCGGTGC CGCTTTCTTG TTGCCGCATC
886

TCCCCTCAGA TTCCTCCTAG AGCTAGATGC GTTTTACCAG GTCTAACATT GACTGCCTCT
946

GCCTGTCGCA TGAGAACATT AACACAAGCG ATTGTATGAC TTCCTCTGTC CGTGACTAGT
1006

GGGCTCTGAG CTACTCGTAG GTGCGTAAGG CTCCAGTGTT TCTGAAATTG ATCTTGAATT
1066

ACTGTGATAC GACATGATAG TCCCTCTCAC CCAGTGCAAT GACAATAAAG GCCTTGAAAA
1126

GTCAAAAAAA AAAAAAAAAA AAAAAATCGA TGTCGACTCG AGATGTGGCT GCAGGTCGAC
1186

TCTAGAG
1193

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 135:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1108
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135:

CCTGCAG CAT CAA GTG TGG GCG GCG AAA GCC GGG GGC TTG AAG AAG GAC TCG CTG
55
His Gln Val Trp Ala Ala Lys Ala Gly Gly Leu Lys Lys Asp Ser Leu
1 5 10 15

CTC ACC GTG CGC CTG GGC GCC TGG GGC CAC CCC GCC TTC CCC TCC TGC
103
Leu Thr Val Arg Leu Gly Ala Trp Gly His Pro Ala Phe Pro Ser Cys
20 25 30

GGG CGC CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC GAG
151

Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro Glu
35 40 45

GCC AAC AGC AGC GGC GGG CCC GGC CGC CTT CCG AGC CTC CTT CCC CCC
199
Ala Asn Ser Ser Gly Gly Pro Gly Arg Leu Pro Ser Leu Leu Pro Pro
50 55 60

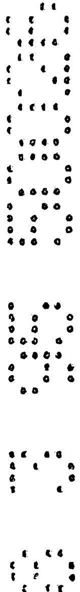
TCT CGA GAC GGG CCG GAA CCT CAA GAA GGA GGT CAG CCG GGT GCT GTG
247
Ser Arg Asp Gly Pro Glu Pro Gln Glu Gly Gly Gln Pro Gly Ala Val
65 70 75 80

CAA CGG TGC GCC TTG CCT CCC CGC TTG AAA GAG ATG AAG AGT CAG GAG
295
Gln Arg Cys Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu
85 90 95

TCT GTG GCA GGT TCC AAA CTA GTG CTT CGG TGC GAG ACC AGT TCT GAA
343
Ser Val Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu
100 105 110

TAC TCC TCT CTC AAG TTC AAG TGG TTC AAG AAT GGG AGT GAA TTA AGC
391
Tyr Ser Ser Leu Lys Phe Lys Trp Phe Lys Asn Gly Ser Glu Leu Ser
115 120 125

CGA AAG AAC AAA CCA GAA AAC ATC AAG ATA CAG AAA AGG CCG GGG AAG
439
Arg Lys Asn Lys Pro Glu Asn Ile Lys Ile Gln Lys Arg Pro Pro Lys
130 135 140



TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA TAT
487
Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr
145 150 155 160

ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC AAC
535
Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn
165 170 175

ATC ACC ATT GTG GAG TCA AAC GCC ACA TCC ACA TCT ACA GCT GGG ACA
583
Ile Arg Ile Val Glu Ser Asn Ala Thr Ser Thr Ser Thr Ala Gly Thr
180 185 190

AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT
631
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
195 200 205

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC
679
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
210 215 220

TTG TGC AAG TGC CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC
727
Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr
225 230 235 240

GTA ATG GCC AGC TTC TAC AGT ACG TCC ACT CCC TTT CTG TCT CTG CCT
775
Val Met Ala Ser Phe Tyr Ser Thr Ser Thr Pro Phe Leu Ser Leu Pro

245 250 255

GAA TAGCGCATCT CAGTCGGTGC CGCTTTCTTG TTGCCGCATC TCCCCTCAGA TTCCGCCTAG
838
Glu

AGCTAGATGC GTTTTACCAG GTCTAACATT GACTGCCTCT GCCTGTCGCA TGAGAACATT
898

AACACAAGCG ATTGTATGAC TTCCTCTGTC CGTGACTAGT GGGCTCTGAG CTACTCGTAG
958

GTGCGTAAGG CTCCAGTGTT TCTGAAATTG ATCTTGAATT ACTGTGATAC GACATGATAG
1018

TCCCTCTCAC CCAGTGCAAT GACAATAAAG GCCTTGAAAA GTCAAAAAAA AAAAAAAAAA
1078

AAAAATCGAT GTCGACTCGA GATGTGGCTG
1108

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 136:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 559
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N in position 214 is unknown.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 136:

AGTTTCCCCC CCCAACTTGT CGGAACTCTG GGCTCGCGCG CAGGGCAGGA GCGGAGCGGC 60

GGCGGCTGCC CAGGCGATGC GAGCGCGGGC CGGACGGTAA TCGCCTCTCC CTCCTCGGGC 120

TGCGAGCGCG CCGGACCGAG GCAGCGACAG GAGCGGACCG CGGCGGGAAC CGAGGACTCC 180

CCAGCGGCGC GCCAGCAGGA GCCACCCCGC GAGNCGTGCG ACCGGGACGG AGCGCCCGCC 240

AGTCCCAGGT GGCCCGGACC GCACGTTGCG TCCCCGCGCT CCCCGCCGGC GACAGGAGAC 300

GCTCCCCCCC ACGCCGCGCG CGCCTCGGCC CGGTCGCTGG CCCGCCTCCA CTCCGGGGAC 360

AAACTTTTCC CGAAGCCGAT CCCAGCCCTC GGACCCAAAC TTGTCGCGCG TCGCCTTCGC 420

CGGGAGCCGT CCGCGCAGAG CGTGCACTTC TCGGGCGAG ATG TCG GAG CGC AGA 474
Met Ser Glu Arg Arg
1 5

GAA GGC AAA GGC AAG GGG AAG GGC GGC AAG AAG GAC CGA GGC TCC GGG 522
Glu Gly Lys Gly Lys Gly Lys Gly Gly Lys Lys Asp Arg Gly Ser Gly
10 15 20

AAG AAG CCC GTG CCC GCG GCT GGC GGC CCG AGC CCA G 559
Lys Lys Pro Val Pro Ala Ala Gly Gly Pro Ser Pro Ala
25 30

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 137:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 252
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N in position 8 could be either A or G.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:

```
CC CAT CAN GTG TGG GCG GCG AAA GCC GGG GGC TTG AAG AAG GAC TCG        47
   His Gln Val Trp Ala Ala Lys Ala Gly Gly Leu Lys Lys Asp Ser
    1               5                  10                  15

CTG CTC ACC GTG CGC CTG GGC GCC TGG GGC CAC CCC GCC TTC CCC TCC       95
Leu Leu Thr Val Arg Leu Gly Ala Trp Gly His Pro Ala Phe Pro Ser
                20                  25                  30

TGC GGG CGC CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC      143
Cys Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro
            35                  40                  45

GAG GCC AAC AGC AGC GGC GGG CCC GGC CGC CTT CCG AGC CTC CTT CCC      191
Glu Ala Asn Ser Ser Gly Gly Pro Gly Arg Leu Pro Ser Leu Leu Pro
        50                  55                  60

CCC TCT CGA GAC GGG CCG GAA CCT CAA GAA GGA GGT CAG CCG GGT GCT      239
Pro Ser Arg Asp Gly Pro Glu Pro Gln Glu Gly Gly Gln Pro Gly Ala
    65                  70                  75

GTG CAA CGG TGC G                                                    252
Val Gln Arg Cys
80
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 138:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 178
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:

```
CCT TGC CTC CCC GCT TGA AAG AGA TGA AGA GTC AGG AGT CTG TGG CAG       48
Leu Pro Pro Arg Leu Lys Glu His Lys Ser Gln Glu Ser Val Ala Gly
1               5                  10                  15

GTT CCA AAC TAG TGC TTC GGT GCG AGA CCA GTT CTG AAT ACT CCT CTC       96
Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser Ser Leu
            20                  25                  30

TCA AGT TCA AGT GGT TCA AGA ATG GGA GTG AAT TAA GCC GAA AGA ACA      144
Lys Phe Lys Trp Phe Lys Asn Gly Ser Glu Leu Ser Arg Lys Asn Lys
        35                  40                  45
```

```
AAC CAC AAA ACA TCA AGA TAC AGA AAA GGC CGG G                       178
Pro Gly Asn Ile Lys Ile Gln Lys Arg Pro Gly
     50                   55
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 139:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 122
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:

```
G AAG TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA        46
  Lys Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly
    1               5                  10                  15

GAA TAT ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT      94
Glu Tyr Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser
                20                  25                  30

GCC AAC ATC ACC ATT GTG GAG TCA AAC G                               122
Ala Asn Ile Thr Ile Val Glu Ser Asn Ala
            35
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 140:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 417
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:

```
TCTAAAACTA CAGAGACTGT ATTTTCATGA TCATCATAGT TCTGTGAAAT ATACTTAAAC    60

CGCTTTGGTC CTGATCTTGT AGG AAG TCA GAA CTT CGC ATT AGC AAA GCG       110
                          Lys Ser Glu Leu Arg Ile Ser Lys Ala
                            1               5

TCA CTG GCT GAT TCT GGA GAA TAT ATG TGC AAA GTG ATC AGC AAA CTA     158
Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys Lys Val Ile Ser Lys Leu
 10                  15                  20                  25

GGA AAT GAC AGT GCC TCT GCC AAC ATC ACC ATT GTG GAG TCA AAC GGT     206
Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr Ile Val Glu Ser Asn Gly
                30                  35                  40

AAG AGA TGC CTA CTG CGT GCT ATT TCT CAG TCT CTA AGA GGA GTG ATC     254
Lys Arg Cys Leu Leu Arg Ala Ile Ser Gln Ser Leu Arg Gly Val Ile
            45                  50                  55

AAG GTA TGT GGT CAC ACT TGAATCACGC AGGTGTGTGA AATCTCATTG            302
Lys Val Cys Gly His Thr
        60

TGAACAAATA AAAATCATGA AAGGAAAACT CTATGTTTGA AATATCTTAT GGGTCCTCCT   362
```

GTAAAGCTCT TCACTCCATA AGGTGAAATA GACCTGAAAT ATATATAGAT TATTT 417

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 141:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 102
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141:

```
 AG ATC ACC ACT GGC ATG CCA GCC TCA ACT GAG ACA GCG TAT GTG TCT      47
Glu Ile Thr Thr Gly Met Pro Ala Ser Thr Glu Thr Ala Tyr Val Ser
 1               5                  10                  15

TCA GAG TCT CCC ATT AGA ATA TCA GTA TCA ACA GAA GGA ACA AAT ACT     95
Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr Glu Gly Thr Asn Thr
            20                  25                  30

TCT TCA T                                                          102
Ser Ser Ser
        35
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 142:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 69
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:

```
AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT GTG CCC     48
Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn Val Pro
  1               5                  10                  15

ATG AAA GTC CAA ACC CAA GAA                                         69
Met Lys Val Gln Thr Gln Glu
            20
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 143:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 60
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 143

```
AAG TGC CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC GTA ATG     48
Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr Val Met
  1               5                  10                  15
```

```
GCC AGC TTC TAC                                                    60
Ala Ser Phe Tyr
            20
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 144:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 36
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 144:

```
AGT ACG TCC ACT CCC TTT CTG TCT CTG CCT GAA TAG                    36
Ser Thr Ser Thr Pro Phe Leu Ser Leu Pro Glu
 1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 145:

(i) SEQUENCE CHARACTERISTICS:

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

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 145:

```
AAG CAT CTT GGG ATT GAA TTT ATG GAG                                27
Lys His Leu Gly Ile Glu Phe Met Glu
 1               5
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 146:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 569
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 146:

```
AAA GCG GAG GAG CTC TAC CAG AAG AGA GTG CTC ACC ATT ACC GGC ATT    48
Lys Ala Glu Glu Leu Tyr Gln Lys Arg Val Leu Thr Ile Thr Gly Ile
 1               5                  10                  15

TGC ATC GCG CTG CTC GTG GTT GGC ATC ATG TGT GTG GTG GTC TAC TGC    96
Cys Ile Ala Leu Leu Val Val Gly Ile Met Cys Val Val Val Tyr Cys
            20                  25                  30

AAA ACC AAG AAA CAA CGG AAA AAG CTT CAT GAC CGG CTT CGG CAG AGC   144
Lys Thr Lys Lys Gln Arg Lys Lys Leu His Asp Arg Leu Arg Gln Ser
        35                  40                  45
```

```
CTT CGG TCT GAA AGA AAC ACC ATG ATG AAC GTA GCC AAC GGG CCC CAC        192
Leu Arg Ser Glu Arg Asn Thr Met Met Asn Val Ala Asn Gly Pro His
     50                  55                  60

CAC CCC AAT CCG CCC CCC GAG AAC GTG CAG CTG GTG AAT CAA TAC GTA        240
His Pro Asn Pro Pro Pro Glu Asn Val Gln Leu Val Asn Gln Tyr Val
 65                  70                  75                  80

TCT AAA AAT GTC ATC TCT AGC GAG CAT ATT GTT GAG AGA GAG GCG GAG        288
Ser Lys Asn Val Ile Ser Ser Glu His Ile Val Glu Arg Glu Ala Glu
                 85                  90                  95

AGC TCT TTT TCC ACC AGT CAC TAC ACT TCG ACA GCT CAT CAT TCC ACT        336
Ser Ser Phe Ser Thr Ser His Tyr Thr Ser Thr Ala His His Ser Thr
            100                 105                 110

ACT GTC ACT CAG ACT CCC AGT CAC AGC TGG AGC AAT GGA CAC ACT GAA        384
Thr Val Thr Gln Thr Pro Ser His Ser Trp Ser Asn Gly His Thr Glu
        115                 120                 125

AGC ATC ATT TCG GAA AGC CAC TCT GTC ATC GTG ATG TCA TCC GTA GAA        432
Ser Ile Ile Ser Glu Ser His Ser Val Ile Val Met Ser Ser Val Glu
    130                 135                 140

AAC AGT AGG CAC AGC AGC CCG ACT GGG GGC CCG AGA GGA CGT CTC AAT        480
Asn Ser Arg His Ser Ser Pro Thr Gly Gly Pro Arg Gly Arg Leu Asn
145                 150                 155                 160

GGC TTG GGA GGC CCT CGT GAA TGT AAC AGC TTC CTC AGG CAT GCC AGA        528
Gly Leu Gly Gly Pro Arg Glu Cys Asn Ser Phe Leu Arg His Ala Arg
                165                 170                 175

GAA ACC CCT GAC TCC TAC CGA GAC TCT CCT CAT AGT G AAAG                 569
Glu Thr Pro Asp Ser Tyr Arg Asp Ser Pro His Ser
            180                 185
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 147:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 735
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 147:

```
G TAT GTA TCA GCA ATG ACC ACC CCG GCT CGT ATG TCA CCT GTA GAT           46
  Tyr Val Ser Ala Met Thr Thr Pro Ala Arg Met Ser Pro Val Asp
    1               5                  10                  15

TTC CAC ACG CCA AGC TCC CCC AAG TCA CCC CCT TCG GAA ATG TCC CCG         94
Phe His Thr Pro Ser Ser Pro Lys Ser Pro Pro Ser Glu Met Ser Pro
                 20                  25                  30

CCC GTG TCC AGC ACG ACG GTC TCC ATG CCC TCC ATG GCG GTC AGT CCC        142
Pro Val Ser Ser Thr Thr Val Ser Met Pro Ser Met Ala Val Ser Pro
            35                  40                  45

TTC GTG GAA GAG GAG AGA CCC CTG CTC CTT GTG ACG CCA CCA CGG CTG        190
Phe Val Glu Glu Glu Arg Pro Leu Leu Leu Val Thr Pro Pro Arg Leu
        50                  55                  60
```

CGG GAG AAG TAT GAC CAC CAC GCC CAG CAA TTC AAC TCG TTC CAC TGC 238
Arg Glu Lys Tyr Asp His His Ala Gln Gln Phe Asn Ser Phe His Cys
65 70 75

AAC CCC GCG CAT GAG AGC AAC AGC CTG CCC CCC AGC CCC TTG AGG ATA 286
Asn Pro Ala His Glu Ser Asn Ser Leu Pro Pro Ser Pro Leu Arg Ile
80 85 90 95

GTG GAG GAT GAG GAA TAT GAA ACG ACC CAG GAG TAC GAA CCA GCT CAA 334
Val Glu Asp Glu Glu Tyr Glu Thr Thr Gln Glu Tyr Glu Pro Ala Gln
100 105 110

GAG CCG GTT AAG AAA CTC ACC AAC AGC AGC CGG CGG GCC AAA AGA ACC 382
Glu Pro Val Lys Lys Leu Thr Asn Ser Ser Arg Arg Ala Lys Arg Thr
115 120 125

AAG CCC AAT GGT CAC ATT GCC CAC AGG TTG GAA ATG GAC AAC AAC ACA 430
Lys Pro Asn Gly His Ile Ala His Arg Leu Glu Met Asp Asn Asn Thr
130 135 140

GGC GCT GAC AGC AGT AAC TCA GAG AGC GAA ACA GAG GAT GAA AGA GTA 478
Gly Ala Asp Ser Ser Asn Ser Glu Ser Glu Thr Glu Asp Glu Arg Val
145 150 155

GGA GAA GAT ACG CCT TTC CTG GCC ATA CAG AAC CCC CTG GCA GCC AGT 526
Gly Glu Asp Thr Pro Phe Leu Ala Ile Gln Asn Pro Leu Ala Ala Ser
160 165 170 175

CTC GAG GCG GCC CCT GCC TTC CGC CTG GTC GAC AGC AGG ACT AAC CCA 574
Leu Glu Ala Ala Pro Ala Phe Arg Leu Val Asp Ser Arg Thr Asn Pro
180 185 190

ACA GGC GGC TTC TCT CCG CAG GAA GAA TTG CAG GCC AGG CTC TCC GGT 622
Thr Gly Gly Phe Ser Pro Gln Glu Glu Leu Gln Ala Arg Leu Ser Gly
195 200 205

GTA ATC GCT AAC CAA GAC CCT ATC GCT GTC TAAAACCGAA ATACACCCAT 672
Val Ile Ala Asn Gln Asp Pro Ile Ala Val
210 215

AGATTCACCT GTAAAACTTT ATTTTATATA ATAAAGTATT CCACCTTAAA TTAAACAA 730

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 148:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1652
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 148:

AGTTTCCCCC CCCAACTTGT CGGAACTCTG GGCTCGCGCG CAGGGCAGGA GCGGAGCGGC 60

GGCGGCTGCC CAGGCGATGC GAGCGCGGGC CGGACGGTAA TCGCCTCTCC CTCCTCGGGC 120

TGCGAGCGCG CCGGACCGAG GCAGCGACAG GAGCGGACCG CGGCGGGAAC CGAGGACTCC 180

CCAGCGGCGC GCCAGCAGGA GCCACCCCGC GAGCGTGCGA CCGGGACGGA GCGCCCGCCA 240

GTCCCAGGTG GCCCGGACCG CACGTTGCGT CCCCGCGCTC CCCGCCGGCG ACAGGAGACG 300

```
CTCCCCCCCA CGCCGCGCGC GCCTCGGCCC GGTCGCTGGC CCGCCTCCAC TCCGGGGACA      360

AACTTTTCCC GAAGCCGATC CCAGCCCTCG GACCCAAACT TGTCGCGCGT CGCCTTCGCC      420

GGGAGCCGTC CGCGCAGAGC GTGCACTTCT CGGGCGAG ATG TCG GAG CGC AGA          475
                                          Met Ser Glu Arg Arg
                                            1               5

GAA GGC AAA GGC AAG GGG AAG GGC GGC AAG AAG GAC CGA GGC TCC GGG        523
Glu Gly Lys Gly Lys Gly Lys Gly Gly Lys Lys Asp Arg Gly Ser Gly
                 10                  15                  20

AAG AAG CCC GTG CCC GCG GCT GGC GGC CCG AGC CCA GCC TTG CCT CCC        571
Lys Lys Pro Val Pro Ala Ala Gly Gly Pro Ser Pro Ala Leu Pro Pro
                 25                  30                  35

CGC TTG AAA GAG ATG AAG ATG CAG GAG TCT GTG GCA GGT TCC AAA CTA       619
Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Val Ala Gly Ser Lys Leu
         40                  45                  50

GTG CTT CGG TGC GAG ACC AGT TCT GAA TAC TCC TCT CTC AAG TTC AAG        667
Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser Ser Leu Lys Phe Lys
     55                  60                  65

TGG TTC AAG AAT GGG AGT GAA TTA AGC CGA AAG AAC AAA CCA CAA AAC        715
Trp Phe Lys Asn Gly Ser Glu Leu Ser Arg Lys Asn Lys Pro Gln Asn
 70                  75                  80                  85

ATC AAG ATA CAG AAA AGG CCG GGG AAG TCA GAA CTT CGC ATT AGC AAA        763
Ile Lys Ile Gln Lys Arg Pro Gly Lys Ser Glu Leu Arg Ile Ser Lys
                 90                  95                 100

GCG TCA CTG GCT GAT TCT GGA GAA TAT ATG TGC AAA GTG ATC AGC AAA        811
Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys Lys Val Ile Ser Lys
            105                 110                 115

CTA GGA AAT GAC AGT GCC TCT GCC AAC ATC ACC ATT GTG GAG TCA AAC        859
Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr Ile Val Glu Ser Asn
        120                 125                 130

GAG ATC ACC ACT GGC ATG CCA GCC TCA ACT GAG ACA GCG TAT GTG TCT        907
Glu Ile Thr Thr Gly Met Pro Ala Ser Thr Glu Thr Ala Tyr Val Ser
    135                 140                 145

TCA GAG TCT CCC ATT AGA ATA TCA GTA TCA ACA GAA GGA ACA AAT ACT        955
Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr Glu Gly Thr Asn Thr
150                 155                 160                 165

TCT TCA TCC ACA TCC ACA TCT ACA GCT GGG ACA AGC CAT CTT GTC AAG       1003
Ser Ser Ser Thr Ser Thr Ser Thr Ala Gly Thr Ser His Leu Val Lys
                170                 175                 180

TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT GGA GGC GAG TGC TTC       1051
Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Cys Phe
            185                 190                 195

ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC TTG TGC AAG TGC CCA       1099
Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr Leu Cys Lys Cys Pro
        200                 205                 210

AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC GTA ATG GCC AGC TTC       1147
Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser Phe
    215                 220                 225

TAC AGT ACG TCC ACT CCC TTT CTG TCT CTG CCT GAA TAGGCGCATG            1193
Tyr Ser Thr Ser Thr Pro Phe Leu Ser Leu Pro Glu
230                 235                 240
```

```
CTCAGTCGGT GCCGCTTTCT TGTTGCCGCA TCTCCCCTCA GATTCAACCT AGAGCTAGAT    1253

GCGTTTTACC AGGTCTAACA TTGACTGCCT CTGCCTGTCG CATGAGAACA TTAACACAAG    1313

CGATTGTATG ACTTCCTCTG TCCGTGACTA GTGGGCTCTG AGCTACTCGT AGGTGCGTAA    1373

GGCTCCAGTG TTTCTGAAAT TGATCTTGAA TTACTGTGAT ACGACATGAT AGTCCCTCTC    1433

ACCCAGTGCA ATGACAATAA AGGCCTTGAA AAGTCTCACT TTTATTGAGA AAATAAAAAT    1493

CGTTCCACGG GACAGTCCCT CTTCTTTATA AAATGACCCT ATCCTTGAAA AGGAGGTGTG    1553

TTAAGTTGTA ACCAGTACAC ACTTGAAATG ATGGTAAGTT CGCTTCGGTT CAGAATGTGT    1613

TCTTTCTGAC AAATAAACAG AATAAAAAAA AAAAAAAAAA A                       1652
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 149:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1140
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 149:

```
CAT CAN GTG TGG GCG GCG AAA GCC GGG GGC TTG AAG AAG GAC TCG CTG
48
His Gln Val Trp Ala Ala Lys Ala Gly Gly Leu Lys Lys Asp Ser Leu
1               5                   10                  15

CTC ACC GTG CGC CTG GGC GCC TGG GGC CAC CCC GCC TTC CCC TCC TGC
96
Leu Thr Val Arg Leu Gly Ala Trp Gly His Pro Ala Phe Pro Ser Cys
            20                  25                  30

GGG CGC CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC GAG
144
Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro Glu
        35                  40                  45

GCC AAC AGC AGC GGC GGG CCC GGC CGC CTT CCG AGC CTC CTT CCC CCC
192
Ala Asn Ser Ser Gly Gly Pro Gly Arg Leu Pro Ser Leu Leu Pro Pro
    50                  55                  60

TCT CGA GAC GGG CCG GAA CCT CAA GAA GGA GGT CAG CCG GGT GCT GTG
240
Ser Arg Asp Gly Pro Glu Pro Gln Glu Gly Gly Gln Pro Gly Ala Val
65                  70                  75                  80

CAA CGG TGC GCC TTG CCT CCC CGC TTG AAA GAG ATG AAG AGT CAG GAG
288
Gln Arg Cys Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu
                85                  90                  95

TCT GTG GCA GGT TCC AAA CTA GTG CTT CGG TGC GAG ACC AGT TCT GAA
336
Ser Val Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu
            100                 105                 110

TAC TCC TCT CTC AAG TTC AAG TGG TTC AAG AAT GGG AGT GAA TTA AGC
384
```

```
Tyr Ser Ser Leu Lys Phe Lys Trp Phe Lys Asn Gly Ser Glu Leu Ser
        115                 120                 125

CGA AAG AAC AAA CCA GAA AAC ATC AAG ATA CAG AAA AGG CCG GGG AAG
432
Arg Lys Asn Lys Pro Glu Asn Ile Lys Ile Gln Lys Arg Pro Gly Lys
    130                 135                 140

TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA TAT
480
Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr
145                 150                 155                 160

ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC AAC
528
Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn
                165                 170                 175

ATC ACC ATT GTG GAG TCA AAC GCC ACA TCC ACA TCT ACA GCT GGG ACA
576
Ile Thr Ile Val Glu Ser Asn Ala Thr Ser Thr Ser Thr Ala Gly Thr
            180                 185                 190

AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT
624
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
        195                 200                 205

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC
672
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
    210                 215                 220

TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT
720
Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn
225                 230                 235                 240

GTG CCC ATG AAA GTC CAA ACC CAA GAA AAG TGC CCA AAT GAG TTT ACT
768
Val Pro Met Lys Val Gln Thr Gln Glu Lys Cys Pro Asn Glu Phe Thr
                245                 250                 255

GGT GAT CGC TGC CAA AAC TAC GTA ATG GCC AGC TTC TAC AGT ACG TCC
816
Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser Phe Tyr Ser Thr Ser
            260                 265                 270

ACT CCC TTT CTG TCT CTG CCT GAA TAGCGCATCT CAGTCGGTGC CGCTTTCTTG
870
Thr Pro Phe Leu Ser Leu Pro Glu
        275                 280

TTGCCGCATC TCCCCTCAGA TTCCNCCTAG AGCTAGATGC GTTTTACCAG GTCTAACATT
930

GACTGCCTCT GCCTGTCGCA TGAGAACATT AACACAAGCG ATTGTATGAC TTCCTCTGTC
990

CGTGACTAGT GGGCTCTGAG CTACTCGTAG GTGCGTAAGG CTCCAGTGTT TCTGAAATTG
1050

ATCTTGAATT ACTGTGATAC GACATGATAG TCCCTCTCAC CCAGTGCAAT GACAATAAAG
1110

GCCTTGAAAA GTCAAAAAAA AAAAAAAAAA
1140
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 150:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1764
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 150:

```
G AAG TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA        49
  Lys Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu
   1               5                  10                  15

TAT ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC          97
Tyr Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala
            20                  25                  30

AAC ATC ACC ATT GTG GAG TCA AAC GCC ACA TCC ACA TCT ACA GCT GGG         145
Asn Ile Thr Ile Val Glu Ser Asn Ala Thr Ser Thr Ser Thr Ala Gly
        35                  40                  45

ACA AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG         193
Thr Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val
    50                  55                  60

AAT GGA GGC GAC TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA         241
Asn Gly Gly Asp Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg
65                  70                  75                  80

TAC TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG         289
Tyr Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu
                85                  90                  95

AAT GTG CCC ATG AAA GTC CAA ACC CAA GAA AAA GCG GAG GAG CTC TAC         337
Asn Val Pro Met Lys Val Gln Thr Gln Glu Lys Ala Glu Glu Leu Tyr
            100                 105                 110

CAG AAG AGA GTG CTC ACC ATT ACC GGC ATT TGC ATC GCG CTG CTC GTG         385
Gln Lys Arg Val Leu Thr Ile Thr Gly Ile Cys Ile Ala Leu Leu Val
        115                 120                 125

GTT GGC ATC ATG TGT GTG GTG GTC TAC TGC AAA ACC AAG AAA CAA CGG         433
Val Gly Ile Met Cys Val Val Val Tyr Cys Lys Thr Lys Lys Gln Arg
    130                 135                 140

AAA AAG CTT CAT GAC CGG CTT CGG CAG AGC CTT CGG TCT GAA AGA AAC         481
Lys Lys Leu His Asp Arg Leu Arg Gln Ser Leu Arg Ser Glu Arg Asn
145                 150                 155                 160

ACC ATG ATG AAC GTA GCC AAC GGG CCC CAC CAC CCC AAT CCG CCC CCC         529
Thr Met Met Asn Val Ala Asn Gly Pro His His Pro Asn Pro Pro Pro
                165                 170                 175

GAG AAC GTG CAG CTG GTG AAT CAA TAC GTA TCT AAA AAT GTC ATC TCT         577
Glu Asn Val Gln Leu Val Asn Gln Tyr Val Ser Lys Asn Val Ile Ser
            180                 185                 190

AGC GAG CAT ATT GTT GAG AGA GAG GCG GAG AGC TCT TTT TCC ACC AGT         625
Ser Glu His Ile Val Glu Arg Glu Ala Glu Ser Ser Phe Ser Thr Ser
        195                 200                 205

CAC TAC ACT TCG ACA GCT CAT CAT TCC ACT ACT GTC ACT CAG ACT CCC         673
```

```
His Tyr Thr Ser Thr Ala His His Ser Thr Thr Val Thr Gln Thr Pro
    210                 215                 220

AGT CAC AGC TGG AGC AAT GGA CAC ACT GAA AGC ATC ATT TCG GAA AGC      721
Ser His Ser Trp Ser Asn Gly His Thr Glu Ser Ile Ile Ser Glu Ser
225                 230                 235                 240

CAC TCT GTC ATC GTG ATG TCA TCC GTA GAA AAC AGT AGG CAC AGC AGC      769
His Ser Val Ile Val Met Ser Ser Val Glu Asn Ser Arg His Ser Ser
                245                 250                 255

CCG ACT GGG GGC CCG AGA GGA CGT CTC AAT GGC TTG GGA GGC CCT CGT      817
Pro Thr Gly Gly Pro Arg Gly Arg Leu Asn Gly Leu Gly Gly Pro Arg
            260                 265                 270

GAA TGT AAC AGC TTC CTC AGG CAT GCC AGA GAA ACC CCT GAC TCC TAC      865
Glu Cys Asn Ser Phe Leu Arg His Ala Arg Glu Thr Pro Asp Ser Tyr
        275                 280                 285

CGA GAC TCT CCT CAT AGT GAA AGA CAT AAC CTT ATA GCT GAG CTA AGG      913
Arg Asp Ser Pro His Ser Glu Arg His Asn Leu Ile Ala Glu Leu Arg
    290                 295                 300

AGA AAC AAG GCC CAC AGA TCC AAA TGC ATG CAG ATC CAG CTT TCC GCA      961
Arg Asn Lys Ala His Arg Ser Lys Cys Met Gln Ile Gln Leu Ser Ala
305                 310                 315                 320

ACT CAT CTT AGA GCT TCT TCC ATT CCC CAT TGG GCT TCA TTC TCT AAG     1009
Thr His Leu Arg Ala Ser Ser Ile Pro His Trp Ala Ser Phe Ser Lys
                325                 330                 335

ACC CCT TGG CCT TTA GGA AGG TAT GTA TCA GCA ATG ACC ACC CCG GCT     1057
Thr Pro Trp Pro Leu Gly Arg Tyr Val Ser Ala Met Thr Thr Pro Ala
            340                 345                 350

CGT ATG TCA CCT GTA GAT TTC CAC ACG CCA AGC TCC CCC AAG TCA CCC     1105
Arg Met Ser Pro Val Asp Phe His Thr Pro Ser Ser Pro Lys Ser Pro
        355                 360                 365

CCT TCG GAA ATG TCC CCG CCC GTG TCC AGC ACG ACG GTC TCC ATG CCC     1153
Pro Ser Glu Met Ser Pro Pro Val Ser Ser Thr Thr Val Ser Met Pro
    370                 375                 380

TCC ATG GCG GTC AGT CCC TTC GTG GAA GAG GAG AGA CCC CTG CTC CTT     1201
Ser Met Ala Val Ser Pro Phe Val Glu Glu Glu Arg Pro Leu Leu Leu
385                 390                 395                 400

GTG ACG CCA CCA CGG CTG CGG GAG AAG TAT GAC CAC CAC GCC CAG CAA     1249
Val Thr Pro Pro Arg Leu Arg Glu Lys Tyr Asp His His Ala Gln Gln
                405                 410                 415

TTC AAC TCG TTC CAC TGC AAC CCC GCG CAT GAG AGC AAC AGC CTG CCC     1297
Phe Asn Ser Phe His Cys Asn Pro Ala His Glu Ser Asn Ser Leu Pro
            420                 425                 430

CCC AGC CCC TTG AGG ATA GTG GAG GAT GAG GAA TAT GAA ACG ACC CAG     1345
Pro Ser Pro Leu Arg Ile Val Glu Asp Glu Glu Tyr Glu Thr Thr Gln
        435                 440                 445

GAG TAC GAA CCA GCT CAA GAG CCG GTT AAG AAA CTC ACC AAC AGC AGC     1393
Glu Tyr Glu Pro Ala Gln Glu Pro Val Lys Lys Leu Thr Asn Ser Ser
    450                 455                 460

CGG CGG GCC AAA AGA ACC AAG CCC AAT GGT CAC ATT GCC CAC AGG TTG     1441
Arg Arg Ala Lys Arg Thr Lys Pro Asn Gly His Ile Ala His Arg Leu
465                 470                 475                 480
```

```
GAA ATG GAC AAC AAC ACA GGC GCT GAC AGC AGT AAC TCA GAG AGC GAA        1489
Glu Met Asp Asn Asn Thr Gly Ala Asp Ser Ser Asn Ser Glu Ser Glu
                485                 490                 495

ACA GAG GAT GAA AGA GTA GGA GAA GAT ACG CCT TTC CTG GCC ATA CAG        1537
Thr Glu Asp Glu Arg Val Gly Glu Asp Thr Pro Phe Leu Ala Ile Gln
            500                 505                 510

AAC CCC CTG GCA GCC AGT CTC GAG GCG GCC CCT GCC TTC CGC CTG GTC        1585
Asn Pro Leu Ala Ala Ser Leu Glu Ala Ala Pro Ala Phe Arg Leu Val
        515                 520                 525

GAC AGC AGG ACT AAC CCA ACA GGC GGC TTC TCT CCG CAG GAA GAA TTG        1633
Asp Ser Arg Thr Asn Pro Thr Gly Gly Phe Ser Pro Gln Glu Glu Leu
    530                 535                 540

CAG GCC AGG CTC TCC GGT GTA ATC GCT AAC CAA GAC CCT ATC GCT GTC        1681
Gln Ala Arg Leu Ser Gly Val Ile Ala Asn Gln Asp Pro Ile Ala Val
545                 550                 555                 560

TAAAACCGAA ATACACCCAT AGATTCACCT GTAAAACTTT ATTTTATATA ATAAAGTATT      1741

CCACCTTAAA TTAAACAAAA AAA                                              1764
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 151:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 50
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 151:

```
Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Cys
 1               5                  10                  15

Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr Leu Cys Lys Cys
            20                  25                  30

Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser
        35                  40                  45

Phe Tyr
    50
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 152:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 50
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 152:

```
Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Cys
 1               5                  10                  15
```

Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr Leu Cys Lys Cys
            20   25   30

Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn Val Pro Met Lys
        35   40   45

Val Gln
    50

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 153:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 46
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 153:

Glu Cys Leu Arg Lys Tyr Lys Asp Phe Cys Ile His Gly Glu Cys Lys
  1   5   10   15

Tyr Val Lys Glu Leu Arg Ala Pro Ser Cys Lys Cys Gln Gln Glu Tyr
            20   25   30

Phe Gly Glu Arg Cys Gly Glu Lys Ser Asn Lys Thr His Ser
        35   40   45

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 154:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 198
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 154:

AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT
48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
1   5   10   15

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC
96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
            20   25   30

TTG TGC AAG TGC CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC
144
Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr
        35   40   45

GTA ATG GCC AGC TTC TAC AGT ACG TCC ACT CCC TTT CTG TCT CTG CCT
192
Val Met Ala Ser Phe Tyr Ser Thr Ser Thr Pro Phe Leu Ser Leu Pro
    50   55   60

GAA TAG
198
Glu
65

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 155:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 192
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 155:

```
AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT
48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
1               5                   10                  15

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC
96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
            20                  25                  30

TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT
144
Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn
        35                  40                  45

GTG CCC ATG AAA GTC CAA ACC CAA GAA AAA GCG GAG GAG CTC TAC TAA
192
Val Pro Met Lys Val Gln Thr Gln Glu Lys Ala Glu Glu Leu Tyr
    50                  55                  60
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 156:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 183
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 156:

```
AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT
48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
1               5                   10                  15

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC
96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
            20                  25                  30

TTG TGC AAG TGC CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC
144
Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr
        35                  40                  45
```

GTA ATG GCC AGC TTC TAC AAA GCG GAG GAG CTC TAC TAA
183
Val Met Ala Ser Phe Tyr Lys Ala Glu Glu Leu Tyr
50 55 60

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 157:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 210
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 157:

AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT
48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
1 5 10 15

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC
96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
20 25 30

TTG TGC AAG TGC CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC
144
Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr
35 40 45

GTA ATG GCC AGC TTC TAC AAG CAT CTT GGG ATT GAA TTT ATG GAG AAA
192
Val Met Ala Ser Phe Tyr Lys His Leu Gly Ile Glu Phe Met Glu Lys
50 55 60

GCG GAG GAG CTC TAC TAA
210
Ala Glu Glu Leu Tyr
65

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 158:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 267
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 158:

AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT
48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
1 5 10 15

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC
96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
20 25 30

TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT
144
Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn
35 40 45

GTG CCC ATG AAA GTC CAA ACC CAA GAA AAG TGC CCA AAT GAG TTT ACT
192
Val Pro Met Lys Val Gln Thr Gln Glu Lys Cys Pro Asn Glu Phe Thr
50 55 60

GGT GAT CGC TGC CAA AAC TAC GTA ATG GCC AGC TTC TAC AGT ACG TCC
240
Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser Phe Tyr Ser Thr Ser
65 70 75 80

ACT CCC TTT CTG TCT CTG CCT GAA TAG
267
Thr Pro Phe Leu Ser Leu Pro Glu
85

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 159:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 252
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 159:

AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT
48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
1 5 10 15

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC
96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
20 25 30

TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT
144
Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn
35 40 45

GTG CCC ATG AAA GTC CAA ACC CAA GAA AAG TGC CCA AAT GAG TTT ACT
192
Val Pro Met Lys Val Gln Thr Gln Glu Lys Cys Pro Asn Glu Phe Thr
50 55 60

GGT GAT CGC TGC CAA AAC TAC GTA ATG GCC AGC TTC TAC AAA GCG GAG
240
Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser Phe Tyr Lys Ala Glu
65 70 75 80

GAG CTC TAC TAA
252
Glu Leu Tyr

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 160:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 128
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 160:

```
CC ACA TCC ACA TCT ACA GCT GGG ACA AGC CAT CTT GTC AAG TGT GCA          47
   Thr Ser Thr Ser Thr Ala Gly Thr Ser His Leu Val Lys Cys Ala
     1               5                  10                  15

GAG AAG GAG AAA ACT TTC TGT GTG AAT GGA GGC GAG TGC TTC ATG GTG         95
Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Cys Phe Met Val
                20                  25                  30

AAA GAC CTT TCA AAT CCC TCA AGA TAC TTG T GC                           128
Lys Asp Leu Ser Asn Pro Ser Arg Tyr Leu
            35                  40
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 161:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 141
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 161:

```
A CAT AAC CTT ATA GCT GAG CTA AGG AGA AAC AAG GCC CAC AGA TCC           46
  His Asn Leu Ile Ala Glu Leu Arg Arg Asn Lys Ala His Arg Ser
    1               5                  10                  15

AAA TGC ATG CAG ATC CAG CTT TCC GCA ACT CAT CTT AGA GCT TCT TCC         94
Lys Cys Met Gln Ile Gln Leu Ser Ala Thr His Leu Arg Ala Ser Ser
                20                  25                  30

ATT CCC CAT TGG GCT TCA TTC TCT AAG ACC CCT TGG CCT TTA GGA AG         141
Ile Pro His Trp Ala Ser Phe Ser Lys Thr Pro Trp Pro Leu Gly Arg
            35                  40                  45
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 162:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in positions 15 and 22 is unknown.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 162:

```
Ala Ala Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Xaa Phe
 1              5                   10                  15

Met Val Lys Asp Leu Xaa Asn Pro
            20
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 163:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 745
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 163:

```
ATG AGA TGG CGA CGC GCC CCG CGC CGC TCC GGG CGT CCC GGC CCC CGG
48
Met Arg Trp Arg Arg Ala Pro Arg Arg Ser Gly Arg Pro Gly Pro Arg
1               5                   10                  15

GCC CAG CGC CCC GGC TCC GCC GCC CGC TCG TCG CCG CCG CTG CCG CTG
96
Ala Gln Arg Pro Gly Ser Ala Ala Arg Ser Ser Pro Pro Leu Pro Leu
            20                  25                  30

CTG CCA CTA CTG CTG CTG CTG GGG ACC GCG GCC CTG GCG CCG GGG GCG
144
Leu Pro Leu Leu Leu Leu Leu Gly Thr Ala Ala Leu Ala Pro Gly Ala
        35                  40                  45

GCG GCC GGC AAC GAG GCG GCT CCC GCG GGG GCC TCG GTG TGC TAC TCG
192
Ala Ala Gly Asn Glu Ala Ala Pro Ala Gly Ala Ser Val Cys Tyr Ser
    50                  55                  60

TCC CCG CCC AGC GTG GGA TCG GTG CAG GAG CTA GCT CAG CGC GCC GCG
240
Ser Pro Pro Ser Val Gly Ser Val Gln Glu Leu Ala Gln Arg Ala Ala
65                  70                  75                  80

GTG GTG ATC GAG GGA AAG GTG CAC CCG CAG CGG CGG CAG CAG GGG GCA
288
Val Val Ile Glu Gly Lys Val His Pro Gln Arg Arg Gln Gln Gly Ala
                85                  90                  95

CTC GAC AGG AAG GCG GCG GCG GCG GCG GGC GAG GCA GGG GCG TGG GGC
336
Leu Asp Arg Lys Ala Ala Ala Ala Ala Gly Glu Ala Gly Ala Trp Gly
            100                 105                 110

GGC GAT CGC GAG CCG CCA GCC GCG GGC CCA CGG GCG CTG GGG CCG CCC
384
Gly Asp Arg Glu Pro Pro Ala Ala Gly Pro Arg Ala Leu Gly Pro Pro
        115                 120                 125

GCC GAG GAG CCG CTG CTC GCC GCC AAC GGG ACC GTG CCC TCT TGG CCC
432
Ala Glu Glu Pro Leu Leu Ala Ala Asn Gly Thr Val Pro Ser Trp Pro
    130                 135                 140
```

```
ACC GCC CCG GTG CCC AGC GCC GGC GAG CCC GGG GAG GAG GCG CCC TAT
480
Thr Ala Pro Val Pro Ser Ala Gly Glu Pro Gly Glu Glu Ala Pro Tyr
145                 150                 155                 160

CTG GTG AAG GTG CAC CAG GTG TGG GCG GTG AAA GCC GGG GGC TTG AAG
528
Leu Val Lys Val His Gln Val Trp Ala Val Lys Ala Gly Gly Leu Lys
                165                 170                 175

AAG GAC TCG CTG CTC ACC GTG CGC CTG GGG ACC TGG GGC CAC CCC GCC
576
Lys Asp Ser Leu Leu Thr Val Arg Leu Gly Thr Trp Gly His Pro Ala
            180                 185                 190

TTC CCC TCC TGC GGG AGG CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC
624
Phe Pro Ser Cys Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe
        195                 200                 205

ATG GAG CCC GAC GCC AAC AGC ACC AGC CGC GCG CCG GCC GCC TTC CGA
672
Met Glu Pro Asp Ala Asn Ser Thr Ser Arg Ala Pro Ala Ala Phe Arg
    210                 215                 220

GCC TCT TTC CCC CCT CTG GAG ACG GGC CGG AAC CTC AAG AAG GAG GTC
720
Ala Ser Phe Pro Pro Leu Glu Thr Gly Arg Asn Leu Lys Lys Glu Val
225                 230                 235                 240

AGC CGG GTG CTG TGC AAG CGG TGC G
745
Ser Arg Val Leu Cys Lys Arg Cys
                245
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 164:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is unknown.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 164:

```
Xaa Ala Leu Ala Ala Ala Gly Tyr Asp Val Glu Lys
  1               5                  10
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 165:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in position 1 is unknown.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 165:

Xaa Leu Val Leu Arg
1 5

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 166:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: Xaa in positions 1, 2, and 3 is unknown.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 166:

Xaa Xaa Xaa Tyr Pro Gly Gln Ile Thr Ser Asn
1 5 10

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 167:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 60
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N in positions 25 and 36 is unknown.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 167:

ATAGGGAAGG GCGGGGGAAG GGTCNCCCTC NGCAGGGCCG GGCTTGCCTC TGGAGCCTCT
60

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 168:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: N in position 16 is unknown.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 168:

TTTACACATA TATTCNCC
18

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 169:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 169:

```
Glu Thr Gln Pro Asp Pro Gly Gln Ile Leu Lys Lys Val Pro Met Val
  1               5                  10                  15

Ile Gly Ala Tyr Thr
             20
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 170:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 422
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 170:

```
Met Arg Trp Arg Arg Ala Pro Arg Arg Ser Gly Arg Pro Gly Pro Arg
  1               5                  10                  15

Ala Gln Arg Pro Gly Ser Ala Ala Arg Ser Ser Pro Pro Leu Pro Leu
             20                  25                  30

Leu Pro Leu Leu Leu Leu Leu Gly Thr Ala Ala Leu Ala Pro Gly Ala
         35                  40                  45

Ala Ala Gly Asn Glu Ala Ala Pro Ala Gly Ala Ser Val Cys Tyr Ser
     50                  55                  60

Ser Pro Pro Ser Val Gly Ser Val Gln Glu Leu Ala Gln Arg Ala Ala
 65                  70                  75                  80

Val Val Ile Glu Gly Lys Val His Pro Gln Arg Arg Gln Gln Gly Ala
                 85                  90                  95

Leu Asp Arg Lys Ala Ala Ala Ala Ala Gly Glu Ala Gly Ala Trp Gly
            100                 105                 110

Gly Asp Arg Glu Pro Pro Ala Ala Gly Pro Arg Ala Leu Gly Pro Pro
        115                 120                 125

Ala Glu Glu Pro Leu Leu Ala Ala Asn Gly Thr Val Pro Ser Trp Pro
```

```
    130                 135                 140

Thr Ala Pro Val Pro Ser Ala Gly Glu Pro Gly Glu Glu Ala Pro Tyr
145                 150                 155                 160

Leu Val Lys Val His Gln Val Trp Ala Val Lys Ala Gly Gly Leu Lys
                165                 170                 175

Lys Asp Ser Leu Leu Thr Val Arg Leu Gly Thr Trp Gly His Pro Ala
            180                 185                 190

Phe Pro Ser Cys Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe
        195                 200                 205

Met Glu Pro Asp Ala Asn Ser Thr Ser Arg Ala Pro Ala Ala Phe Arg
    210                 215                 220

Ala Ser Phe Pro Pro Leu Glu Thr Gly Arg Asn Leu Lys Lys Glu Val
225                 230                 235                 240

Ser Arg Val Leu Cys Lys Arg Cys Ala Leu Pro Pro Gln Leu Lys Glu
                245                 250                 255

Met Lys Ser Gln Glu Ser Ala Ala Gly Ser Lys Leu Val Leu Arg Cys
            260                 265                 270

Glu Thr Ser Ser Glu Tyr Ser Ser Leu Arg Phe Lys Trp Phe Lys Asn
        275                 280                 285

Gly Asn Glu Leu Asn Arg Lys Asn Lys Pro Gln Asn Ile Lys Ile Gln
    290                 295                 300

Lys Lys Pro Gly Lys Ser Glu Leu Arg Ile Asn Lys Ala Ser Leu Ala
305                 310                 315                 320

Asp Ser Gly Glu Tyr Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp
                325                 330                 335

Ser Ala Ser Ala Asn Ile Thr Ile Val Glu Ser Asn Ala Thr Ser Thr
            340                 345                 350

Ser Thr Thr Gly Thr Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys
        355                 360                 365

Thr Phe Cys Val Asn Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser
    370                 375                 380

Asn Pro Ser Arg Tyr Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp
385                 390                 395                 400

Arg Cys Gln Asn Tyr Val Met Ala Ser Phe Tyr Ser Thr Ser Thr Pro
                405                 410                 415

Phe Leu Ser Leu Pro Glu
            420
```

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 171:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 69
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 171:

Met Ser Glu Arg Lys Glu Gly Arg Gly Lys Gly Lys Gly Lys Lys Lys
1 5 10 15

Glu Arg Gly Ser Gly Lys Lys Pro Glu Ser Ala Ala Gly Ser Gln Ser
20 25 30

Pro Arg Glu Ile Ile Thr Gly Met Pro Ala Ser Thr Glu Gly Ala Tyr
35 40 45

Val Ser Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr Glu Gly Ala
50 55 60

Asn Thr Ser Ser Ser
65

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 172:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 172:

Arg Lys Gly Asp Val Pro Gly Pro Arg Val Lys Ser Ser Arg Ser Thr
1 5 10 15

Thr Thr Ala

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 173:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 231
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 173:

CGCGAGCGCC TCAGCGCGGC CGCTCGCTCT CCCCCTCGAG GGACAAACTT TTCCCAAACC
60

CGATCCGAGC CCTTGGACCA AACTCGCCTG CGCCGAGAGC CGTCCGCGTA GAGCGCTCCG
120

TCTCCGGCGA GATGTCCGAG CGCAAAGAAG GCAGAGGCAA AGGGAAGGGC AAGAAGAAGG
180

AGCGAGGCTC CGGCAAGAAG CCGGAGTCCG CGGCGGGCAG CCAGAGCCCA G
231

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 174:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 178
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 174:

CCTTGCCTCC CCGATTGAAA GAGATGAAAA GCCAGGAATC GGCTGCAGGT TCCAAACTAG
60

TCCTTCGGTG TGAAACCAGT TCTGAATACT CCTCTCTCAG ATTCAAGTGG TTCAAGAATG
120

GGAATGAATT GAATCGAAAA AACAAACCAC AAAATATCAA GATACAAAAA AAGCCAGG
178

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 175:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 122
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 175:

GAAGTCAGAA CTTCGCATTA ACAAAGCATC ACTGGCTGAT TCTGGAGAGT ATATGTGCAA
60

AGTGATCAGC AAATTAGGAA ATGACAGTGC CTCTGCCAAT ATCACCATCG TGGAATCAAA
120

CG
122

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 176:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 102
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 176:

AGATCATCAC TGGTATGCCA GCCTCAACTG AAGGAGCATA TGTGTCTTCA GAGTCTCCCA
60

TTAGAATATC AGTATCCACA GAAGGAGCAA ATACTTCTTC AT
102

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 177:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 128
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 177:

CTACATCTAC ATCCACCACT GGGACAAGCC ATCTTGTAAA ATGTGCGGAG AAGGAGAAAA
60

CTTTCTGTGT GAATGGAGGG GAGTGCTTCA TGGTGAAAGA CCTTTCAAAC CCCTCGAGAT
120

ACTTGTGC
128

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 178:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 69
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 178:

AAGTGCCAAC CTGGATTCAC TGGAGCAAGA TGTACTGAGA ATGTGCCCAT GAAAGTCCAA
60

AACCAAGAA
69

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 179:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 60
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 179:

AAGTGCCCAA ATGAGTTTAC TGGTGATCGC TGCCAAAACT ACGTAATGGC CAGCTTCTAC
60

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 180:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 36
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 180:

AGTACGTCCA CTCCCTTTCT GTCTCTGCCT GAATAG
36

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 181:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 569
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 181:

AAGGCGGAGG AGCTGTACCA GAAGAGAGTG CTGACCATAA CCGGCATCTG CATCGCCCTC
60

CTTGTGGTCG GCATCATGTG TGTGGTGGCC TACTGCAAAA CCAAGAAACA GCGGAAAAAG
120

CTGCATGACC GTCTTCGGCA GAGCCTTCGG TCTGAACGAA ACAATATGAT GAACATTGCC
180

AATGGGCCTC ACCATCCTAA CCCACCCCCC GAGAATGTCC AGCTGGTGAA TCAATACGTA
240

TCTAAAAACG TCATCTCCAG TGAGCATATT GTTGAGAGAG AAGCAGAGAC ATCCTTTTCC
300

ACCAGTCACT ATACTTCCAC AGCCCATCAC TCCACTACTG TCACCCAGAC TCCTAGCCAC
360

AGCTGGAGCA ACGGACACAC TGAAAGCATC CTTTCCGAAA GCCACTCTGT AATCGTGATG
420

TCATCCGTAG AAAACAGTAG GCACAGCAGC CCAACTGGGG GCCCAAGAGG ACGTCTTAAT
480

GGCACAGGAG GCCCTCGTGA ATGTAACAGC TTCCTCAGGC ATGCCAGAGA AACCCCTGAT
540

TCCTACCGAG ACTCTCCTCA TAGTGAAAG
569

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 182:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 730
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 182:

GTATGTGTCA GCCATGACCA CCCCGGCTCG TATGTCACCT GTAGATTTCC ACACGCCAAG
60

CTCCCCCAAA TCGCCCCCTT CGGAAATGTC TCCACCCGTG TCCAGCATGA CGGTGTCCAT
120

GCCTTCCATG GCGGTCAGCC CCTTCATGGA AGAAGAGAGA CCTCTACTTC TCGTGACACC
180

ACCAAGGCTG CGGGAGAAGA AGTTTGACCA TCACCCTCAG CAGTTCAGCT CCTTCCACCA
240

CAACCCCGCG CATGACAGTA ACAGCCTCCC TGCTAGCCCC TTGAGGATAG TGGAGGATGA
300

GGAGTATGAA ACGACCCAAG AGTACGAGCC AGCCCAAGAG CCTGTTAAGA AACTCGCCAA
360

TAGCCGGCGG GCCAAAAGAA CCAAGCCCAA TGGCCACATT GCTAACAGAT TGGAAGTGGA
420

CAGCAACACA AGCTCCCAGA GCAGTAACTC AGAGAGTGAA ACAGAAGATG AAAGAGTAGG
480

TGAAGATACG CCTTTCCTGG GCATACAGAA CCCCCTGGCA GCCAGTCTTG AGGCAACACC
540

TGCCTTCCGC CTGGCTGACA GCAGGACTAA CCCAGCAGGC CGCTTCTCGA CACAGGAAGA
600

AATCCAGGCC AGGCTGTCTA GTGTAATTGC TAACCAAGAC CCTATTGCTG TATAAAACCT
660

AAATAAACAC ATAGATTCAC CTGTAAAACT TTATTTATA TAATAAAGTA TTCCACCTTA
720

AATTAAACAA
730

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 183:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 183:

AAAGCCGGGG GCTTGAAGAA
20

(2) INFORMATION FOR SEQUENCE IDENTIFICATION NUMBER: 184:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 184:

ATGARGTGTG GGCGGCGAAA
20

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A DNA sequence encoding a polypeptide synthesized by the plasmid pGGF2HBS11 deposited with the A.T.C.C. November 6, 1992 (A.T.C.C. Deposit No. 75347).

2. A polypeptide encoded by pGGF2HBS11 deposited with the A.T.C.C. November 6, 1992 (A.T.C.C. Deposit No. 75347).

3. A polypeptide comprising the peptide encoded by the E sequence (SEQ ID Nos. 137 and 163) and at least a portion of the peptide encoded by the brain-derived DNA sequences flanking the E encoding sequence on clone pGGF2HBS11, ATCC Deposit No. 75347.

4. The polypeptide of claim 3, wherein said peptide encoded by the E sequence (SEQ ID Nos. 137 and 163) has a deletion of the 48 N-terminal amino acids and wherein said E-flanking peptide sequences contain between 20 and 100 N-terminal amino acids and amino acids and between 30 and 50 C-terminal amino acids encoded by said clone.

5. The polypeptide of claim 3, wherein said peptide encoded by the E sequence (SEQ ID Nos. 137 and 163) has a deletion of the 48 N-terminal amino acids and wherein said E-flanking peptide sequences contain between 25 and 70 N-terminal amino acids and between 30 and 45 C-terminal amino acids encoded by said clone.

6. A method for inhibiting proliferation of a cell, said method comprising contacting said cell with a polypeptide comprising FBA polypeptide segments, FBA' polypeptide segments, EBA polypeptide segments, EBA' polypeptide segments, FEBA polypeptide segments, or FEBA' polypeptide segments having the amino acid sequences corresponding to polypeptide segments shown in Figure 31 (SEQ ID Nos. 136-140, 163) or SEQ ID No. 168, said polypeptide lacking an EGF-like domain.

7. A method of inhibiting proliferation of a cell, said method comprising contacting said cell with a polypeptide of claims 1-5.

8. A method of inhibiting proliferation of a cell, said method comprising contacting said cell with a polypeptide selected from GGF2BPP1, GGF2BPP2, GGF2BPP5 and GGF2HBS11.

9. The method of any one of claims 6-8, wherein said cell is a cell of the nervous system.

10. The method of claim 9, wherein said cell is a glial cell.

11. The method of claim 10, wherein said cell is a Schwann cell.

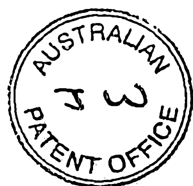
12. A method of any one of claims 6-8, wherein said cell is a cancer cell.

13. A method of claim 12, wherein said cell is an adenocarcinoma cell.

14. The method of any one of claims 6-8, wherein said method is used in the treatment or prophylaxis of a nervous disease or disorder.

15. The method of any one of claims 6-8, wherein said cell is a cell in a mammal and said contacting is carried out by administering said peptide to said mammal for the prophylaxis or treatment of a pathophysiological condition in said mammal in which said condition involves said cell.

16. The method of any one of claims 6-8, wherein said method is used for the treatment or prophylaxis of a demyelination disease or disorder.



17. A method as claimed in claim 15, wherein said condition involves a disease of cell proliferation, such as a tumor or peripheral nerve damage caused by a cell tumor.

18. The method of any one of claims 6-8, wherein said cell is in a mammal and said contacting is carried out by administering said peptide to said mammal for the prophylaxis or treatment of a condition which involves a tumor of said cell, for example, neurofibromatosis, malignant Schwannomas or neurofibrosarcomas.

19. The method of any one of claims 6-8, wherein said cell is in a mammal and said contacting is carried out by administering said peptide to said mammal for prophylaxis or treatment of a condition which involves a meningioma, a bilateral acoustic neuroma, a astrocytoma, a retinoblastoma, a neuroglioma, a neuroblastoma, or a glioma.

20. A method for producing an antibody specific for a polypeptide, said method comprising

i) immunizing a mammal with a polypeptide selected from the group consisting of a polypeptide defined by the formula

VYBAZWX

wherein VYBAZWX is composed of the polypeptide segments shown in Figure 31 (SEQ ID Nos. 136-139, 141, 146, 147, 160, 161, and 163); wherein V comprises F, or is absent; wherein Y comprises polypeptide segment E, or is absent; wherein Z comprises polypeptide segment G or is absent; wherein W comprises C or is absent; and wherein X comprises polypeptide segments H, HK, or HKL, and

ii) purifying said antibody from tissue of said animal, or from a hybridoma made using said tissue.

21. A method for detecting, in a sample, the presence of a molecule capable of binding to a receptor which binds to a polypeptide selected from the group consisting of polypeptides defined by the formula

VYBAZWX

wherein VYBAZWX is composed of the polypeptide segments shown in Figure 31 (SEQ ID Nos. 136-139, 141, 146, 147, 160, 161, and 163); wherein V comprises F, or is absent; wherein Y comprises polypeptide segment E, or is absent; wherein Z comprises polypeptide segment G or is absent; wherein W comprises C or is absent; and wherein X comprises polypeptide segments H, HK, or HKL,

said method comprising the steps of

i) contacting said sample with said polypeptide together with said receptor, and

ii) detecting competitive inhibition of the binding of said polypeptide to said receptor as an indication of the presence of a receptor binding molecule in said sample.

22. A DNA sequence according to claim 1, or a polypeptide according to any one of claims 2 to 5, or a method according to any one of claims 6 to 21, substantially as hereinbefore defined with reference to the Figures and/or Examples.

DATED this 27th day of April, 1998

Cambridge Neuroscience, Inc.
by their Patent Attorneys
DAVIES COLLISON CAVE

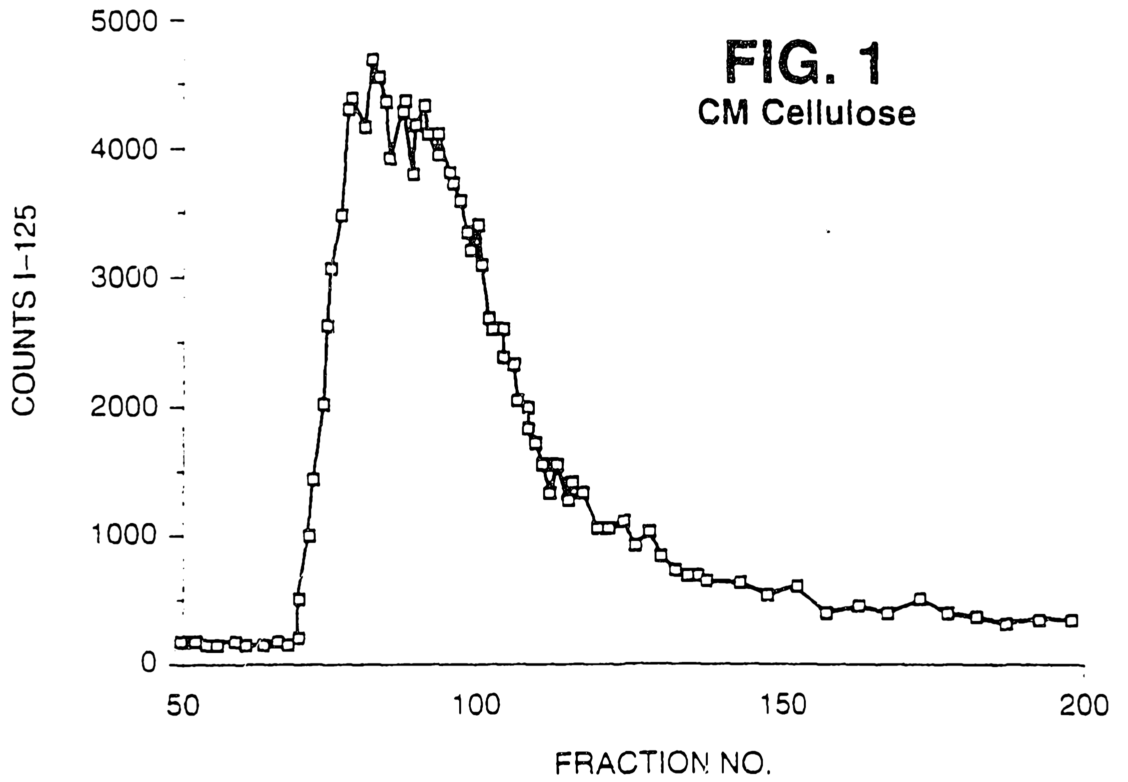
INHIBITORS OF CELL PROLIFERATION, THEIR PREPARATION AND USE

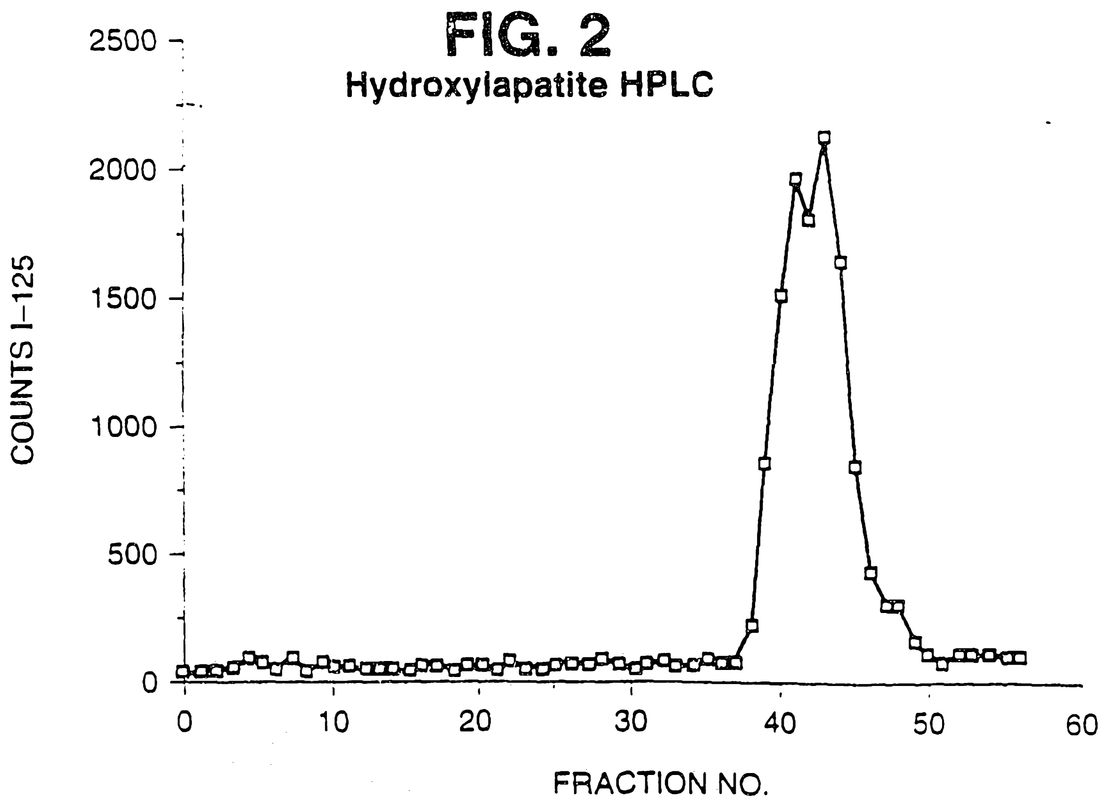
Abstract of the Disclosure

Disclosed is the characterization and purification of DNA encoding numerous polypeptides factors useful for the inhibition of cell (particularly, Schwann cell) proliferation. These factors are useful for the treatment of neural tumors. Also disclosed are the DNA sequences encoding novel polypeptides which may have use as agents which inhibit cell proliferation. Methods for the synthesis, purification, and testing of both known and novel polypeptides for their use as therapeutic and diagnostic aids in the treatment of diseases are also provided. Methods are also provided for the use of these polypeptides for the preparation of antibody probes. Such probes have diagnostic and therapeutic use in diseases involving neural and glial cells.

61852.B11

50026/93





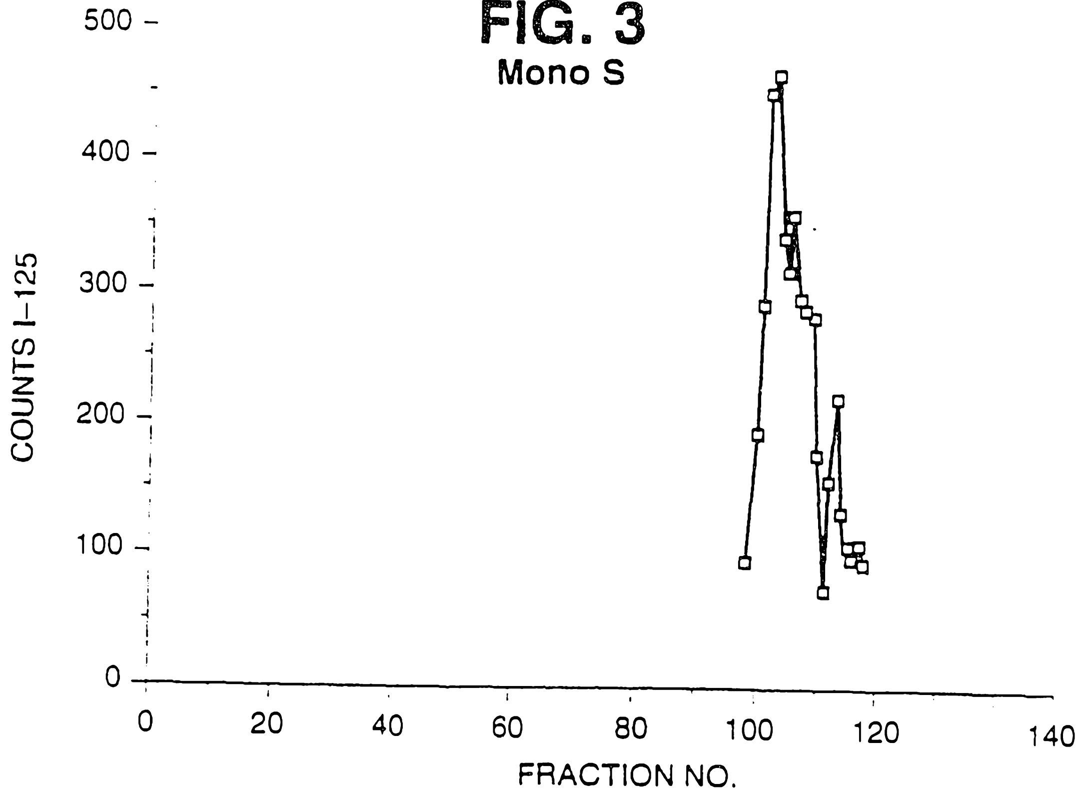


FIG. 3
Mono S
COUNTS I-125
500
400
300
200
100
0
0
20
40
60
80
100
120
140
FRACTION NO.

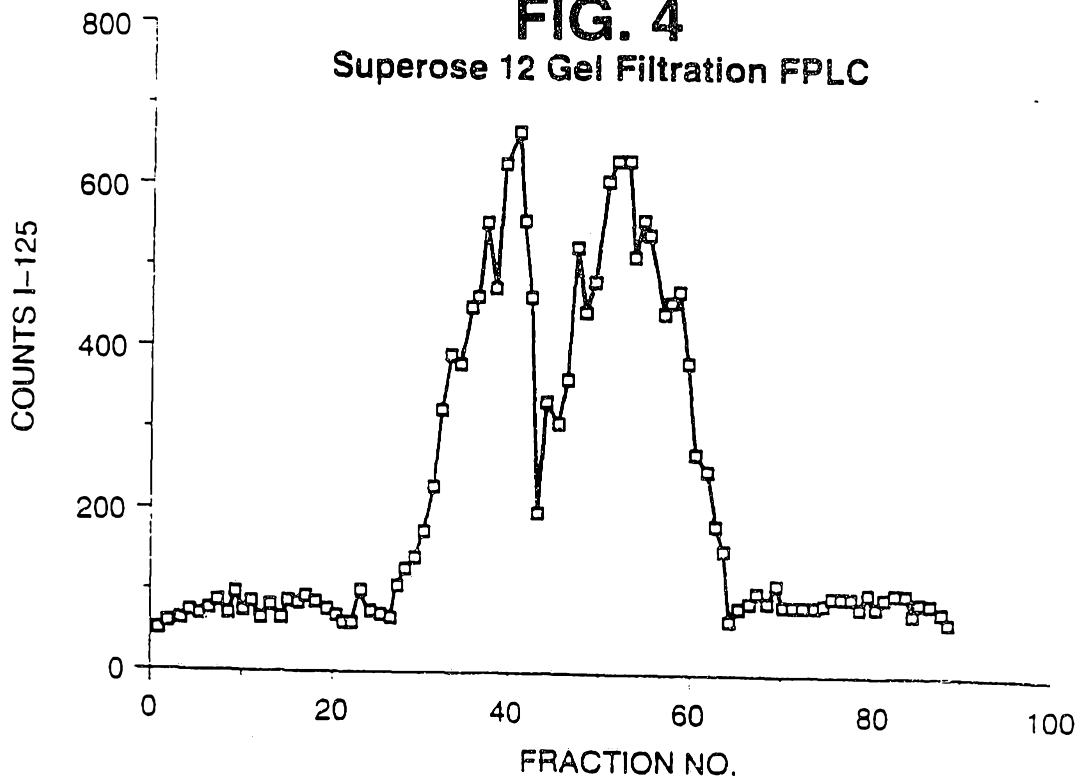


FIG. 4
Superose 12 Gel Filtration FPLC
COUNTS I-125
800
600
400
200
0
0
20
40
60
80
100
FRACTION NO.

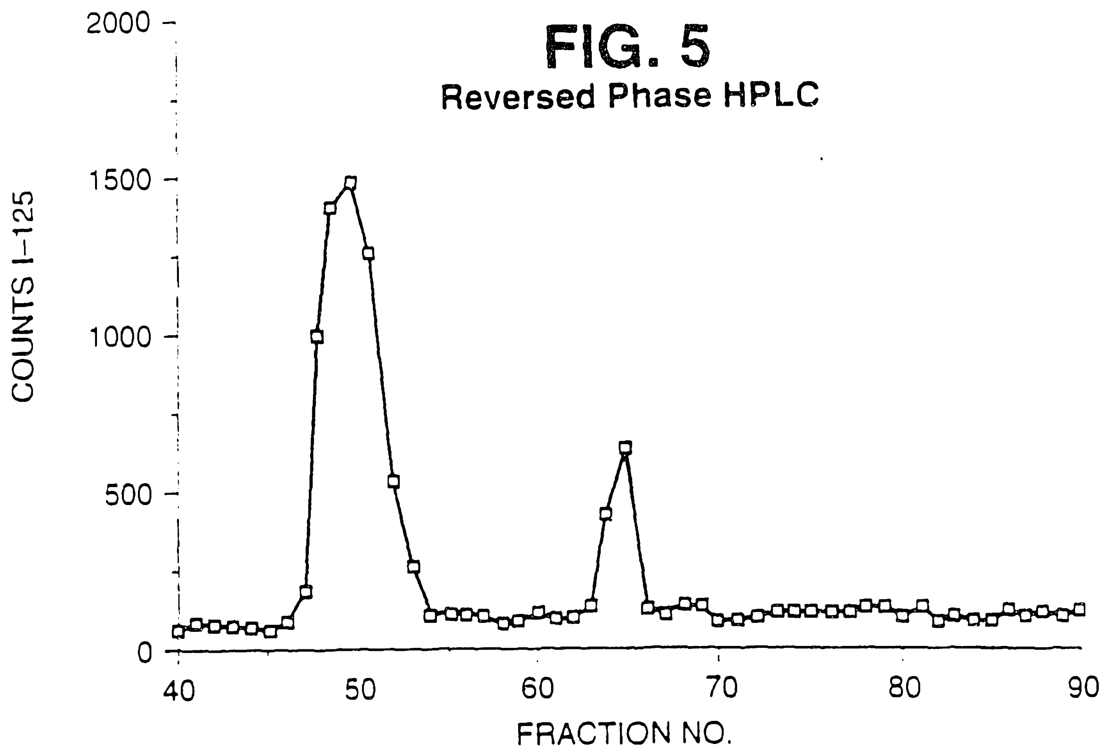


FIG. 5
Reversed Phase HPLC
COUNTS I–125
2000
1500
1000
500
0
40
50
60
70
80
90
FRACTION NO.

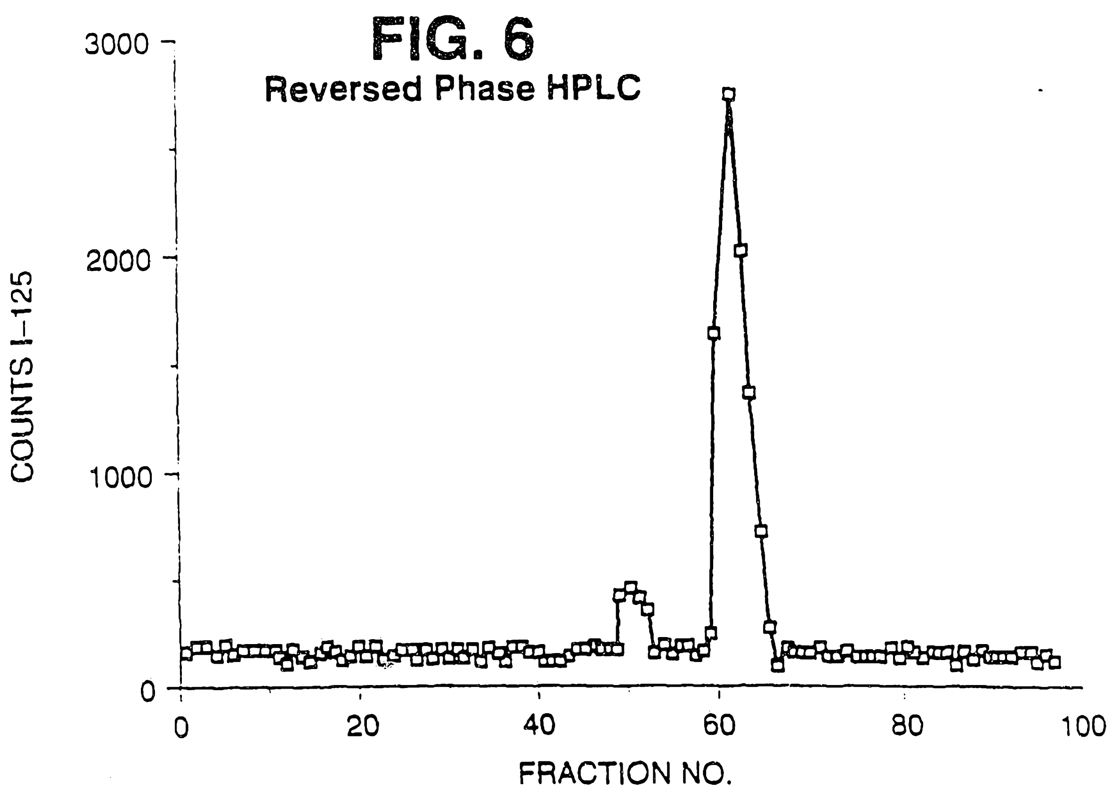


FIG. 6
Reversed Phase HPLC
COUNTS I–125
3000
2000
1000
0
0
20
40
60
80
100
FRACTION NO.

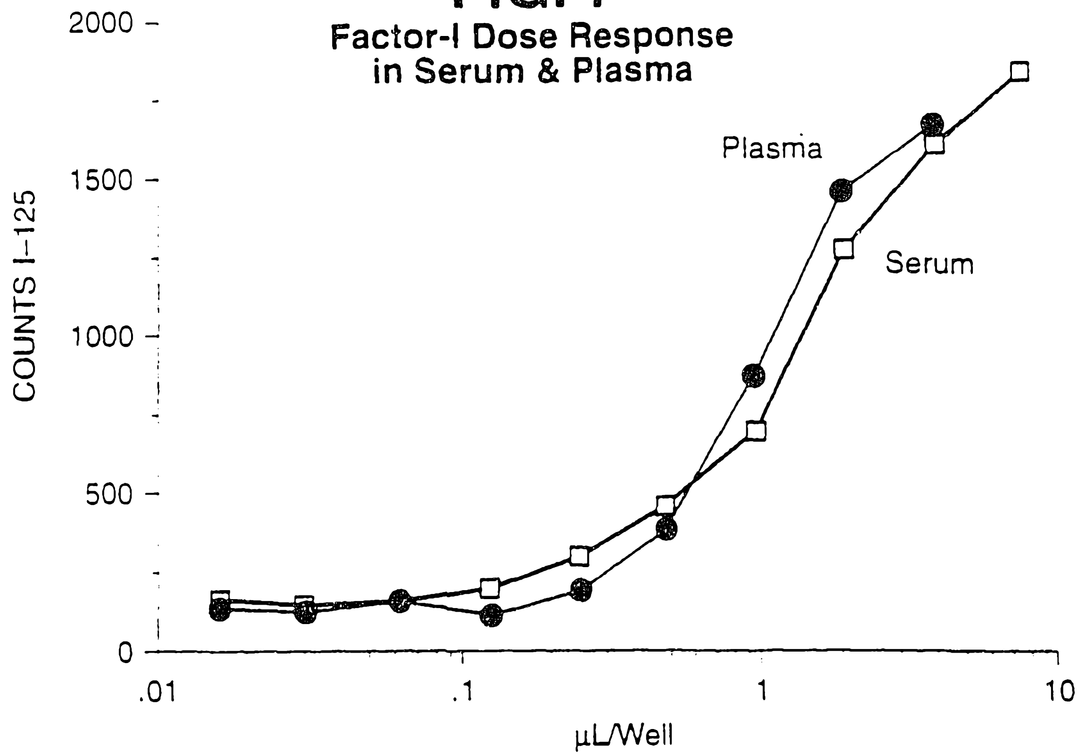


FIG. 7
Factor-I Dose Response
in Serum & Plasma
2000
1500
1000
500
0
COUNTS I-125
Plasma
Serum
.01
.1
1
10
µL/Well

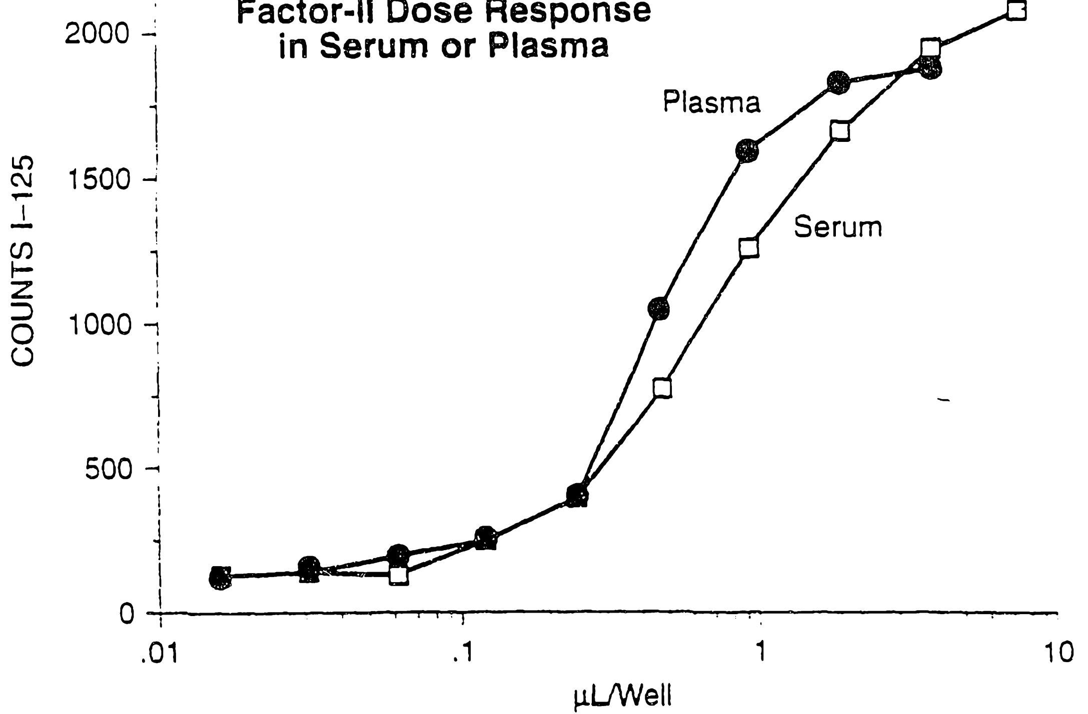


FIG. 8
Factor-II Dose Response
in Serum or Plasma
2000
1500
1000
500
0
COUNTS I-125
Plasma
Serum
.01
.1
1
10
µL/Well

FIG. 9

	N-terminus		
GGF-I 01	F K G D A H T E	(SEQ ID NO: 1)	
	Trypsin peptides		
GGF-I 02	K/R A S L A D E Y E Y M X K *	(SEQ ID NO: 2)	
GGF-I 03	K/R T E T S S S G L X L K *	(SEQ ID NO: 3)	
GGF-I 04	K/R K L G E M W A E	(SEQ ID NO: 4)	HMG 1
GGF-I 05	K/R L G E K R A	(SEQ ID NO: 5)	HMG 12
GGF-I 06	K/R I K S E H A G L S I G D T A K *	(SEQ ID NO: 6)	HMG 2
GGF-I 07	K/R A S L A D E Y E Y M R K *	(SEQ ID NO: 7)	
GGF-I 08	K/R I K G E H P G L S I G D V A K *	(SEQ ID NO: 8)	HMG 1
GGF-I 09	K/R M S E Y A F F V Q T X R *	(SEQ ID NO: 9)	HMG 2
GGF-I 10	K/R S E H P G L S I G D T A K *	(SEQ ID NO: 10)	HMG 1
GGF-I 11	K/R A G Y F A E X A R *	(SEQ ID NO: 11)	
GGF-I 12	K/R K L E F L X A K *	(SEQ ID NO: 12)	
GGF-I 13	K/R T T E M A S E Q G A	(SEQ ID NO: 13)	
GGF-I 14	K/R A K E A L A A L K *	(SEQ ID NO: 14)	
GGF-I 15	K/R F V L Q A K K *	(SEQ ID NO: 15)	
GGF-I 16	K/R L G E M W	(SEQ ID NO: 16)	HMG 1
	Protease V8 peptides		
GGF-I 17	E T Q P D P G Q I L K K V P M V I G A Y T	(SEQ ID NO: 169)	
GGF-I 18	E Y K C L K F K W F K K A T V M	(SEQ ID NO: 17)	
GGF-I 19	E A K Y F S K X D A	(SEQ ID NO: 18)	LH alpha
GGF-I 20	E X K F Y V P	(SEQ ID NO: 19)	
GGF-I 21	E L S F A S V R L P G C P P G V D P M V S F P V A L	(SEQ ID NO: 20)	LH beta

FIG. 10

A

GGF-I 01	F K G D A H T E	(SEQ ID NO: 1)
GGF-I 02	A S L A D E Y E Y M X K	(SEQ ID NO: 22)
GGF-I 03	T E T S S S G L X L K	(SEQ ID NO: 23)
GGF-I 07	A S L A D E Y E Y M R K	(SEQ ID NO: 24)
GGF-I 11	A G Y F A E X A R	(SEQ ID NO: 25)
GGF-I 13	T T E M A S E Q G A	(SEQ ID NO: 26)
GGF-I 14	A K E A L A A L K	(SEQ ID NO: 27)
GGF-I 15	F V L Q A K K	(SEQ ID NO: 28)
GGF-I 17	E T Q P D P G Q I L K K V P M V I G A Y T	(SEQ ID NO: 29)
GGF-I 18	E Y K C L K F K W F K K A T V M	(SEQ ID NO: 17)

B

GGF-I 20	E X K F Y V P	(SEQ ID NO: 19)
GGF-I 12	K L E F L X A K	(SEQ ID NO: 32)

8 3 95 50

FIG. 11

	Trypsin peptides		
GGF II 01	K/R V H Q V W A A K *		(SEQ ID NO: 33)
GGF II 02	K/R Y I F F M E P E A X S S G		(SEQ ID NO: 34)
GGF II 03	K/R L G A W G P P A F P V X Y		(SEQ ID NO: 35)
GGF II 04	K/R W F V V I E G K *		(SEQ ID NO: 36)
GGF II 05	K/R A L A A A G Y D V E K *	Histone H1	(SEQ ID NO: 164)
GGF II 06	K/R L V L R *		(SEQ ID NO: 165)
GGF II 07	K/R X X Y P G Q I T S N	Trypsin	(SEQ ID NO: 166)
GGF II 08	K/R A S P V S V G S V Q E L V Q R *		(SEQ ID NO: 37)
GGF II 09	K/R V C L L T V A A P P T		(SEQ ID NO: 38)
GGF II 10	K/R D L L L X V		(SEQ ID NO: 39)
	Lysyl Endopeptidase C peptides		
GGF II 11	K V H Q V W A A K *		(SEQ ID NO: 51)
GGF II 12	K A S L A D S G E Y M X K*		(SEQ ID NO: 52)

0 3 95 5002

FIG. 12

A

GGF-II 01	V H Q V W A A K	(SEQ ID NO: 45)
GGF-II 02	Y I F F M E P E A X S S G	(SEQ ID NO: 46)
GGF-II 03	L G A W G P P A F P V X Y	(SEQ ID NO: 47)
GGF-II 04	W F V V I E G K	(SEQ ID NO: 48)
GGF-II 08	A S P V S V G S V Q E L V Q R	(SEQ ID NO: 49)
GGF-II 09	V C L L T V A A P P T	(SEQ ID NO: 50)
GGF-II 11	K V H Q V W A A K	(SEQ ID NO: 51)
GGF-II 12	K A S L A D S G E Y M X K	(SEQ ID NO: 52)

B Novel Factor II Peptides others

GGF-II 10	D L L L X V	(SEQ ID NO: 53)

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FIG. 13

Comparison of BrdU-ELISA and [125 I]UdR Counting Method for the DNA Synthesis Assay in Schwann Cell Cultures

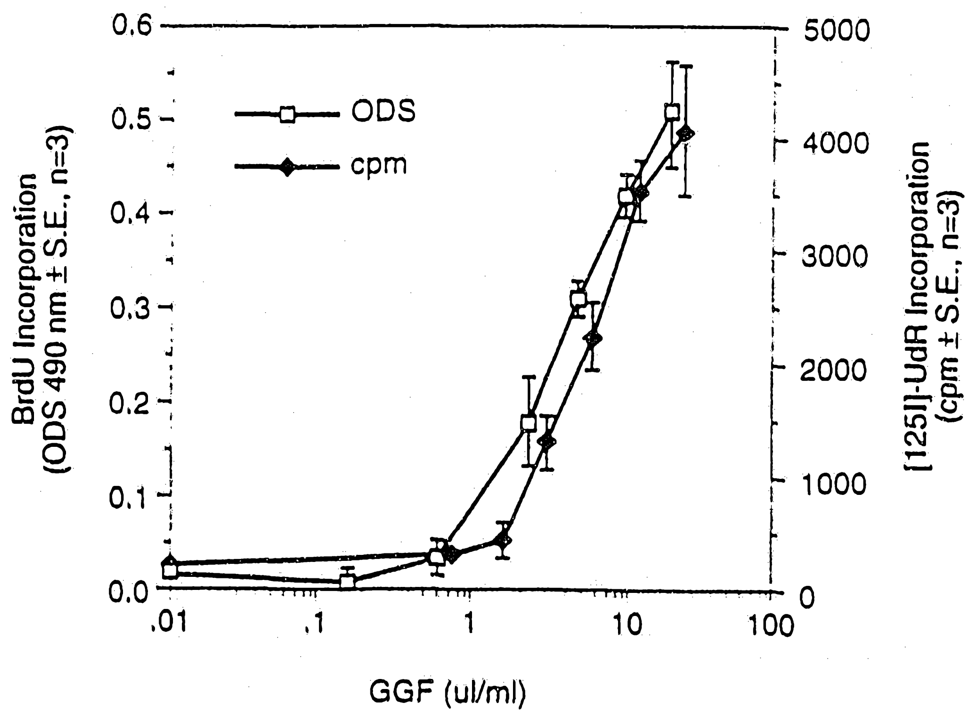


FIG. 14A

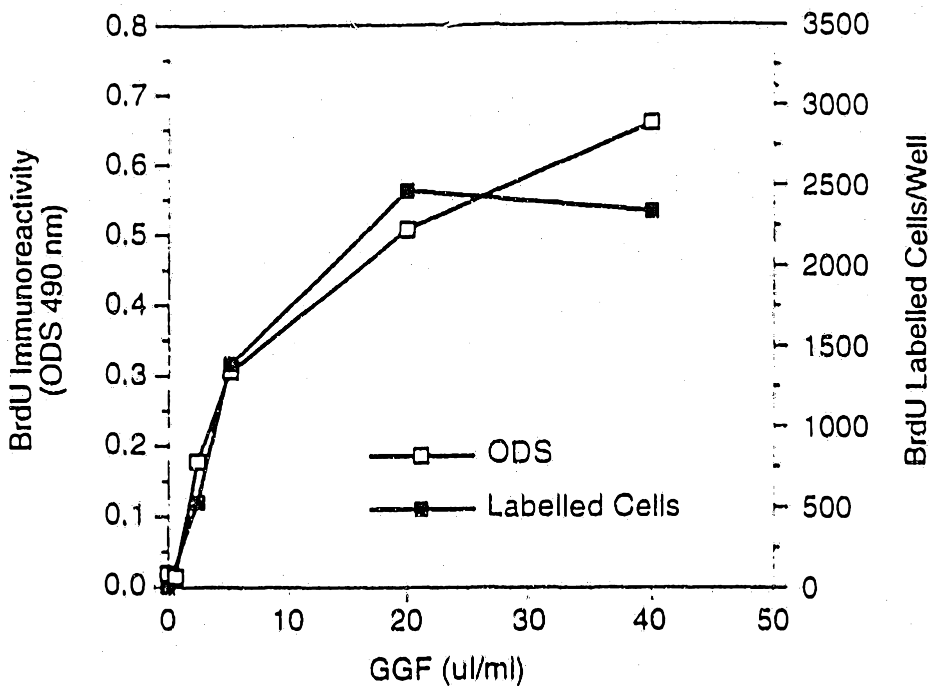


FIG. 14B

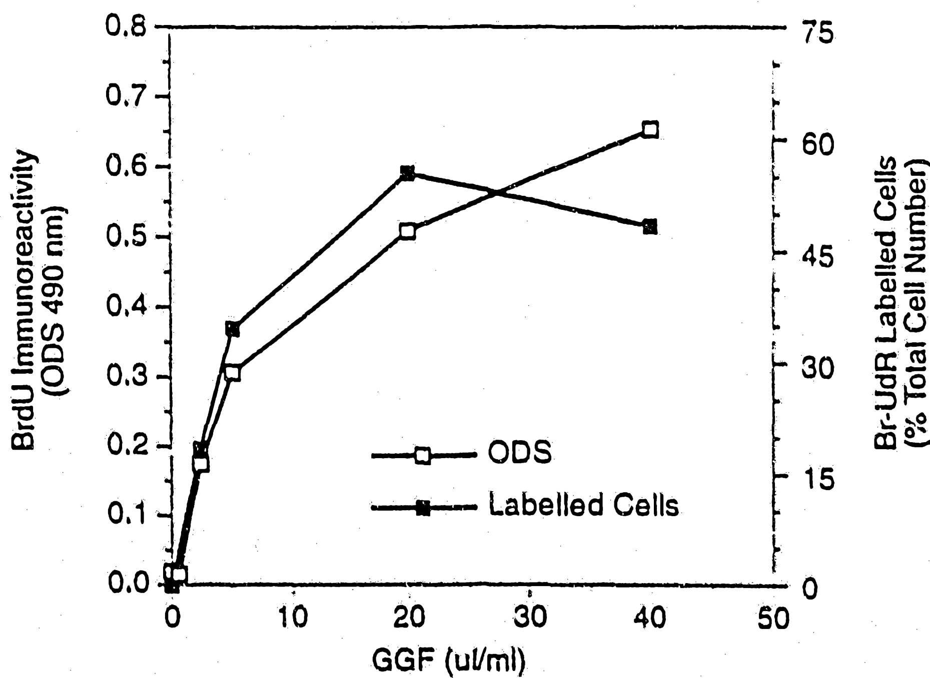


FIG. 15

Mitogenic Response of Rat Sciatic Nerve Schwann cell to GGFs

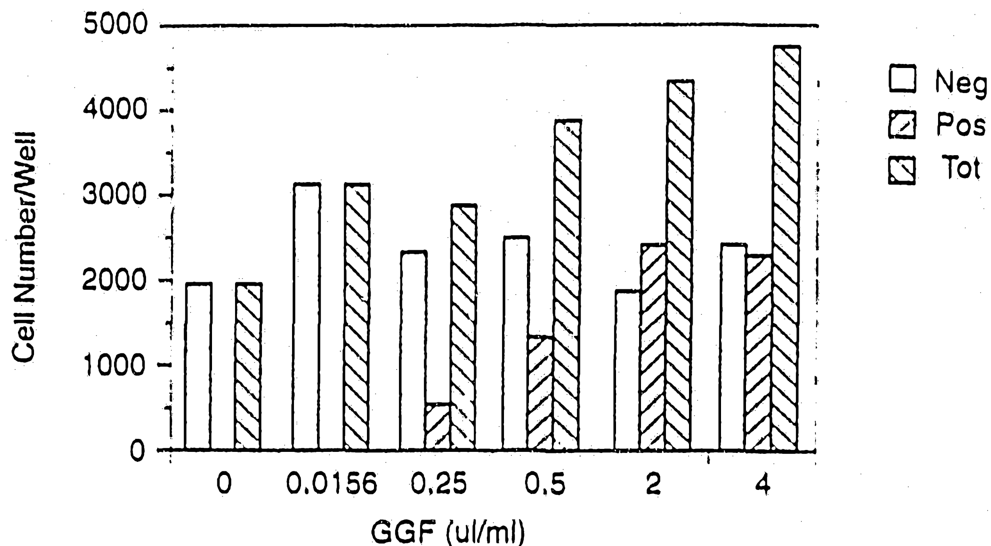


FIG. 16

DNA Synthesis in Rat Sciatic Nerve Schwann Cells and 3T3 Fibroblasts in the presence of GGFs

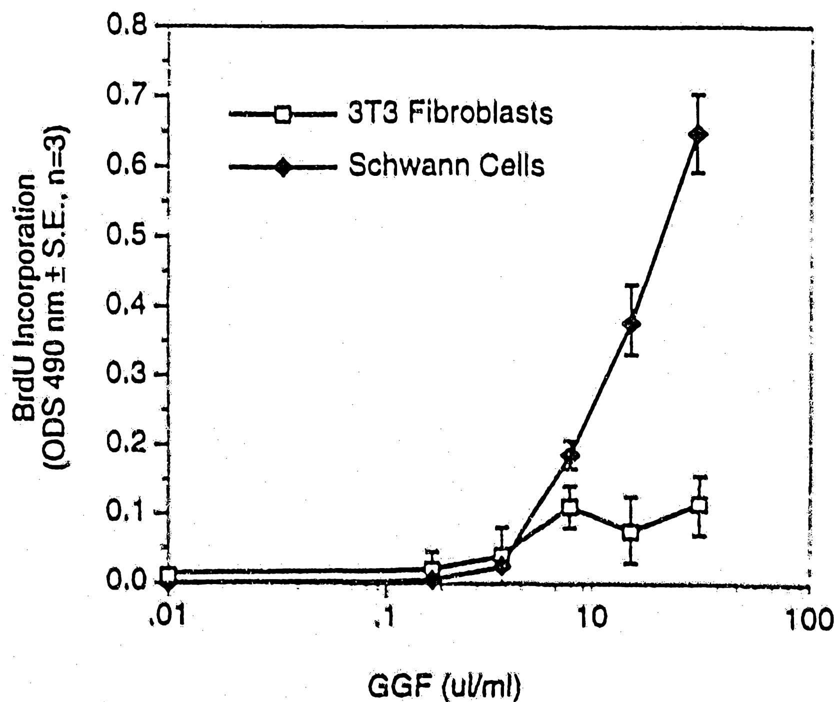


FIG. 17

Mitogenic Response of
BHK 21 C13 Cells to FCS and GGFs

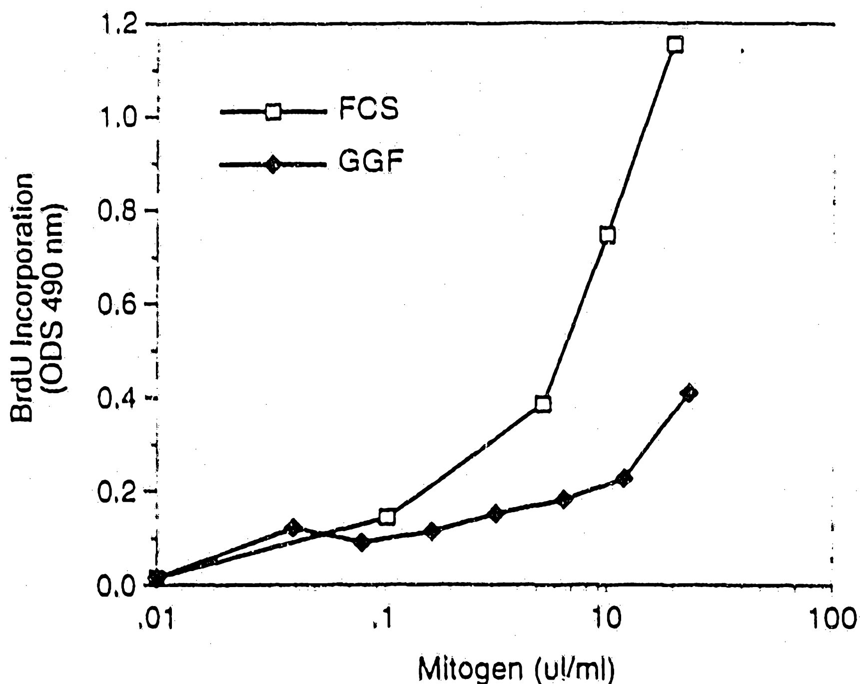


FIG. 18

Survival and Proliferation of BHK21 C13 Cell
Microcultures After 48 Hours in Presence of GGFs

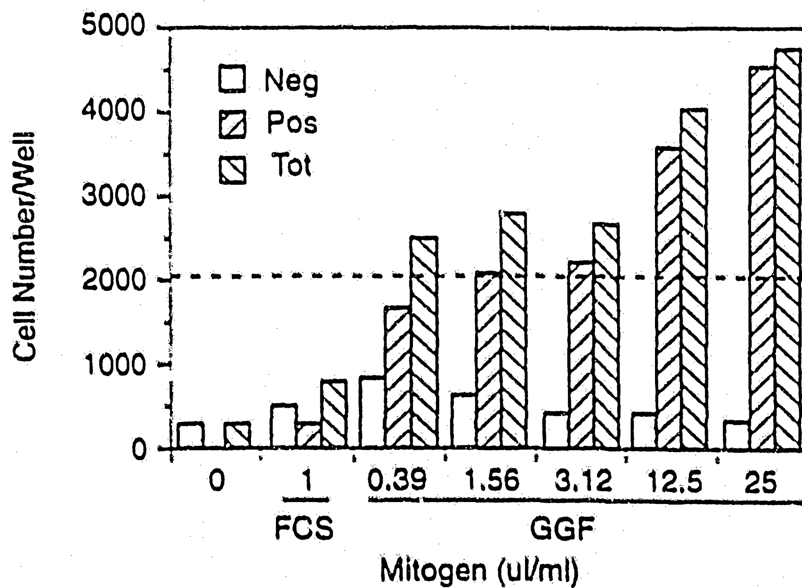
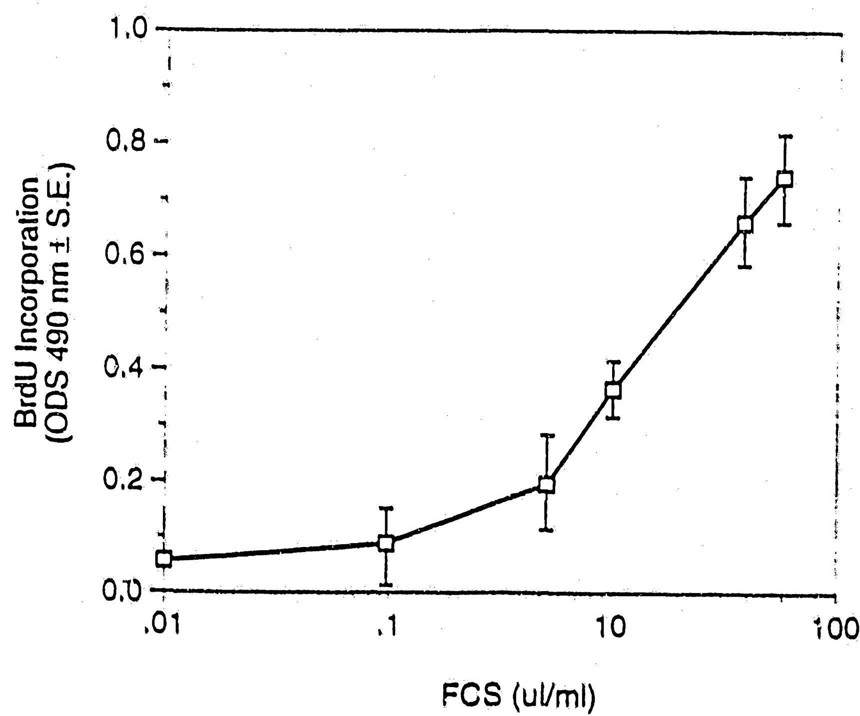


FIG. 19

Mitogenic Response of C6 Cells to FCS



0 3 05 5002

8 3 95 50026

FIG. 20A

Mitogenic Response of C6 Cells to aFGF & GGFs

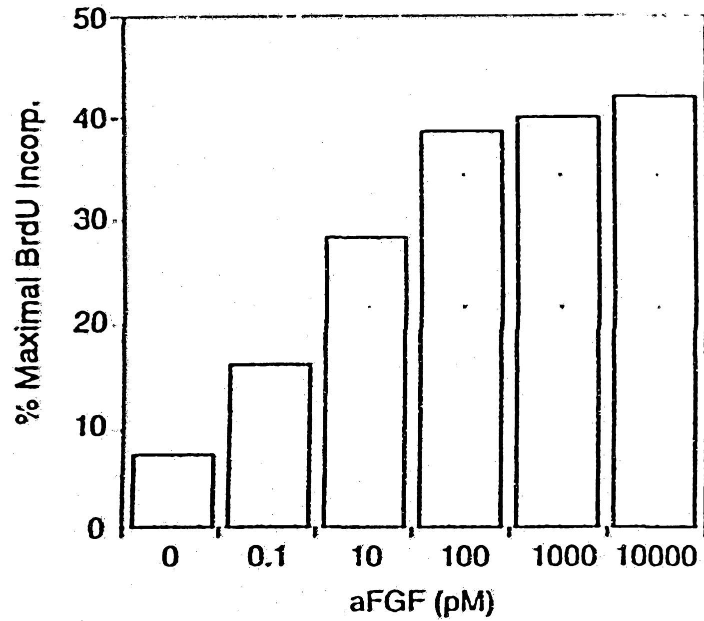


FIG. 20B

Mitogenic Response of C6 Cells to aFGF & GGFs

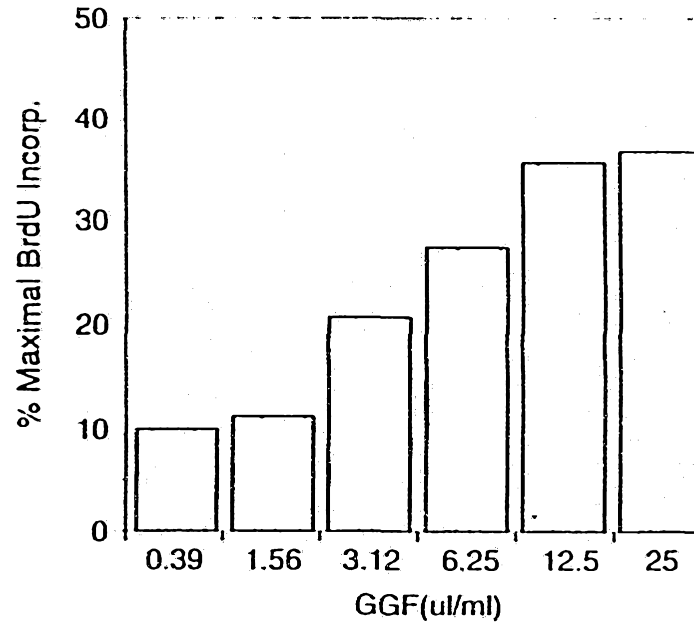


FIG. 21

Degenerate Oligonucleotide Probes for Factor I & Factor II

Oligo	Sequence	Peptide	
535	TTYAARGGNGAYGCNCAYAC	GGFI-1	(SEQ ID NO: 54)
536	CATRTAYTCRTAYTCRTCNGC	GGFI-2	(SEQ ID NO: 55)
537	TGYTCNGANGCCATYTCNGT	GGFI-13	(SEQ ID NO: 56)
538	TGYTCRCTNGCCATYTCNGT	GGFI-13	(SEQ ID NO: 57)
539	CCDATNACCATNGGNACYTT	GGFI-17	(SEQ ID NO: 58)
540	GCNGCCCANACYTGRTGNAC	GGFII-1	(SEQ ID NO: 59)
541	GCYTCNGGYTCCATRAARAA	GGFII-2	(SEQ ID NO: 60)
542	CCYTCDATNACNACRAACCA	GGFII-4	(SEQ ID NO: 61)
543	TCNGCRAARTANCCNGC	GGFI-11	(SEQ ID NO: 62)
544	GCNGCNAGNGCYTCYTTNGC	GGFI-14	(SEQ ID NO: 63)
545	GCNGCYAANGCYTCYTTNGC	GGFI-14	(SEQ ID NO: 64)
546	TTYTTNGCYTGNAGNACRAA	GGFI-15	(SEQ ID NO: 65)
551	TTYTTNGCYTGYAANACRAA	GGFI-15	(SEQ ID NO: 66)
568	TGNACNAGYTCYTGNAC	GGFII-8	(SEQ ID NO: 67)
569	TGNACYAAYTCYTGNAC	GGFII-8	(SEQ ID NO: 68)
609	CATRTAYTCNCCNGARTCNGC	GGFII-12	(SEQ ID NO: 69)
610	CATRTAYTCNCCRCTRTCNGC	GGFII-12	(SEQ ID NO: 70)
649	NGARTCNGCYAANGANGCYTT	GGFII-12	(SEQ ID NO: 71)
650	NGARTCNGCNAGNGANGCYTT	GGFII-12	(SEQ ID NO: 72)
651	RCTRTCNGCYAANGANGCYTT	GGFII-12	(SEQ ID NO: 73)
652	RCTRTCNGCNAGNGANGCYTT	GGFII-12	(SEQ ID NO: 74)
653	NGARTCNGCYAARCTNGCYTT	GGFII-12	(SEQ ID NO: 75)
654	NGARTCNGCNAGRCTNGCYTT	GGFII-12	(SEQ ID NO: 76)
655	RCTRTCNGCYAARCTNGCYTT	GGFII-12	(SEQ ID NO: 78)
656	RCTRCTNGCNAGRCTNGCYTT	GGFII-12	(SEQ ID NO: 79)
659	ACNACNGARATGGCTCNNGA	GGFI-13	(SEQ ID NO: 80)
660	ACNACNGARATGGCAGYNGA	GGFI-13	(SEQ ID NO: 81)
661	CAYCARGTNTGGGCNGCNAA	GGFII-1	(SEQ ID NO: 82)
662	TTYGTNGTNATHGARGGNAA	GGFII-4	(SEQ ID NO: 83)
663	AARGGNGAYGCNCAYACNGA	GGFI-1	(SEQ ID NO: 84)
664	GARGCNYTNGCNGCNYTNAA	GGDI-14	(SEQ ID NO: 85)
665	GTNGGNTCNGTNCARGARYT	GGFII-8	(SEQ ID NO: 86)
666	GTNGGNAGYGTNCARGARYT	GGFII-8	(SEQ ID NO: 87)
694	NACYTTYTTNARHATYTGNCC	GGFI-17	(SEQ ID NO: 88)

FIG. 22

Putative Bovine Factor II Gene Sequences

SEQ ID NO: 89:

```
TCTAA AAC TAC AGA GAC TGT ATT TTC ATG ATC ATC ATA GTT CTG TGA AAT ATA    53
      Asn Tyr Arg Asp Cys Ile Phe Met Ile Ile Ile Val Leu Xaa Asn Ile

CTT AAA CCG CTT TGG TCC TGA TCT TGT AGG AAG TCA GAA CTT CGC ATT    101
Leu Lys Pro Leu Trp Ser Xaa Ser Cys Arg Lys Ser Glu Leu Arg Ile

AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA TAT ATG TGC AAA GTG ATC    149
Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Ser Met Cys Lys Val Ile

AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC AAC ATC ACC ATT GTG GAG    197
Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Arg Ile Val Glu

TCA AAC GGT AAG AGA TGC CTA CTG CGT GCT ATT TCT CAG TCT CTA AGA    245
Ser Asn Gly Lys Arg Cys Leu Leu Arg Ala Ile Ser Gln Ser Leu Arg

GGA GTG ATC AAG GTA TGT GGT CAC ACT TGA ATC ACG CAG GTG TGT GAA    293
Gly Val Ile Lys Val Cys Gly His Thr Xaa Ile Thr Gln Val Cys Glu

ATC TCA TTG TGA ACA AAT AAA AAT CAT GAA AGG AAA ACT CTA TGT TTG    341
Ile Ser Cys Xaa Thr Asn Lys Asn His Glu Arg Lys Thr Leu Cys Leu

AAA TAT CTT ATG GGT CCT CCT GTA AAG CTC TTC ACT CCA TAA GGT GAA    389
Lys Tyr Leu Met Gly Pro Pro Val Lys Leu Phe Thr Pro Xaa Gly Glu

ATA GAC CTG AAA TAT ATA TAG ATT ATT T    417
Ile Asp Leu Lys Tyr Ile Xaa Ile Ile
```

FIG. 23A

PCR Primers for Factor I & Factor II

Degenerate PCR Primers

Oligo	Sequence	Peptide	
657	CCGAATTCTGCAGGARACNCARCCNGAYCCNGG!	GGFI 17	(SEQ ID NO: 90)
658	AAGGATCCTGCAGNGTRTANGCNCCHATNACCATNGG!	GGFI 17	(SEQ ID NO: 91)
667	CCGAATTCTGCAGGCNGAYTCNGGNGARTAYATG!	GGFII 12	(SEQ ID NO: 92)
668	CCGAATTCTGCAGGCNGAYATYGGNGARTAYAT!	GGFII 12	(SEQ ID NO: 93)
669	AAGGATCCTGCAGNNNCATRTAYTCNCCNGARTC!	GGFII 12	(SEQ ID NO: 94)
670	AAGGATCCTGCAGNNNCATRTAYTCNCCRRTRTC!	GGFII 12	(SEQ ID NO: 95)
671	CCGAATTCTGCAGCAYCARGTNTGGGCNGCNAA!	GGFII 1	(SEQ ID NO: 96)
672	CCGAATTCTGCAGATRTTYTTYATGGARCCNGARG!	GGFII 2	(SEQ ID NO: 97)
673	CCGAATTCTGCAGGGGGNCCNCCNGCNTTYCCNGT!	GGFII 3	(SEQ ID NO: 98)
674	CCGAATTCTGCAGTGGTTYGTNGTNATHGARGG!	GGFII 4	(SEQ ID NO: 99)
677	AAGGATCCTGCAGYTTNGCNGCCCANACYTGRTG!	GGFII 1	(SEQ ID NO: 100)
678	AAGGATCCTGCAGGCYTCNGGYTCCATRAARAA!	GGFII 2	(SEQ ID NO: 101)
679	AAGGATCCTGCAGACNGGRAANGCNGGNGGNCC!	GGFII 3	(SEQ ID NO: 102)
680	AAGGATCCTGCAGYTTNCCYTCDATNACNACRAAC!	GGFII 4	(SEQ ID NO: 103)
681	CATRTAYTCRTAYTCTCNGCAAGGATCCTGCAG!	GGFI 2	(SEQ ID NO: 104)
682	CCGAATTCTGCAGAARGGNGAYGCNCAYACNGA!	GGFI 1	(SEQ ID NO: 105)
683	GCNGCYAANGCYRCYTTNGCAAGGATCCTGCAG!	GGFI 14	(SEQ ID NO: 106)
684	GCNGCNAGNGCYTCYTTNGCAAGGATCCTGCAG!	GGFI 14	(SEQ ID NO: 107)
685	TCNGCRAARTANCCNGCAAGGATCCTGCAG!	GGFII 1	(SEQ ID NO: 108)

8395 50026

FIG. 23B

PCR Primers for Factor I & Factor II

Unique PCR Primers for Factor II

Oligo	Sequence	Comment	
711	CATCGATCTGCAGGCTGATTCTGGAGAATATATGTGCA!	3' RACE	(SEQ ID NO: 109)
712	AAGGATCCTGCAGCCACATCTCGAGTCGACATCGATT!	3' RACE	(SEQ ID NO: 110)
713	CCGAATTCTGCAGTGATCAGCAAACTAGGAAATGACA!	3' RACE	(SEQ ID NO: 111)
721	CATCGATCTGCAGCCTAGTTTGCTGATCACTTTGCAC!	5' RACE	(SEQ ID NO: 112)
722	AAGGATCCTGCAGTATATTCTCCAGAATCAGCCAGTG!	5' RACE;ANCHORED	(SEQ ID NO: 113)
725	AAGGATCCTGCAGGCACGCAGTAGGCATCTCTTA!	EXON A	(SEQ ID NO: 114)
726	CCGAATTCTGCAGCAGAACTTCGCATTAGCAAAGC!	EXON A	(SEQ ID NO: 115)
771	CATCCCGGGATGAAGAGTCAGGAGTCTGTGGCA!	EXONS B+A	(SEQ ID NO: 116)
772	ATACCCGGGCTGCAGACAATGAGATTTCACACACCTGCG!		(SEQ ID NO: 117)
773	AAGGATCCTGCAGTTTGGAACCTGCCACAGACTCCT!	ANCHORED	(SEQ ID NO: 118)
776	ATACCCGGGCTGCAGATGAGATTTCACACACCTGCGTGA!	EXONS B+A	(SEQ ID NO: 119)

FIG. 24

Summary of Contiguous GGF-II cDNA Structures & Sequences

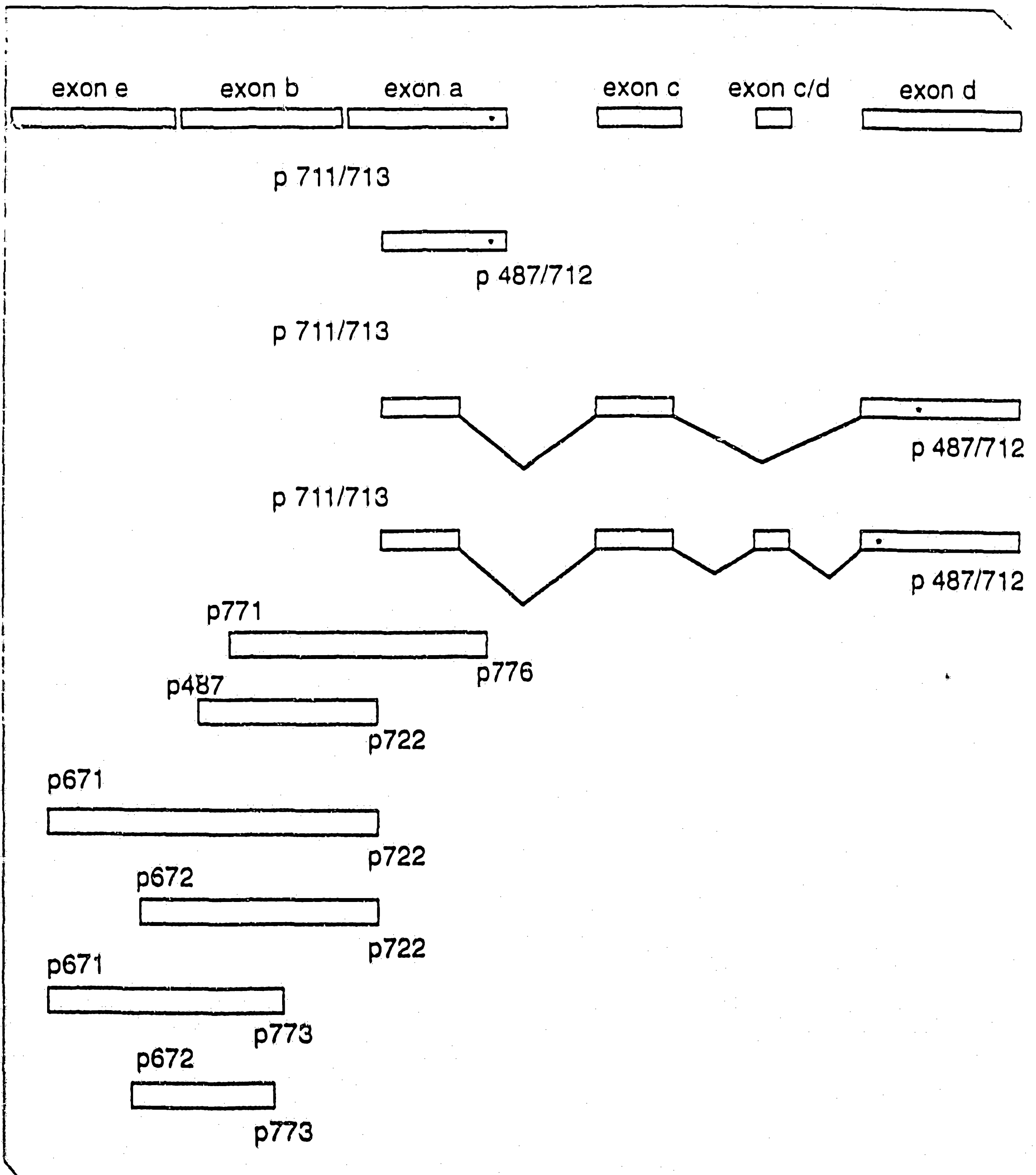
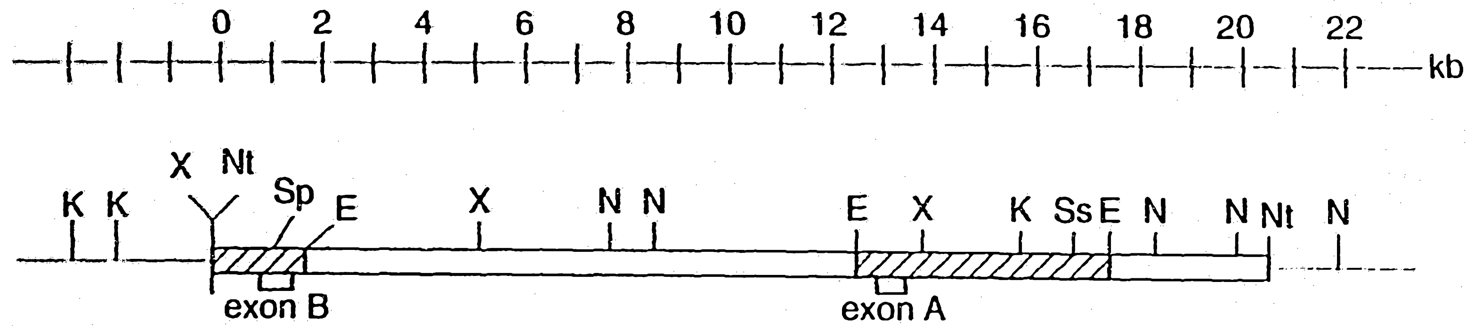


FIG. 25



8 3 95 50026

FIG. 26

Alternative Gene Products of Putative Bovine GGF-II

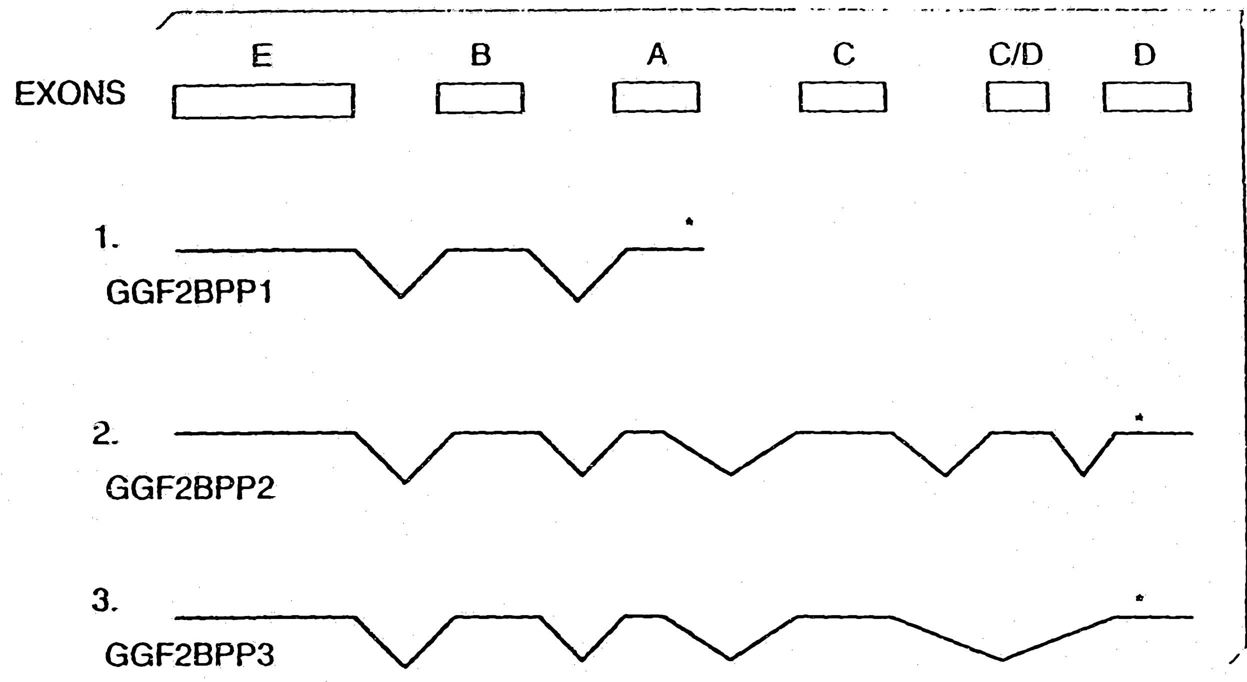


FIG. 27

GGF-II Peptides Identified in Deduced Amino Acid Sequences of Putative Bovine GGF-II Proteins

Peptide	Pos.		Sequence match	ID Sequences
II-1			VHQVWAAK	
	1:		HQVWAAK AAGLK	(SEQ ID NO:120)
II-10			DLLLXV	
	14:	GGLKK	dslltv RLGAW	(SEQ ID NO:121)
II-03			LGAWGPPAFPVXY	(SEQ ID NO:122)
	21:	LLTVR	lgawghpafpscg RLKED	(SEQ ID NO:123)
II-02			YIFFMEPEAXSSG	(SEQ ID NO:124)
	41:	KEDSR	YIFFMEPEANSSG GPGRL	(SEQ ID NO:125)
II-6			LVLR	
	103:	VAGSK	LVLR CETSS	(SEQ ID NO:126)
I-18			EYKCLKFKWFKKATVM	(SEQ ID NO:127)
	112:	CETSS	eysslkfkwfkngsel SRKNK	(SEQ ID NO:128)
II-12			KASLADSGEYMXK	(SEQ ID NO:129)
	151:	ELRIS	KASLADSGEYMCK VISKL	(SEQ ID NO:130)
I-07			ASLADEYEYMRK	(SEQ ID NO:131)
	152:	LRISK	asladsgeymck VISKL	(SEQ ID NO:132)

8 3 95 50026

FIG. 28A

SEQ ID NO: 133:

```
CCTGCAG CAT CAA GTG TGG GCG GCG AAA GCC GGG GGC TTG AAG AAG GAC TCG CTG   55
        His Gln Val Trp Ala Ala Lys Ala Gly Gly Leu Lys Lys Asp Ser Leu

CTC ACC GTG CGC CTG GGC GCC TGG GGC CAC CCC GCC TTC CCC TCC TGC          103
Leu Thr Val Arg Leu Gly Ala Trp Gly His Pro Ala Phe Pro Ser Cys

GGG CGC CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC GAG          151
Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro Glu

GCC AAC AGC AGC GGC GGG CCC GGC CGC CTT CCG AGC CTC CTT CCC CCC          199
Ala Asn Ser Ser Gly Gly Pro Gly Arg Leu Pro Ser Leu Leu Pro Pro

TCT CGA GAC GGG CCG GAA CCT CAA GAA GGA GGT CAG CCG GGT GCT GTG          247
Ser Arg Asp Gly Pro Glu Pro Gln Glu Gly Gly Gln Pro Gly Ala Val

CAA CGG TGC GCC TTG CCT CCC CGC TTG AAA GAG ATG AAG AGT CAG GAG          295
Gln Arg Cys Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu

TCT GTG GCA GGT TCC AAA CTA GTG CTT CGG TGC GAG ACC AGT TCT GAA          343
Ser Val Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu

TAC TCC TCT CTC AAG TTC AAG TGG TTC AAG AAT GGG AGT GAA TTA AGC          391
Tyr Ser Ser Leu Lys Phe Lys Trp Phe Lys Asn Gly Ser Glu Leu Ser

CGA AAG AAC AAA CCA GAA AAC ATC AAG ATA CAG AAA AGG CCG GGG AAG          439
Arg Lys Asn Lys Pro Glu Asn Ile Lys Ile Gln Lys Arg Pro Gly Lys

TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA TAT          487
Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr

ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC AAC          535
Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn

ATC ACC ATT GTG GAG TCA AAC GGT AAG AGA TGC CTA CTG CGT GCT ATT          583
Ile Thr Ile Val Glu Ser Asn Gly Lys Arg Cys Leu Leu Arg Ala Ile

TCT CAG TCT CTA AGA GGA GTG ATC AAG GTA TGT GGT CAC ACT                  625
Ser Gln Ser Leu Arg Gly Val Ile Lys Val Cys Gly His Thr

TGAATCACGC AGGTGTGTGA AATCTCATTG TGAACAAATA AAAATCATGA AAGGAAAAAA        685

AAAAAAAAAA AATCGATGTC GACTCGAGAT GTGGCTGCAG GTCGACTCTA GAGGATCCC         744
```

FIG. 28B

Nucleotide Sequences & Deduced Amino Acid Sequences of GGF2BPP2

SEQ ID NO: 134:

```
CCTGCAG CAT CAA GTG TGG GCG GCG AAA GCC GGG GGC TTG AAG AAG GAC TCG CTG  55
        His Gln Val Trp Ala Ala Lys Ala Gly Gly Leu Lys Lys Asp Ser Leu

CTC ACC GTG CGC CTG GGC GCC TGG GGC CAC CCC GCC TTC CCC TCC TGC         103
Leu Thr Val Arg Leu Gly Ala Trp Gly His Pro Ala Phe Pro Ser Cys

GGG CGC CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC GAG         151
Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro Glu

GCC AAC AGC AGC GGC GGG CCC GGC CGC CTT CCG AGC CTC CTT CCC CCC         199
Ala Lys Ser Ser Gly Gly Pro Gly Arg Leu Pro Ser Leu Leu Pro Pro

TCT CGA GAC GGG CCG GAA CCT CAA GAA GGA GGT CAG CCG GGT GCT GTG         247
Ser Arg Asp Gly Pro Glu Pro Gln Glu Gly Gly Gln Pro Gly Ala Val

CAA CGG TGC GCC TTG CCT CCC CGC TTG AAA GAG ATG AAG AGT CAG GAG         295
Gln Arg Cys Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu

TCT GTG GCA GGT TCC AAA CTA GTG CTT CGG TGC GAG ACC AGT TCT GAA         343
Ser Val Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu

TAC TCC TCT CTC AAG TTC AAG TGG TTC AAG AAT GGG AGT GAA TTA AGC         391
Tyr Ser Ser Leu Lys Phe Lys Trp Phe Lys Asn Gly Ser Glu Leu Ser

CGA AAG AAC AAA CCA GAA AAC ATC AAG ATA CAG AAA AGG CCG GGG AAG         439
Arg Lys Asn Lys Gly Gly Asn Ile Lys Ile Gln Lys Arg Pro Gly Lys

TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA TAT         487
Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr

ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC AAC         535
Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn
```

FIG. 28B'

Nucleotide Sequences & Deduced Amino Acid Sequences of GG2BPP2

```
ATC ACC ATT GTG GAG TCA AAC GCC ACA TCC ACA TCT ACA GCT GGG ACA          583
Ile Thr Ile Val Glu Ser Asn Ala Thr Ser Thr Ser Thr Ala Gly Thr

AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT          631
Ser His Leu Val Lys Ser Ala Glu Lys Glu Lys Thr Phe Cys Val Asn

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC          679
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr

TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT          727
Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn

GTG CCC ATG AAA GTC CAA ACC CAA GAA AGT GCC CAA ATG AGT TTA CTG          775
Val Pro Met Lys Val Gln Thr Gln Glu Ser Ala Gln Met Ser Leu Leu

GTG ATC GCT GCC AAA ACT ACG TAATGGCCAG CTTCTACAGT ACGTCCACTC             826
Val Ile Ala Ala Lys Thr Thr

CCTTTCTGTC TCTGCCTGAA TAGCGCATCT CAGTCGGTGC CGCTTTCTTG TTGCCGCATC        886

TCCCCTCAGA TTCCTCCTAG AGCTAGATGC GTTTTACCAG GTCTAACATT GACTGCCTCT        946

GCCTGTCGCA TGAGAACATT AACACAAGCG ATTGTATGAC TTCCTCTGTC CGTGACTAGT       1006

GGGCTCTGAG CTACTCGTAG GTGCGTAAGG CTCCAGTGTT TCTGAAATTG ATCTTGAATT       1066

ACTGTGATAC GACATGATAG TCCCTCTCAC CCAGTGCAAT GACAATAAAG GCCTTGAAAA       1126

GTCAAAAAAA AAAAAAAAAA AAAAAATCGA TGTCGACTCG AGATGTGGCT GCAGGTCGAC       1186

TCTAGAG                                                                 1193
```

FIG. 28C

Nucleotide Sequences & Deduced Amino Acid Sequences of GGF2BPP3

SEQ ID NO: 135:

```
CCTGCAG CAT CAA GTG TGG GCG GCG AAA GCC GGG GGC TTG AAG AAG GAC TCG CTG  55
        His Gln Val Trp Ala Ala Lys Ala Gly Gly Leu Lys Lys Asp Ser Leu

CTC ACC GTG CGC CTG GGC GCC TGG GGC CAC CCC GCC TTC CCC TCC TGC         103
Leu Thr Val Arg Leu Gly Ala Trp Gly His Pro Ala Phe Pro Ser Cys

GGG CGC CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC GAG         151
Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro Glu

GCC AAC AGC AGC GGC GGG CCC GGC CGC CTT CCG AGC CTC CTT [illegible]C CCC         199
Ala Asn Ser Ser Gly Gly Pro Gly Arg Leu Pro Ser Leu Leu Pro Pro

TCT CGA GAC GGG CCG GAA CCT CAA GAA GGA GGT CAG CCG GGT GCT GTG         247
Ser Arg Asp Gly Pro Glu Pro Gln Glu Gly Gly Gln Pro Gly Ala Val

CAA CGG TGC GCC TTG CCT CCC CGC TTG AAA GAG ATG AAG AGT CAG GAG         295
Gln Arg Cys Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu

TCT GTG GCA GGT TCC AAA CTA GTG CTT CGG TGC GAG ACC AGT TCT GAA         343
Ser Val Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu

TAC TCC TCT CTC AAG TTC AAG TGG TTC AAG AAT GGG AGT GAA TTA AGC         391
Tyr Ser Ser Leu Lys Phe Lys Trp Phe Lys Asn Gly Ser Glu Leu Ser

CGA AAG AAC AAA CCA GAA AAC ATC AAG ATA CAG AAA AGG CCG GGG AAG         439
Arg Lys Asn Lys Pro Glu Asn Ile Lys Ile Gln Lys Arg Pro Pro Lys

TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA TAT         487
Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr
```

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FIG. 28C'

Nucleotide Sequences & Deduced Amino Acid Sequences of GGF2BPP3

```
ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC AAC      535
Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn

ATC AGG ATT GTG GAG TCA AAC GCC ACA TCC ACA TCT ACA GCT GGG ACA      583
Ile Arg Ile Val Glu Ser Asn Ala Thr Ser Thr Ser Thr Ala Gly Thr

AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT      631
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC      679
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr

TTG TGC AAG TGC CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC      727
Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr

GTA ATG GCC AGC TTC TAC AGT ACG TCC ACT CCC TTT CTG TCT CTG CCT      775
Val Met Ala Ser Phe Tyr Ser Thr Ser Thr Pro Phe Leu Ser Leu Pro

GAA TAGCGCATCT CAGTCGGTGC CGCTTTCTTG TTGCCGCATC TCCCCTCAGA TTCCGCCTAG   838
Glu

AGCTAGATGC GTTTTACCAG GTCTAACATT GACTGCCTCT GCCTGTCGCA TGAGAACATT       898

AACACAAGCG ATTGTATGAC TTCCTCTGTC CGTGACTAGT GGGCTCTGAG CTACTCGTAG       958

GTGCGTAAGG CTCCAGTGTT TCTGAAATTG ATCTTGAATT ACTGTGATAC GACATGATAG      1018

TCCCTCTCAC CCAGTGCAAT GACAATAAAG GCCTTGAAAA GTCAAAAAAA AAAAAAAAAA      1078

AAAAATCGAT GTCGACTCGA GATGTGGCTG                                       1108
```

YEAST
CHICKEN
RABBIT
BOVINE
DOG
MOUSE
RAT
MONKEY
HUMAN
MARKER

FIG. 29

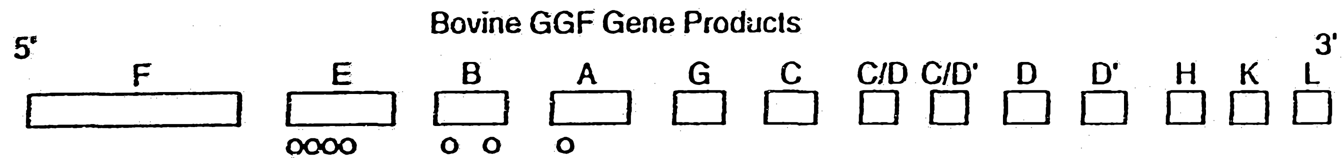

FIG. 30

GGF2BPP1(206)

GGF2BPP2(201)

GGF2BPP3(257)

GGF2BPP5(241)

GGF2BPP4(560)

Heregulins

HRGß3(241)

HRGα(640)

HRGß2(637)

HRGß1(645)

NDF(422)

FIG. 31A

Coding Segments of Glial Growth Factor/Heregulin Gene

```
CODING SEGMENT F: (SEQ ID NO: 136 (bovine) and 173 (human))
AGTTTCCCCC CCCAACTTGT CGGAACTCTG GGCTCGCGCG CAGGGCAGGA GCGGAGCGGC    60

GGCGGCTGCC CAGGCGATGC GAGCGCGGGC CGGACGGTAA TCGCCTCTCC CTCCTCGGGC   120

TGCGAGCGCG CCGGACCGAG GCAGCGACAG GAGCGGACCG CGGCGGGAAC CGAGGACTCC   180

CCAGCGGCGC GCCAGCAGGA GCCACCCCGC GAGNCGTGCG ACCGGGACGG AGCGCCCGCC   240

AGTCCCAGGT GGCCCGGACC GCACGTTGCG TCCCCGCGCT CCCCGCCGGC GACAGGAGAC   300

GCTCCCCCCC ACGCCGCGCG CGCCTCGGCC CGGTCGCTGG CCCGCCTCCA CTCCGGGGAC   360
              |||| | |||||| ||  ||| |||| | | | |  ||  |||  |||||
              CGCGAG CGCCTCAGCG CGGCCGCTCG CTCTC..CCC CTCGAGGGAC

AAACTTTTCC CGAAGCCGAT CCCAGCCCTC GGACCCAAAC TTGTCGCGCG TCGCCTTCGC   420
|||||||||| | || ||||| || ||||||  ||||| ||             |||||| |||
AAACTTTTCC CAAACCCGAT CCGAGCCCTT GGACCAAA.. .........C TCGCCTGCGC

                                            Met Ser Glu Arg Arg
CGGGAGCCGT CCGCGCAGAG CGTGCACTTC TCGGGCGAG ATG TCG GAG CGC AGA     474
|| ||||||| ||||| |||| ||   | | || || |||||| ||| ||  ||| ||| | |
CGAGAGCCGT CCGCGTAGAG CGCTC.CGTC TCCGGCGAG ATG TCC GAG CGC AAA
                                                            K

Glu Gly Lys Gly Lys Gly Lys Gly Gly Lys Lys Asp Arg Gly Ser Gly
GAA GGC AAA GGC AAG GGG AAG GGC GGC AAG AAG GAC CGA GGC TCC GGG    522
||| ||| | | ||| ||  ||| ||| |||     ||| ||| ||  ||| ||| ||| ||
GAA GGC AGA GGC AAA GGG AAG GGC AAG AAG AAG GAG CGA GGC TCC GGC
        R                       K           E

Lys Lys Pro Val Pro Ala Ala Gly Gly Pro Ser Pro Ala or Xaa
AAG AAG CCC GTG CCC GCG GCT GGC GGC CCG AGC CCA GNN                559
||| ||| ||   | |  || ||| ||  |||  || | | ||| ||| |||
AAG AAG CCG GAG TCC GCG GCG GGC AGC CAG AGC CCA GNN
            E   S
```

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FIG. 31B

CODING SEGMENT E: (SEQ ID NO: 137)

```
     CAT CAN GTG TGG GCG GCG AAA GCC GGG GGC TTG AAG AAG GAC TCG      47
     His Gln Val Trp Ala Ala Lys Ala Gly Gly Leu Lys Lys Asp Ser

CTG CTC ACC GTG CGC CTG GGC GCC TGG GGC CAC CCC GCC TTC CCC TCC      95
Leu Leu Thr Val Arg Leu Gly Ala Trp Gly His Pro Ala Phe Pro Ser

TGC GGG CGC CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC     143
Cys Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro

GAG GCC AAC AGC AGC GGC GGG CCC GGC CGC CTT CCG AGC CTC CTT CCC     191
Glu Ala Asn Ser Ser Gly Gly Pro Gly Arg Leu Pro Ser Leu Leu Pro

CCC TCT CGA GAC GGG CCG GAA CCT CAA GAA GGA GGT CAG CCG GGT GCT     239
Pro Ser Arg Asp Gly Pro Glu Pro Gln Glu Gly Gly Gln Pro Gly Ala

GTG CAA CGG TGC G                                                   252
Val Gln Arg Cys
```

171297 50026

FIG. 31C

CODING SEGMENT B: (SEQ ID NO: 138 (bovine, top) and 174 (human, bottom)

```
    Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Val Ala
    TTG CCT CCC CGC TTG AAA GAG ATG AAG AGT CAG GAG TCT GTG GCA  45
    ||| ||| ||| ||  ||| ||| ||| ||| ||  ||  ||| ||  ||  |   |||
    TTG CCT CCC CGA TTG AAA GAG ATG AAA AGC CAG GAA TCG GCT GCA
                 Q                                       A

Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser Ser
GGT TCC AAA CTA GTG CTT CGG TGC GAG ACC AGT TCT GAA TAC TCC TCT  93
||| ||| ||| ||| ||  ||| ||| ||  ||  ||| ||| ||| ||| ||| ||| |||
GGT TCC AAA CTA GTC CTT CGG TGT GAA ACC AGT TCT GAA TAC TCC TCT


Leu Lys Phe Lys Trp Phe Lys Asn Gly Ser Glu Leu Ser Arg Lys Asn
CTC AAG TTC AAG TGG TTC AAG AAT GGG AGT GAA TTA AGC CGA AAG AAC  141
||| |   ||| ||| ||| ||| ||| ||| ||| | | ||| ||  |   ||| ||  |||
CTC AGA TTC AAG TGG TTC AAG AAT GGG AAT GAA TTG AAT CGA AAA AAC
     R                                   N           N

Lys Pro Gln Asn Ile Lys Ile Gln Lys Arg Pro Gly
AAA CCA CAA AAC ATC AAG ATA CAG AAA AGG CCG GGG                  177
||| ||| ||| ||  ||| ||| ||| ||  ||| | | ||  |||
AAA CCA CAA AAT ATC AAG ATA CAA AAA AAG CCA GGG
                                     K
```

17129750026

FIG. 31D

CODING SEGMENT A: (SEQ ID NO: 139 (bovine, top) and 175 (human, bottom)

```
  Lys Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly
G AAG TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA      46
  ||| ||| ||| ||| ||| ||| | | ||| ||  ||| ||| ||| ||| ||| |||
G AAG TCA GAA CTT CGC ATT AAC AAA GCA TCA CTG GCT GAT TCT GGA
                          N

Glu Tyr Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser
GAA TAT ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT    94
||  ||| ||| ||| ||| ||| ||| ||| |||  || ||| ||| ||| ||| ||| |||
GAG TAT ATG TGC AAA GTG ATC AGC AAA TTA GGA AAT GAC AGT GCC TCT

Ala Asn Ile Thr Ile Val Glu Ser Asn Ala or Glu
GCC AAC ATC ACC ATT GTG GAG TCA AAC GMB                           122
||| ||  ||| ||| ||  ||| ||  ||| ||| |||
GCC AAT ATC ACC ATC GTG GAA TCA AAC GMB
```

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FIG. 31E

CODING SEGMENT A': (SEQ ID NO: 140)

```
TCTAAAACTA CAGAGACTGT ATTTTCATGA TCATCATAGT TCTGTGAAAT ATACTTAAAC        60

CGCTTTGGTC CTGATCTTGT AGG AAG TCA GAA CTT CGC ATT AGC AAA GCG          110
                          Lys Ser Glu Leu Arg Ile Ser Lys Ala

TCA CTG GCT GAT TCT GGA GAA TAT ATG TGC AAA GTG ATC AGC AAA CTA       158
Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys Lys Val Ile Ser Lys Leu

GGA AAT GAC AGT GCC TCT GCC AAC ATC ACC ATT GTG GAG TCA AAC GGT       206
Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr Ile Val Glu Ser Asn Gly

AAG AGA TGC CTA CTG CGT GCT ATT TCT CAG TCT CTA AGA GGA GTG ATC       254
Lys Arg Cys Leu Leu Arg Ala Ile Ser Gln Ser Leu Arg Gly Val Ile

AAG GTA TGT GGT CAC ACT TGAATCACGC AGGTGTGTGA AATCTCATTG              302
Lys Val Cys Gly His Thr

TGAACAAATA AAAATCATGA AAGGAAAACT CTATGTTTGA AATATCTTAT GGGTCCTCCT     362

GTAAAGCTCT TCACTCCATA AGGTGAAATA GACCTGAAAT ATATATAGAT TATTT          417
```

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FIG. 31F

CODING SEGMENT G: (SEQ ID NO: 141 (bovine, top) and 176 (human, bottom)

```
    Ile Thr Thr Gly Met Pro Ala Ser Thr Glu Thr Ala Tyr Val Ser
    ATC ACC ACT GGC ATG CCA GCC TCA ACT GAG ACA GCG TAT GTG TCT      47
    ||| | | ||| ||  ||| ||| ||| ||| ||| ||    | ||  ||| ||| |||
    ATC ATC ACT GGT ATG CCA GCC TCA ACT GAA GGA GCA TAT GTG TCT
        I                                   G

Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr Glu Gly Thr Asn Thr
TCA GAG TCT CCC ATT AGA ATA TCA GTA TCA ACA GAA GGA ACA AAT ACT      95
||| ||| ||| ||| ||| ||| ||| ||| ||| ||  ||| ||| |||  || ||| |||
TCA GAG TCT CCC ATT AGA ATA TCA GTA TCC ACA GAA GGA GCA AAT ACT
                                                    A

Ser Ser Ser
TCT TCA TCY                                                         102
||| ||| |||
TCT TCA TCY
```

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FIG. 31G

CODING SEGMENT C: (SEQ ID NO: 160 (bovine, top) and 177 (human, bottom)

```
    Thr Ser Thr Ser Thr Ala Gly Thr Ser His Leu Val Lys Cys Ala
    ACA TCC ACA TCT ACA GCT GGG ACA AGC CAT CTT GTC AAG TGT GCA     47
    ||| ||  ||| ||  ||   || ||| ||| ||| ||| ||| ||   ||  ||| ||
    ACA TCT ACA TCC ACC ACT GGG ACA AGC CAT CTT GTA AAA TGT GCG
                        T

Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Cys Phe Met Val
GAG AAG GAG AAA ACT TTC TGT GTG AAT GGA GGC GAG TGC TTC ATG GTG     95
||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||  ||| ||| ||| ||| |||
GAG AAG GAG AAA ACT TTC TGT GTG AAT GGA GGG GAG TGC TTC ATG GTG

Lys Asp Leu Ser Asn Pro Ser Arg Tyr Leu Cys
AAA GAC CTT TCA AAT CCC TCA AGA TAC TTG TGC                        128
||| ||| ||| ||| ||  ||| ||  ||| ||| ||| |||
AAA GAC CTT TCA AAC CCC TCG AGA TAC TTG TGC
```

171297 500

FIG. 31H

CODING SEGMENT C/D: (SEQ ID NO: 142 (bovine, top) and 178 (human, bottom)

```
Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn Val Pro
AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT GTG CCC      48
||| ||| ||| ||| ||| ||| ||| ||| ||  ||| ||| ||| ||| ||| ||| |||
AAG TGC CAA CCT GGA TTC ACT GGA GCA AGA TGT ACT GAG AAT GTG CCC

Met Lys Val Gln Thr Gln Glu
ATG AAA GTC CAA ACC CAA GAA                                          69
||| ||| ||| ||| | | ||| |||
ATG AAA GTC CAA AAC CAA GAA
                N
```

FIG. 31I CODING SEGMENT C/D': (SEQ ID NO: 143 **(bovine, top)** and 179 **(human, bottom)**

```
Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr Val Met
AAG TGC CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC GTA ATG     48
||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
AAG TGC CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC GTA ATG

Ala Ser Phe Tyr
GCC AGC TTC TAC                                                     60
||| ||| ||| |||
GCC AGC TTC TAC
```

FIG. 31J CODING SEGMENT D: (SEQ ID NO: 144 **(bovine, top)** and 180 **(human, bottom)**

```
Ser Thr Ser Thr Pro Phe Leu Ser Leu Pro Glu *
AGT ACG TCC ACT CCC TTT CTG TCT CTG CCT GAA TAG                     36
||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
AGT ACG TCC ACT CCC TTT CTG TCT CTG CCT GAA TAG
```

FIG. 31K CODING SEGMENT D': (SEQ ID NO: 145 **(bovine)**

```
Lys His Leu Gly Ile Glu Phe Met Glu
AAG CAT CTT GGG ATT GAA TTT ATG GAG                                 27
```


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17297 5002[illegible]

FIG. 31L

CODING SEGMENT H: (SEQ ID NO: 146 (bovine, top) and 181 (human, bottom)

```
Lys Ala Glu Glu Leu Tyr Gln Lys Arg Val Leu Thr Ile Thr Gly Ile
AAA GCG GAG GAG CTC TAC CAG AAG AGA GTG CTC ACC ATT ACC GGC ATT    48
||  ||| ||| ||| ||  ||| ||| ||| ||| ||| ||  ||| ||  ||| ||| ||
AAG GCG GAG GAG CTG TAC CAG AAG AGA GTG CTG ACC ATA ACC GGC ATC

Cys Ile Ala Leu Leu Val Val Gly Ile Met Cys Val Val Val Tyr Cys
TGC ATC GCG CTG CTC GTG GTT GGC ATC ATG TGT GTG GTG GTC TAC TGC    96
||| ||| ||  ||  ||  ||| ||  ||| ||| ||| ||| ||| ||| | | ||| |||
TGC ATC GCC CTC CTT GTG GTC GGC ATC ATG TGT GTG GTG GCC TAC TGC
                                                A

Lys Thr Lys Lys Gln Arg Lys Lys Leu His Asp Arg Leu Arg Gln Ser
AAA ACC AAG AAA CAA CGG AAA AAG CTT CAT GAC CGG CTT CGG CAG AGC   144
||| ||| ||| ||| ||  ||| ||| ||| ||  ||| ||| ||  ||| ||| ||| |||
AAA ACC AAG AAA CAG CGG AAA AAG CTG CAT GAC CGT CTT CGG CAG AGC

Leu Arg Ser Glu Arg Asn Thr Met Met Asn Val Ala Asn Gly Pro His
CTT CGG TCT GAA AGA AAC ACC ATG ATG AAC GTA GCC AAC GGG CCC CAC   192
||| ||| ||| |||  || ||| |   ||| ||| |||  |  ||| ||  ||| ||  |||
CTT CGG TCT GAA CGA AAC AAT ATG ATG AAC ATT GCC AAT GGG CCT CAC
                        N                I

His Pro Asn Pro Pro Pro Glu Asn Val Gln Leu Val Asn Gln Tyr Val
CAC CCC AAT CCG CCC CCC GAG AAC GTG CAG CTG GTG AAT CAA TAC GTA   240
||  ||  ||  ||  ||| ||| ||| ||  ||  ||| ||| ||| ||| ||| ||| |||
CAT CCT AAC CCA CCC CCC GAG AAT GTC CAG CTG GTG AAT CAA TAC GTA

Ser Lys Asn Val Ile Ser Ser Glu His Ile Val Glu Arg Glu Ala Glu
TCT AAA AAT GTC ATC TCT AGC GAG CAT ATT GTT GAG AGA GAG GCG GAG   288
||| ||| ||  ||| ||| ||  ||  ||| ||| ||| ||| ||| ||| ||  ||  |||
TCT AAA AAC GTC ATC TCC AGT GAG CAT ATT GTT GAG AGA GAA GCA GAG
```

FIG. 31L'

```
Ser Ser Phe Ser Thr Ser His Tyr Thr Ser Thr Ala His His Ser Thr
AGC TCT TTT TCC ACC AGT CAC TAC ACT TCG ACA GCT CAT CAT TCC ACT     336
|   ||  ||| ||| ||| ||| ||| ||  ||| ||  ||| ||  ||| ||  ||| |||
ACA TCC TTT TCC ACC AGT CAC TAT ACT TCC ACA GCC CAT CAC TCC ACT
T

Thr Val Thr Gln Thr Pro Ser His Ser Trp Ser Asn Gly His Thr Glu
ACT GTC ACT CAG ACT CCC AGT CAC AGC TGG AGC AAT GGA CAC ACT GAA     384
||| ||| ||  ||| ||| ||  ||  ||| ||| ||| ||| ||  ||| ||| ||| |||
ACT GTC ACC CAG ACT CCT AGC CAC AGC TGG AGC AAC GGA CAC ACT GAA

Ser Ile Ile Ser Glu Ser His Ser Val Ile Val Met Ser Ser Val Glu
AGC ATC ATT TCG GAA AGC CAC TCT GTC ATC GTG ATG TCA TCC GTA GAA     432
||| |||  || ||  ||| ||| ||| ||| ||  ||| ||| ||| ||| ||| ||| |||
AGC ATC CTT TCC GAA AGC CAC TCT GTA ATC GTG ATG TCA TCC GTA GAA
        L

Asn Ser Arg His Ser Ser Pro Thr Gly Gly Pro Arg Gly Arg Leu Asn
AAC AGT AGG CAC AGC AGC CCG ACT GGG GGC CCG AGA GGA CGT CTC AAT     480
||| ||| ||| ||| ||| ||| ||  ||| ||| ||| ||  ||| ||| ||| ||  |||
AAC AGT AGG CAC AGC AGC CCA ACT GGG GGC CCA AGA GGA CGT CTT AAT

Gly Leu Gly Gly Pro Arg Glu Cys Asn Ser Phe Leu Arg His Ala Arg
GGC TTG GGA GGC CCT CGT GAA TGT AAC AGC TTC CTC AGG CAT GCC AGA     528
|||     ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
GGC ACA GGA GGC CCT CGT GAA TGT AAC AGC TTC CTC AGG CAT GCC AGA
    T

Glu Thr Pro Asp Ser Tyr Arg Asp Ser Pro His Ser Glu Arg
GAA ACC CCT GAC TCC TAC CGA GAC TCT CCT CAT AGT GAA AGR             569
||| ||| ||| ||  ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
GAA ACC CCT GAT TCC TAC CGA GAC TCT CCT CAT AGT GAA AGR
```

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FIG. 31M

CODING SEGMENT K: (SEQ ID NO: 161)

```
    CAT AAC CTT ATA GCT GAG CTA AGG AGA AAC AAG GCC CAC AGA TCC     46
    His Asn Leu Ile Ala Glu Leu Arg Arg Asn Lys Ala His Arg Ser

AAA TGC ATG CAG ATC CAG CTT TCC GCA ACT CAT CTT AGA GCT TCT TCC     94
Lys Cys Met Gln Ile Gln Leu Ser Ala Thr His Leu Arg Ala Ser Ser

ATT CCC CAT TGG GCT TCA TTC TCT AAG ACC CCT TGG CCT TTA GGA AG     141
Ile Pro His Trp Ala Ser Phe Ser Lys Thr Pro Trp Pro Leu Gly Arg
```

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FIG. 31N

CODING SEGMENT L: (SEQ ID NO: 147 (bovine) and 182 (human))

```
 Tyr Val Ser Ala Met Thr Thr Pro Ala Arg Met Ser Pro Val Asp
 TAT GTA TCA GCA ATG ACC ACC CCG GCT CGT ATG TCA CCT GTA GAT        46
 ||| ||  ||| ||  ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
 TAT GTG TCA GCC ATG ACC ACC CCG GCT CGT ATG TCA CCT GTA GAT

Phe His Thr Pro Ser Ser Pro Lys Ser Pro Pro Ser Glu Met Ser Pro
TTC CAC ACG CCA AGC TCC CCC AAG TCA CCC CCT TCG GAA ATG TCC CCG    94
||| ||| ||| ||| ||| ||| ||| ||  ||  ||| ||| ||| ||| ||| ||  ||
TTC CAC ACG CCA AGC TCC CCC AAA TCG CCC CCT TCG GAA ATG TCT CCA

Pro Val Ser Ser Thr Thr Val Ser Met Pro Ser Met Ala Val Ser Pro
CCC GTG TCC AGC ACG ACG GTC TCC ATG CCC TCC ATG GCG GTC AGT CCC    142
||| ||| ||| ||| | | ||| ||  ||| ||| ||  ||| ||| ||| ||| ||  |||
CCC GTG TCC AGC ATG ACG GTG TCC ATG CCT TCC ATG GCG GTC AGC CCC
                M

Phe Val Glu Glu Glu Arg Pro Leu Leu Leu Val Thr Pro Pro Arg Leu
TTC GTG GAA GAG GAG AGA CCC CTG CTC CTT GTG ACG CCA CCA CGG CTG    190
|||  || ||| ||  ||| ||| ||  ||  ||  ||  ||| ||  ||| |||  || |||
TTC ATG GAA GAA GAG AGA CCT CTA CTT CTC GTG ACA CCA CCA AGG CTG
    M

Arg Glu Lys     Tyr Asp His His Ala Gln Gln Phe Asn Ser Phe His
CGG GAG AAG ... TAT GAC CAC CAC GCC CAG CAA TTC AAC TCG TTC CAC    238
||| ||| |||     | | ||| ||  ||| |   ||| ||  ||| | | ||  ||| |||
CGG GAG AAG AAG TTT GAC CAT CAC CCT CAG CAG TTC AGC TCC TTC CAC
            K   F               P

Cys Asn Pro Ala His Glu Ser Asn Ser Leu Pro Pro Ser Pro Leu Arg
TGC AAC CCC GCG CAT GAG AGC AAC AGC CTG CCC CCC AGC CCC TTG AGG    286
  | ||| ||| ||| ||| ||  ||  ||| ||| ||  ||   |  ||| ||| ||| |||
CAC AAC CCC GCG CAT GAC AGT AAC AGC CTC CCT GCT AGC CCC TTG AGG
H                   D                       A
```

FIG. 31N'

```
Ile Val Glu Asp Glu Glu Tyr Glu Thr Thr Gln Glu Tyr Glu Pro Ala
ATA GTG GAG GAT GAG GAA TAT GAA ACG ACC CAG GAG TAC GAA CCA GCT     334
||| ||| ||| ||| ||| ||  ||| ||| ||| ||| ||  ||| ||| ||  ||| ||
ATA GTG GAG GAT GAG GAG TAT GAA ACG ACC CAA GAG TAC GAG CCA GCC

Gln Glu Pro Val Lys Lys Leu Thr Asn Ser Ser Arg Arg Ala Lys Arg
CAA GAG CCG GTT AAG AAA CTC ACC AAC AGC AGC CGG CGG GCC AAA AGA     382
||| ||| ||  ||| ||| ||| |||  || |||     ||| ||| ||| ||| ||| |||
CAA GAG CCT GTT AAG AAA CTC GCC AA. ..T AGC CGG CGG GCC AAA AGA
                            A

Thr Lys Pro Asn Gly His Ile Ala His Arg Leu Glu Met Asp Asn Asn
ACC AAG CCC AAT GGT CAC ATT GCC CAC AGG TTG GAA ATG GAC AAC AAC     430
||| ||| ||| ||| ||  ||| ||| ||  | | ||  ||| |||  || ||| | | |||
ACC AAG CCC AAT GGC CAC ATT GCT AAC AGA TTG GAA GTG GAC AGC AAC
                                N               V       S

Thr Gly Ala Asp Ser Ser Asn Ser Glu Ser Glu Thr Glu Asp Glu Arg
ACA GGC GCT GAC AGC AGT AAC TCA GAG AGC GAA ACA GAG GAT GAA AGA     478
||| ||   |   |  ||| ||| ||| ||| ||| ||  ||| ||| ||  ||| ||| |||
ACA AGC TCC CAG AGC AGT AAC TCA GAG AGT GAA ACA GAA GAT GAA AGA
     S   S   Q
```

FIG. 31N"

```
Val Gly Glu Asp Thr Pro Phe Leu Ala Ile Gln Asn Pro Leu Ala Ala
GTA GGA GAA GAT ACG CCT TTC CTG GCC ATA CAG AAC CCC CTG GCA GCC    526
||| ||  ||| ||| ||| ||| ||| ||| | | ||| ||| ||| ||| ||| ||| |||
GTA GGT GAA GAT ACG CCT TTC CTG GGC ATA CAG AAC CCC CTG GCA GCC
                                G

Ser Leu Glu Ala Ala Pro Ala Phe Arg Leu Val Asp Ser Arg Thr Asn
AGT CTC GAG GCG GCC CCT GCC TTC CGC CTG GTC GAC AGC AGG ACT AAC    574
||| ||  ||| ||   |  ||| ||| ||| ||| ||| |   ||| ||| ||| ||| |||
AGT CTT GAG GCA ACA CCT GCC TTC CGC CTG GCT GAC AGC AGG ACT AAC
                T                       A

Pro Thr Gly Gly Phe Ser Pro Gln Glu Glu Leu Gln Ala Arg Leu Ser
CCA ACA GGC GGC TTC TCT CCG CAG GAA GAA TTG CAG GCC AGG CTC TCC    622
|||  || |||  || ||| ||   |  ||| ||| |||  |  ||| ||| ||| ||   ||
CCA GCA GGC CGC TTC TCG ACA CAG GAA GAA ATC CAG GCC AGG CTG TCT
    A       R           T               I

Gly Val Ile Ala Asn Gln Asp Pro Ile Ala Val *
GGT GTA ATC GCT AAC CAA GAC CCT ATC GCT GTC TAA AAC CGA AAT ACA    672
 || ||| ||  ||| ||| ||| ||| ||| ||  ||| ||  ||| ||| | | ||| | |
AGT GTA ATT GCT AAC CAA GAC CCT ATT GCT GTA TAA AAC CTA AAT AAA
S

CCC ATA GAT TCA CCT GTA AAA CTT TAT TTT ATA TAA TAA AGT ATT CCA    718
| | ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
CAC ATA GAT TCA CCT GTA AAA CTT TAT TTT ATA TAA TAA AGT ATT CCA

CCT TAA ATT AAA CAA                                                733
||| ||| ||| ||| |||
CCT TAA ATT AAA CAA
```

FIG. 31O

HUMAN CODING SEGMENT E:
(SEQ ID NO: 163)

```
ATG AGA TGG CGA CGC GCC CCG CGC CGC TCC GGG CGT CCC GGC CCC CGG   48
Met Arg Trp Arg Arg Ala Pro Arg Arg Ser Gly Arg Pro Gly Pro Arg

GCC CAG CGC CCC GGC TCC GCC GCC CGC TCG TCG CCG CCG CTG CCG CTG   96
Ala Gln Arg Pro Gly Ser Ala Ala Arg Ser Ser Pro Pro Leu Pro Leu

CTG CCA CTA CTG CTG CTG CTG GGG ACC GCG GCC CTG GCG CCG GGG GCG  144
Leu Pro Leu Leu Leu Leu Leu Gly Thr Ala Ala Leu Ala Pro Gly Ala

GCG GCC GGC AAC GAG GCG GCT CCC GCG GGG GCC TCG GTG TGC TAC TCG  192
Ala Ala Gly Asn Glu Ala Ala Pro Ala Gly Ala Ser Val Cys Tyr Ser

TCC CCG CCC AGC GTG GGA TCG GTG CAG GAG CTA GCT CAG CGC GCC GCG  240
Ser Pro Pro Ser Val Gly Ser Val Gln Glu Leu Ala Gln Arg Ala Ala

GTG GTG ATC GAG GGA AAG GTG CAC CCG CAG CGG CGG CAG CAG GGG GCA  288
Val Val Ile Glu Gly Lys Val His Pro Gln Arg Arg Gln Gln Gly Ala

CTC GAC AGG AAG GCG GCG GCG GCG GCG GGC GAG GCA GGG GCG TGG GGC  336
Leu Asp Arg Lys Ala Ala Ala Ala Ala Gly Glu Ala Gly Ala Trp Gly

GGC GAT CGC GAG CCG CCA GCC GCG GGC CCA CGG GCG CTG GGG CCG CCC  384
Gly Asp Arg Glu Pro Pro Ala Ala Gly Pro Arg Ala Leu Gly Pro Pro

GCC GAG GAG CCG CTG CTC GCC GCC AAC GGG ACC GTG CCC TCT TGG CCC  432
Ala Glu Glu Pro Leu Leu Ala Ala Asn Gly Thr Val Pro Ser Trp Pro

ACC GCC CCG GTG CCC AGC GCC GGC GAG CCC GGG GAG GAG GCG CCC TAT  480
Thr Ala Pro Val Pro Ser Ala Gly Glu Pro Gly Glu Glu Ala Pro Tyr

CTG GTG AAG GTG CAC CAG GTG TGG GCG GTG AAA GCC GGG GGC TTG AAG  528
Leu Val Lys Val His Gln Val Trp Ala Val Lys Ala Gly Gly Leu Lys

AAG GAC TCG CTG CTC ACC GTG CGC CTG GGG ACC TGG GGC CAC CCC GCC  576
Lys Asp Ser Leu Leu Thr Val Arg Leu Gly Thr Trp Gly His Pro Ala

TTC CCC TCC TGC GGG AGG CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC  624
Phe Pro Ser Cys Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe

ATG GAG CCC GAC GCC AAC AGC ACC AGC CGC GCG CCG GCC GCC TTC CGA  672
Met Glu Pro Asp Ala Asn Ser Thr Ser Arg Ala Pro Ala Ala Phe Arg

GCC TCT TTC CCC CCT CTG GAG ACG GGC CGG AAC CTC AAG AAG GAG GTC  720
Ala Ser Phe Pro Pro Leu Glu Thr Gly Arg Asn Leu Lys Lys Glu Val

AGC CGG GTG CTG TGC AAG CGG TGC G                                745
Ser Arg Val Leu Cys Lys Arg Cys
```

8 3 95 5002б

FIG. 32A

GGF2BPP5 Nucleotide Sequence & Deduced Protein Sequence

SEQ ID NO: 148:

```
AGTTTCCCCC CCCAACTTGT CGGAACTCTG GGCTCGCGCG CAGGGCAGGA GCGGAGCGGC       60

GGCGGCTGCC CAGGCGATGC GAGCGCGGGC CGGACGGTAA TCGCCTCTCC CTCCTCGGGC      120

TGCGAGCGCG CCGGACCGAG GCAGCGACAG GAGCGGACCG CGGCGGGAAC CGAGGACTCC      180

CCAGCGGCGC GCCAGCAGGA GCCACCCCGC GAGCGTGCGA CCGGGACGGA GCGCCCGCCA      240

GTCCCAGGTG GCCCGGACCG CACGTTGCGT CCCCGCGCTC CCCGCCGGCG ACAGGAGACG      300

CTCCCCCCCA CGCCGCGCGC GCCTCGGCCC GGTCGCTGGC CCGCCTCCAC TCCGGGGACA      360

AACTTTTCCC GAAGCCGATC CCAGCCCTCG GACCCAAACT TGTCGCGCGT CGCCTTCGCC      420

GGGAGCCGTC CGCGCAGAGC GTGCACTTCT CGGGCGAG ATG TCG GAG CGC AGA          475
                                         Met Ser Glu Arg Arg

GAA GGC AAA GGC AAG GGG AAG GGC GGC AAG AAG GAC CGA GGC TCC GGG        523
Glu Gly Lys Gly Lys Gly Lys Gly Gly Lys Lys Asp Arg Gly Ser Gly

AAG AAG CCC GTG CCC GCG GCT GGC GGC CCG AGC CCA GCC TTG CCT CCC        571
Lys Lys Pro Val Pro Ala Ala Gly Gly Pro Ser Pro Ala Leu Pro Pro
CGC TTG AAA GAG ATG AAG ATG CAG GAG TCT GTG GCA GGT TCC AAA CTA        619
Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Val Ala Gly Ser Lys Leu

GTG CTT CGG TGC GAG ACC AGT TCT GAA TAC TCC TCT CTC AAG TTC AAG        667
Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser Ser Leu Lys Phe Lys

TGG TTC AAG AAT GGG AGT GAA TTA AGC CGA AAG AAC AAA CCA CAA AAC        715
Trp Phe Lys Asn Gly Ser Glu Leu Ser Arg Lys Asn Lys Pro Gln Asn

ATC AAG ATA CAG AAA AGG CCG GGG AAG TCA GAA CTT CGC ATT AGC AAA        763
Ile Lys Ile Gln Lys Arg Pro Gly Lys Ser Glu Leu Arg Ile Ser Lys

GCG TCA CTG GCT GAT TCT GGA GAA TAT ATG TGC AAA GTG ATC AGC AAA        811
Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys Lys Val Ile Ser Lys
```

8 3 95 50026

FIG. 32B

GGF2BPP5 Nucleotide Sequence & Deduced Protein Sequence

CTA GGA AAT GAC AGT GCC TCT GCC AAC ATC ACC ATT GTG GAG TCA AAC 859
Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr Ile Val Glu Ser Asn

GAG ATC ACC ACT GGC ATG CCA GCC TCA ACT GAG ACA GCG TAT GTG TCT 907
Glu Ile Thr Thr Gly Met Pro Ala Ser Thr Glu Thr Ala Tyr Val Ser

TCA GAG TCT CCC ATT AGA ATA TCA GTA TCA ACA GAA GGA ACA AAT ACT 955
Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr Glu Gly Thr Asn Thr

TCT TCA TCC ACA TCC ACA TCT ACA GCT GGG ACA AGC CAT CTT GTC AAG 1003
Ser Ser Ser Thr Ser Thr Ser Thr Ala Gly Thr Ser His Leu Val Lys

TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT GGA GGC GAG TGC TTC 1051
Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Cys Phe

ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC TTG TGC AAG TGC CCA 1099
Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr Leu Cys Lys Cys Pro

AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC GTA ATG GCC AGC TTC 1147
Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser Phe

TAC AGT ACG TCC ACT CCC TTT CTG TCT CTG CCT GAA TAGGCGCATG 1193
Tyr Ser Thr Ser Thr Pro Phe Leu Ser Leu Pro Glu

CTCAGTCGGT GCCGTTTTCT TGTTGCCGCA TCTCCCCTCA GATTCAACCT AGAGCTAGAT 1253

GCGTTTTACC AGGTCTAACA TTGACTGCCT CTGCCTGTCG CATGAGAACA TTAACACAAG 1313

CGATTGTATG ACTTCCTCTG TCCGTGACTA GTGGGCTCTG AGCTACTCGT AGGTGCGTAA 1373

GGCTCCAGTG TTTCTGAAAT TGATCTTGAA TTACTGTGAT ACGACATGAT AGTCCCTCTC 1433

ACCCAGTGCA ATGACAATAA AGGCCTTGAA AAGTCTCACT TTTATTGAGA AAATAAAAAT 1493

CGTTCCACGG GACAGTCCCT CTTCTTTATA AAATGACCCT ATCCTTGAAA AGGAGGTGTG 1553

TTAAGTTGTA ACCAGTACAC ACTTGAAATG ATGGTAAGTT CGCTTCGGTT CAGAATGTGT 1613

TCTTTCTGAC AAATAAACAG AATAAAAAAA AAAAAAAAAA A 1654

8 3 95 50026

FIG. 33A

GGF2BPP2 Nucleotide Sequence & Deduced Protein Sequence

SEQ ID NO: 149:

```
CAT CAN GTG TGG GCG GCG AAA GCC GGG GGC TTG AAG AAG GAC TCG CTG    48
His Gln Val Trp Ala Ala Lys Ala Gly Gly Leu Lys Lys Asp Ser Leu

CTC ACC GTG CGC CTG GGC GCC TGG GGC CAC CCC GCC TTC CCC TCC TGC    96
Leu Thr Val Arg Leu Gly Ala Trp Gly His Pro Ala Phe Pro Ser Cys

GGG CGC CTC AAG GAG GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC GAG   144
Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro Glu

GCC AAC AGC AGC GGC GGG CCC GGC CGC CTT CCG AGC CTC CTT CCC CCC   192
Ala Asn Ser Ser Gly Gly Pro Gly Arg Leu Pro Ser Leu Leu Pro Pro

TCT CGA GAC GGG CCG GAA CCT CAA GAA GGA GGT CAG CCG GGT GCT GTG   240
Ser Arg Asp Gly Pro Glu Pro Gln Glu Gly Gly Gln Pro Gly Ala Val

CAA CGG TGC GCC TTG CCT CCC CGC TTG AAA GAG ATG AAG AGT CAG GAG   288
Gln Arg Cys Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu

TCT GTG GCA GGT TCC AAA CTA GTG CTT CGG TGC GAG ACC AGT TCT GAA   336
Ser Val Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu

TAC TCC TCT CTC AAG TTC AAG TGG TTC AAG AAT GGG AGT GAA TTA AGC   384
Tyr Ser Ser Leu Lys Phe Lys Trp Phe Lys Asn Gly Ser Glu Leu Ser

CGA AAG AAC AAA CCA GAA AAC ATC AAG ATA CAG AAA AGG CCG GGG AAG   432
Arg Lys Asn Lys Pro Glu Asn Ile Lys Ile Gln Lys Arg Pro Gly Lys

TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA TAT   480
Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr

ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC AAC   528
Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn
```

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FIG. 33B

GGF2BPP2 Nucleotide Sequence & Deduced Protein Sequence

```
ATC ACC ATT GTG GAG TCA AAC GCC ACA TCC ACA TCT ACA GCT GGG ACA      576
Ile Thr Ile Val Glu Ser Asn Ala Thr Ser Thr Ser Thr Ala Gly Thr

AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT      624
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC      672
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr

TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT      720
Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn

GTG CCC ATG AAA GTC CAA ACC CAA GAA AAG TGC CCA AAT GAG TTT ACT      768
Val Pro Met Lys Val Gln Thr Gln Glu Lys Cys Pro Asn Glu Phe Thr

GGT GAT CGC TGC CAA AAC TAC GTA ATG GCC AGC TTC TAC AGT ACG TCC      816
Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser Phe Tyr Ser Thr Ser

ACT CCC TTT CTG TCT CTG CCT GAA TAGCGCATCT CAGTCGGTGC CGCTTTCTTG     870
Thr Pro Phe Leu Ser Leu Pro Glu

TTGCCGCATC TCCCCTCAGA TTCCNCCTAG AGCTAGATGC GTTTTACCAG GTCTAACATT    930

GACTGCCTCT GCCTGTCGCA TGAGAACATT AACACAAGCG ATTGTATGAC TTCCTCTGTC    990

CGTGACTAGT GGGCTCTGAG CTACTCGTAG GTGCGTAAGG CTCCAGTGTT TCTGAAATTG   1050

ATCTTGAATT ACTGTGATAC GACATGATAG TCCCTCTCAC CCAGTGCAAT GACAATAAAG   1110

GCCTTGAAAA GTCAAAAAAA AAAAAAAAAA                                    1140
```

8 3 95 50026

FIG. 34A

GGF2BPP4 Nucleotide Sequence & Deduced Protein Sequence

SEQ ID NO: 150:

```
G AAG TCA GAA CTT CGC ATT AGC AAA GCG TCA CTG GCT GAT TCT GGA GAA      49
  Lys Ser Glu Leu Arg Ile Ser Lys Ala Ser Leu Ala Asp Ser Gly Glu

TAT ATG TGC AAA GTG ATC AGC AAA CTA GGA AAT GAC AGT GCC TCT GCC        97
Tyr Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala

AAC ATC ACC ATT GTG GAG TCA AAC GCC ACA TCC ACA TCT ACA GCT GGG       145
Asn Ile Thr Ile Val Glu Ser Asn Ala Thr Ser Thr Ser Thr Ala Gly

ACA AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG       193
Thr Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val

AAT GGA GGC GAC TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA       241
Asn Gly Gly Asp Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg

TAC TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG       289
Tyr Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu

AAT GTG CCC ATG AAA GTC CAA ACC CAA GAA AAA GCG GAG GAG CTC TAC       337
Asn Val Pro Met Lys Val Gln Thr Gln Glu Lys Ala Glu Glu Leu Tyr

CAG AAG AGA GTG CTC ACC ATT ACC GGC ATT TGC ATC GCG CTG CTC GTG       385
Gln Lys Arg Val Leu Thr Ile Thr Gly Ile Cys Ile Ala Leu Leu Val

GTT GGC ATC ATG TGT GTG GTG GTC TAC TGC AAA ACC AAG AAA CAA CGG       433
Val Gly Ile Met Cys Val Val Val Tyr Cys Lys Thr Lys Lys Gln Arg

AAA AAG CTT CAT GAC CGG CTT CGG CAG AGC CTT CGG TCT GAA AGA AAC       481
Lys Lys Leu His Asp Arg Leu Arg Gln Ser Leu Arg Ser Glu Arg Asn

ACC ATG ATG AAC GTA GCC AAC GGG CCC CAC CAC CCC AAT CCG CCC CCC       529
Thr Met Met Asn Val Ala Asn Gly Pro His His Pro Asn Pro Pro Pro

GAG AAC GTG CAG CTG GTG AAT CAA TAC GTA TCT AAA AAT GTC ATC TCT       577
Glu Asn Val Gln Leu Val Asn Gln Tyr Val Ser Lys Asn Val Ile Ser
```

8 3 95 50026

FIG. 34B

GGF2BPP4 Nucleotide Sequence & Deduced Protein Sequence

```
AGC GAG CAT ATT GTT GAG AGA GAG GCG GAG AGC TCT TTT TCC ACC AGT      625
Ser Glu His Ile Val Glu Arg Glu Ala Glu Ser Ser Phe Ser Thr Ser

CAC TAC ACT TCG ACA GCT CAT CAT TCC ACT ACT GTC ACT CAG ACT CCC      673
His Tyr Thr Ser Thr Ala His His Ser Thr Thr Val Thr Gln Thr Pro

AGT CAC AGC TGG AGC AAT GGA CAC ACT GAA AGC ATC ATT TCG GAA AGC      721
Ser His Ser Trp Ser Asn Gly His Thr Glu Ser Ile Ile Ser Glu Ser

CAC TCT GTC ATC GTG ATG TCA TCC GTA GAA AAC AGT AGG CAC AGC AGC      769
His Ser Val Ile Val Met Ser Ser Val Glu Asn Ser Arg His Ser Ser

CCG ACT GGG GGC CCG AGA GGA CGT CTC AAT GGC TTG GGA GGC CCT CGT      817
Pro Thr Gly Gly Pro Arg Gly Arg Leu Asn Gly Leu Gly Gly Pro Arg

GAA TGT AAC AGC TTC CTC AGG CAT GCC AGA GAA ACC CCT GAC TCC TAC      865
Glu Cys Asn Ser Phe Leu Arg His Ala Arg Glu Thr Pro Asp Ser Tyr

CGA GAC TCT CCT CAT AGT GAA AGA CAT AAC CTT ATA GCT GAG CTA AGG      913
Arg Asp Ser Pro His Ser Glu Arg His Asn Leu Ile Ala Glu Leu Arg

AGA AAC AAG GCC CAC AGA TCC AAA TGC ATG CAG ATC CAG CTT TCC GCA      961
Arg Asn Lys Ala His Arg Ser Lys Cys Met Gln Ile Gln Leu Ser Ala

ACT CAT CTT AGA GCT TCT TCC ATT CCC CAT TGG GCT TCA TTC TCT AAG      1009
Thr His Leu Arg Ala Ser Ser Ile Pro His Trp Ala Ser Phe Ser Lys

ACC CCT TGG CCT TTA GGA AGG TAT GTA TCA GCA ATG ACC ACC CCG GCT      1057
Thr Pro Trp Pro Leu Gly Arg Tyr Val Ser Ala Met Thr Thr Pro Ala

CGT ATG TCA CCT GTA GAT TTC CAC ACG CCA AGC TCC CCC AAG TCA CCC      1105
Arg Met Ser Pro Val Asp Phe His Thr Pro Ser Ser Pro Lys Ser Pro

CCT TCG GAA ATG TCC CCG CCC GTG TCC AGC ACG ACG GTC TCC ATG CCC      1153
Pro Ser Glu Met Ser Pro Pro Val Ser Ser Thr Thr Val Ser Met Pro
```

8 3 95 50026

FIG. 34C

GGF2BPP4 Nucleotide Sequence & Deduced Protein Sequence

TCC ATG GCG GTC AGT CCC TTC GTG GAA GAG GAG AGA CCC CTG CTC CTT 1201
Ser Met Ala Val Ser Pro Phe Val Glu Glu Glu Arg Pro Leu Leu Leu

GTG ACG CCA CCA CGG CTG CGG GAG AAG TAT GAC CAC CAC GCC CAG CAA 1249
Val Thr Pro Pro Arg Leu Arg Glu Lys Tyr Asp His His Ala Gln Gln

TTC AAC TCG TTC CAC TGC AAC CCC GCG CAT GAG AGC AAC AGC CTG CCC 1297
Phe Asn Ser Phe His Cys Asn Pro Ala His Glu Ser Asn Ser Leu Pro

CCC AGC CCC TTG AGG ATA GTG GAG GAT GAG GAA TAT GAA ACG ACC CAG 1345
Pro Ser Pro Leu Arg Ile Val Glu Asp Glu Glu Tyr Glu Thr Thr Gln

GAG TAC GAA CCA GCT CAA GAG CCG GTT AAG AAA CTC ACC AAC AGC AGC 1393
Glu Tyr Glu Pro Ala Gln Glu Pro Val Lys Lys Leu Thr Asn Ser Ser

CGG CGG GCC AAA AGA ACC AAG CCC AAT GGT CAC ATT GCC CAC AGG TTG 1441
Arg Arg Ala Lys Arg Thr Lys Pro Asn Gly His Ile Ala His Arg Leu

GAA ATG GAC AAC AAC ACA GGC GCT GAC AGC AGT AAC TCA GAG AGC GAA 1489
Glu Met Asp Asn Asn Thr Gly Ala Asp Ser Ser Asn Ser Glu Ser Glu

ACA GAG GAT GAA AGA GTA GCA GAA GAT ACG CCT TTC CTG GCC ATA CAG 1537
Thr Glu Asp Glu Arg Val Gly Glu Asp Thr Pro Phe Leu Ala Ile Gln

AAC CCC CTG GCA GCC AGT CTC GAG GCG GCC CCT GCC TTC CGC CTG GTC 1585
Asn Pro Leu Ala Ala Ser Leu Glu Ala Ala Pro Ala Phe Arg Leu Val

GAC AGC AGG ACT AAC CCA ACA GGC GGC TTC TCT CCG CAG GAA GAA TTG 1633
Asp Ser Arg Thr Asn Pro Thr Gly Gly Phe Ser Pro Gln Glu Glu Leu

CAG GCC AGG CTC TCC GGT GTA ATC GCT AAC CAA GAC CCT ATC GCT GTC 1681
Gln Ala Arg Leu Ser Gly Val Ile Ala Asn Gln Asp Pro Ile Ala Val

TAAAACCGAA ATACACCCAT AGATTCACCT GTAAAACTTT ATTTTATATA ATAAAGTATT 1741

CCACCTTAAA TTAAACAAAA AAA 1764

FIG. 35

```
                                *          *          * *         *
GGF2bpp5  (SEQ ID NO: 151)  KCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCPNEFTGDRCQNYVMASFY
GGF2bpp4  (SEQ ID NO: 152)  KCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCQPGFTGARCTENVPMKVQ
hEGF      (SEQ ID NO: 153)  ECLRKYKDFCIH GECKYVKELRAPS    CKCQQEYFGERCGEKSMKTHS
```

FIG. 36

200 kDa Tyrosine Phosphorylation Compared with Mitogenic Activity

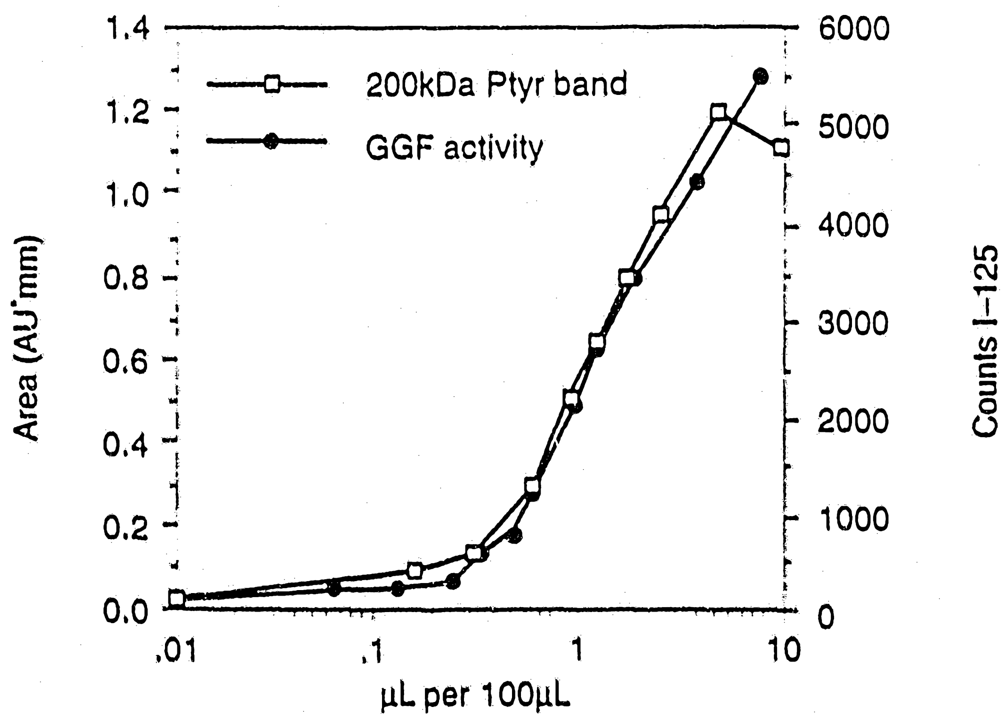


FIG. 37A GGF/Heregulin Splicing Variants

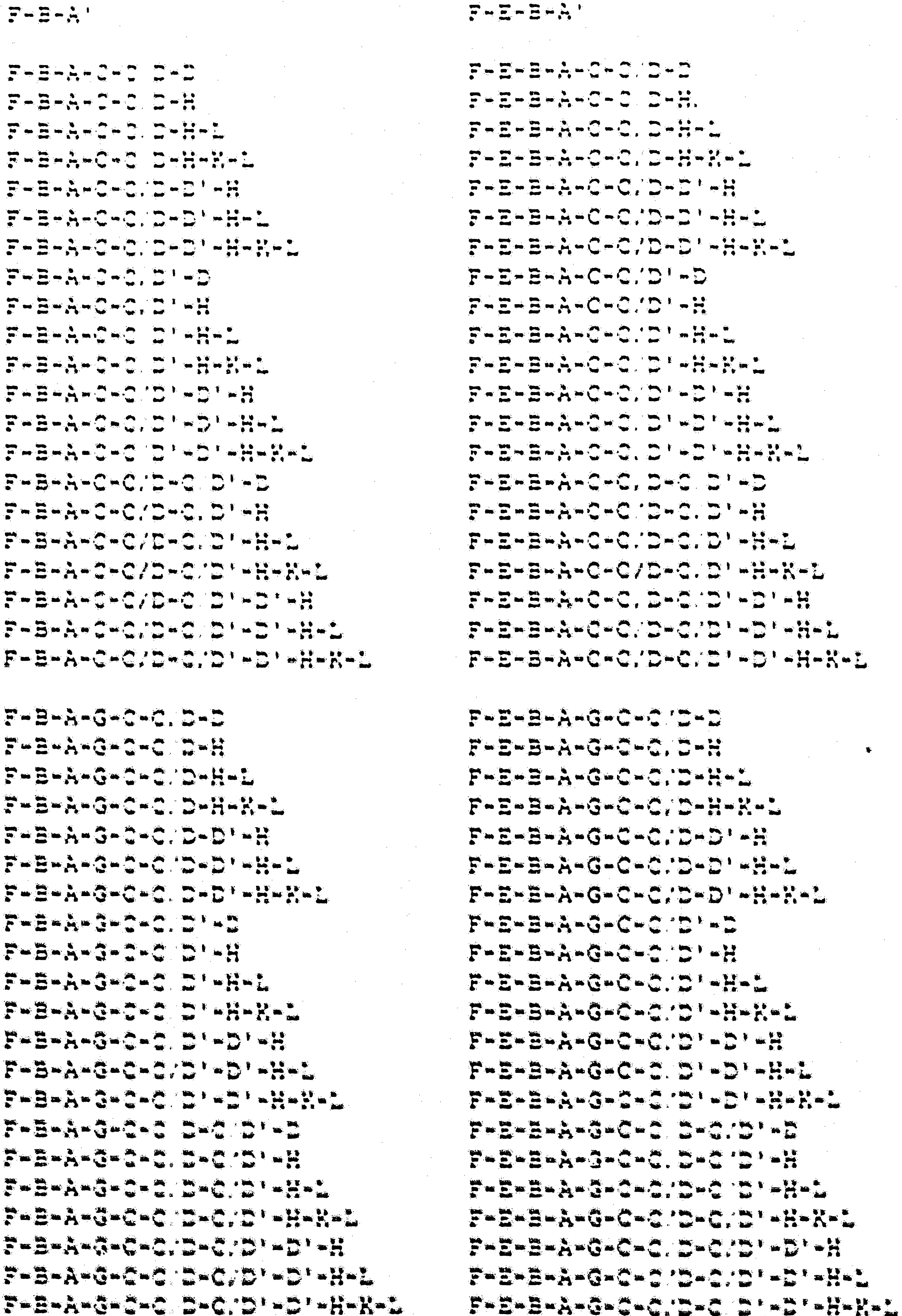


FIG. 37B

GGF/Heregulin Splicing Variants

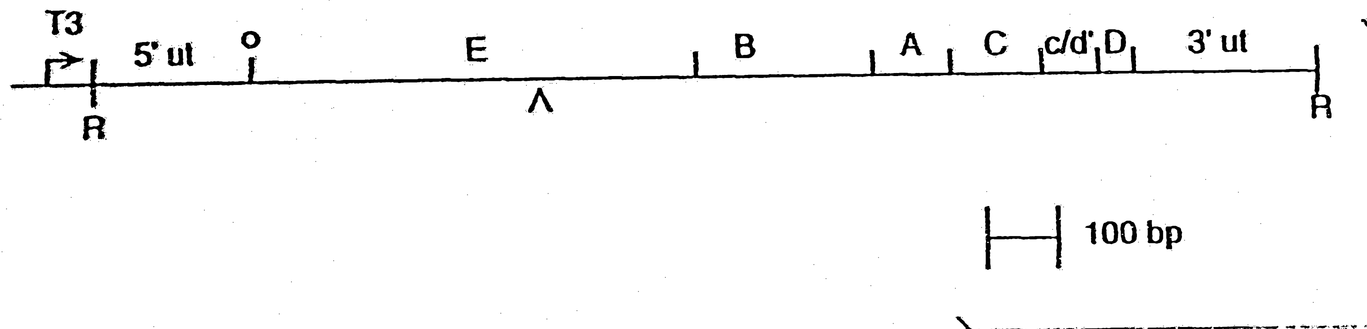
E-B-A'

E-B-A-C-C/D-D
E-B-A-C-C/D-H
E-B-A-C-C/D-H-L
E-B-A-C-C/D-H-K-L
E-B-A-C-C/D-D'-H
E-B-A-C-C/D-D'-H-L
E-B-A-C-C/D-D'-H-K-L
E-B-A-C-C/D'-D
E-B-A-C-C/D'-H
E-B-A-C-C/D'-H-L
E-B-A-C-C/D'-H-K-L
E-B-A-C-C/D'-D'-H
E-B-A-C-C/D'-D'-H-L
E-B-A-C-C/D'-D'-H-K-L
E-B-A-C-C/D-C/D'-D
E-B-A-C-C/D-C/D'-H
E-B-A-C-C/D-C/D'-H-L
E-B-A-C-C/D-C/D'-H-K-L
E-B-A-C-C/D-C/D'-D'-H
E-B-A-C-C/D-C/D'-D'-H-L
E-B-A-C-C/D-C/D'-D'-H-K-L

E-B-A-G-C-C/D-D
E-B-A-G-C-C/D-H
E-B-A-G-C-C/D-H-L
E-B-A-G-C-C/D-H-K-L
E-B-A-G-C-C/D-D'-H
E-B-A-G-C-C/D-D'-H-L
E-B-A-G-C-C/D-D'-H-K-L
E-B-A-G-C-C/D'-D
E-B-A-G-C-C/D'-H
E-B-A-G-C-C/D'-H-L
E-B-A-G-C-C/D'-H-K-L
E-B-A-G-C-C/D'-D'-H
E-B-A-G-C-C/D'-D'-H-L
E-B-A-G-C-C/D'-D'-H-K-L
E-B-A-G-C-C/D-C/D'-D
E-B-A-G-C-C/D-C/D'-H
E-B-A-G-C-C/D-C/D'-H-L
E-B-A-G-C-C/D-C/D'-H-K-L
E-B-A-G-C-C/D-C/D'-D'-H
E-B-A-G-C-C/D-C/D'-D'-H-L
E-B-A-G-C-C/D-C/D'-D'-H-K-L

FIG. 38

GGF2HBS5



8 3 95 50026

FIG. 39

EGFL1

SEQ ID NO: 154:

```
AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT    48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC    96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr

TTG TGC AAG TGC CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC   144
Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr

GTA ATG GCC AGC TTC TAC AGT ACG TCC ACT CCC TTT CTG TCT CTG CCT   192
Val Met Ala Ser Phe Tyr Ser Thr Ser Thr Pro Phe Leu Ser Leu Pro

GAA TAG                                                           198
Glu
```

0 3 95 50026

FIG. 40

EGFL2

SEQ ID NO: 155:

```
AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT    48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC    96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr

TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT   144
Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn

GTG CCC ATG AAA GTC CAA ACC CAA GAA AAA GCG GAG GAG CTC TAC TAA   192
Val Pro Met Lys Val Gln Thr Gln Glu Lys Ala Glu Glu Leu Tyr
```

FIG. 41

EGFL3

SEQ ID NO: 156:

```
AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT    48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC    96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr

TTG TGC AAG TGC CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC   144
Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr

GTA ATG GCC AGC TTC TAC AAA GCG GAG GAG CTC TAC TAA               183
Val Met Ala Ser Phe Tyr Lys Ala Glu Glu Leu Tyr                     .
```

8 3 95 F0026

FIG. 42

EGFL4

SEQ ID NO: 157:

```
AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT    48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC    96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr

TTG TGC AAG TGC CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC   144
Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr

GTA ATG GCC AGC TTC TAC AAG CAT CTT GGG ATT GAA TTT ATG GAG AAA   192
Val Met Ala Ser Phe Tyr Lys His Leu Gly Ile Glu Phe Met Glu Lys

GCG GAG GAG CTC TAC TAA                                           210
Ala Glu Glu Leu Tyr
```

8 3 95 50026

FIG. 43

EGFL5

SEQ ID NO: 158:

```
AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT     48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC     96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr

TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT    144
Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn

GTG CCC ATG AAA GTC CAA ACC CAA GAA AAG TGC CCA AAT GAG TTT ACT    192
Val Pro Met Lys Val Gln Thr Gln Glu Lys Cys Pro Asn Glu Phe Thr

GGT GAT CGC TGC CAA AAC TAC GTA ATG GCC AGC TTC TAC AGT ACG TCC    240
Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser Phe Tyr Ser Thr Ser

ACT CCC TTT CTG TCT CTG CCT GAA TAG                                267
Thr Pro Phe Leu Ser Leu Pro Glu
```

FIG. 44

EGFL6

SEQ ID NO: 159:

```
AGC CAT CTT GTC AAG TGT GCA GAG AAG GAG AAA ACT TTC TGT GTG AAT     48
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn

GGA GGC GAG TGC TTC ATG GTG AAA GAC CTT TCA AAT CCC TCA AGA TAC     96
Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr

TTG TGC AAG TGC CAA CCT GGA TTC ACT GGA GCG AGA TGT ACT GAG AAT    144
Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn

GTG CCC ATG AAA GTC CAA ACC CAA GAA AAG TGC CCA AAT GAG TTT ACT    192
Val Pro Met Lys Val Gln Thr Gln Glu Lys Cys Pro Asn Glu Phe Thr

GGT GAT CGC TGC CAA AAC TAC GTA ATG GCC AGC TTC TAC AAA GCG GAG    240
Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser Phe Tyr Lys Ala Glu

GAG CTC TAC TAA                                                    252
Glu Leu Tyr
```

8 3 95 50026

FIG. 45A

Nucleotide Sequence & Deduced Acid Sequence of GGF2HBS5

SEQ ID NO: 21:

```
GGAATTCCTT TTTTTTTTTT TTTTTTTCTT NNTTTTTTTT TGCCCTTATA CCTCTTCGCC      60

TTTCTGTGGT TCCATCCACT TCTTCCCCCT CCTCCTCCCA TAAACAACTC TCCTACCCCT     120

GCACCCCCAA TAAATAAATA AAAGGAGGAG GGCAAGGGGG GAGGAGGAGG AGTGGTGCTG     180

CGAGGGGAAG GAAAAGGGAG GCAGCGCGAG AAGAGCCGGG CAGAGTCCGA ACCGACAGCC     240

AGAAGCCCGC ACGCACCTCG CACC ATG AGA TGG CGA CGC GCC CCG CGC CGC        291
                           Met Arg Trp Arg Arg Ala Pro Arg Arg

TCC GGG CGT CCC GGC CCC CGG GCC CAG CGC CCC GGC TCC GCC GCC CGC       339
Ser Gly Arg Pro Gly Pro Arg Ala Gln Arg Pro Gly Ser Ala Ala Arg

TCG TCG CCG CCG CTG CCG CTG CTG CCA CTA CTG CTG CTG CTG GGG ACC       387
Ser Ser Pro Pro Leu Pro Leu Leu Pro Leu Leu Leu Leu Leu Gly Thr
                                        Val Cys Leu Leu Thr Val
                                                    GGF II 09

GCG GCC CTG GCG CCG GGG GCG GCG GCC GGC AAC GAG GCG GCT CCC GCG       435
Ala Ala Leu Ala Pro Gly Ala Ala Ala Gly Asn Glu Ala Ala Pro Ala
Ala Ala Leu Pro Pro

GGG GCC TCG GTG TGC TAC TCG TCC CCG CCC AGC GTG GGA TCG GTG CAG       483
Gly Ala Ser Val Cys Tyr Ser Ser Pro Pro Ser Val Gly Ser Val Gln
                        Ala Ser Pro Val Ser Val Gly Ser Val Gln
                                            GGF II 08

GAG CTA GCT CAG CGC|GCC GCG GTG GTG ATC GAG GGA AAG GTG CAC CCG       531
Glu Leu Ala Gln Arg|Ala Ala Val Val Ile Glu Gly Lys Val His Pro
Glu Leu Val Gln Arg|Trp Phe Val Val Ile Glu Gly Lys
                                GGF-II 04
```

0 3 95 50026

FIG. 45B

Nucleotide Sequence & Deduced Acid Sequence of GGF2HBS5

```
CAG CGG CGG CAG CAG GGG GCA CTC GAC AGG AAG GCG GCG GCG GCG GCG        579
Gln Arg Arg Gln Gln Gly Ala Leu Asp Arg Lys Ala Ala Ala Ala Ala

GGC GAG GCA GGG GCG TGG GGC GGC GAT CGC GAG CCG CCA GCC GCG GGC        627
Gly Glu Ala Gly Ala Trp Gly Gly Asp Arg Glu Pro Pro Ala Ala Gly

CCA CGG GCG CTG GGG CCG CCC GCC GAG GAG CCG CTG CTC GCC GCC AAC        675
Pro Arg Ala Leu Gly Pro Pro Ala Glu Glu Pro Leu Leu Ala Ala Asn

GGG ACC GTG CCC TCT TGG CCC ACC GCC CCG GTG CCC AGC GCC GGC GAG        723
Gly Thr Val Pro Ser Trp Pro Thr Ala Pro Val Pro Ser Ala Gly Glu

CCC GGG GAG GAG GCG CCC TAT CTG GTG AAG GTG CAC CAG GTG TGG GCG        771
Pro Gly Glu Glu Ala Pro Tyr Leu Val Lys Val His Gln Val Trp Ala
                                    Lys Val His Glu Val Trp Ala
                                        GGF II 01 & GGF II 11

GTG AAA GCC GGG GGC TTG AAG AAG GAC TCG CTG CTC ACC GTG CGC CTG        819
Val Lys Ala Gly Gly Leu Lys Lys Asp Ser Leu Leu Thr Val Arg Leu
Ala Lys                         Asp Leu Leu Leu Xaa Val     Leu
                                      GGF II 10

GGG ACC TGG GGC CAC CCC GCC TTC CCC TCC TGC GGG AGG CTC AAG GAG        867
Gly Thr Trp Gly His Pro Ala Phe Pro Ser Cys Gly Arg Leu Lys Glu
Gly Ala Trp Gly Pro Pro Ala Phe Pro Val Xaa Tyr
               GGF II 03

GAC AGC AGG TAC ATC TTC TTC ATG GAG CCC GAC GCC AAC AGC ACC AGC        915
Asp Ser Arg Tyr Ile Phe Phe Met Glu Pro Asp Ala Asn Ser Thr Ser
            Tyr Ile Phe Phe Met Glu Pro Gla Ala Xaa Ser Ser Gly
                                  GGF II 02
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8 3 95 5026

FIG. 45C

Nucleotide Sequence & Deduced Acid Sequence of GGF2HBS5

```
CGC GCG CCG GCC GCC TTC CGA GCC TCT TTC CCC CCT CTG GAG ACG GGC          963
Arg Ala Pro Ala Ala Phe Arg Ala Ser Phe Pro Pro Leu Glu Thr Gly

CGG AAC CTC AAG AAG GAG GTC AGC CGG GTG CTG TGC AAG CGG TGC GCC         1011
Arg Asn Leu Lys Lys Glu Val Ser Arg Val Leu Cys Lys Arg Cys Ala

TTG CCT CCC CAA TTG AAA GAG ATG AAA AGC CAG GAA TCG GCT GCA GGT         1059
Leu Pro Pro Gln Leu Lys Glu Met Lys Ser Gln Glu Ser Ala Ala Gly

TCC AAA CTA GTC CTT CGG TGT GAA ACC AGT TCT GAA TAC TCC TCT CTC         1107
Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser Ser Leu
        Leu Val Leu Arg
           GGF-II 06

AGA TTC AAG TGG TTC AAG AAT GGG AAT GAA TTG AAT CGA AAA AAC AAA         1155
Arg Phe Lys Trp Phe Lys Asn Gly Asn Glu Leu Asn Arg Lys Asn Lys

CCA CAA AAT ATC AAG ATA CAA AAA AAG CCA GGG AAG TCA GAA CTT CGC         1203
Pro Gln Asn Ile Lys Ile Gln Lys Lys Pro Gly Lys Ser Glu Leu Arg

ATT AAC AAA GCA TCA CTG GCT GAT TCT GGA GAG TAT ATG TGC AAA GTG         1251
Ile Asn Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys Lys Val
        Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Xaa Lyx
                             GGF II 12

ATC AGC AAA TTA GGA AAT GAC AGT GCC TCT GCC AAT ATC ACC ATC GTG         1299
Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr Ile Val

GAA TCA AAC GCT ACA TCT ACA TCC ACC ACT GGG ACA AGC CAT CTT GTA         1347
Glu Ser Asn Ala Thr Ser Thr Ser Thr Thr Gly Thr Ser His Leu Val
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FIG. 45D

Nucleotide Sequence & Deduced Acid Sequence of GGF2HBS5

AAA TGT GCG GAG AAG GAG AAA ACT TTC TGT GTG AAT GGA GGG GAG TGC 1395
Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Cys

TTC ATG GTG AAA GAC CTT TCA AAC CCC TCG AGA TAC TTG TGC AAG TGC 1443
Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr Leu Cys Lys Cys

CCA AAT GAG TTT ACT GGT GAT CGC TGC CAA AAC TAC GTA ATG GCC AGC 1491
Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser

TTC TAC AGT ACG TCC ACT CCC TTT CTG TCT CTG CCT GAA 1530
Phe Tyr Ser Thr Ser Thr Pro Phe Leu Ser Leu Pro Glu

TAGGAGCATG CTCAGTTGGT GCTGCTTTCT TGTTGCTGCA TCTCCCCTCA GATTCCACCT 1590

AGAGCTAGAT GTGTCTTACC AGATCTAATA TTGACTGCCT CTGCCTGTCG CATGAGAACA 1650

TTAACAAAAG CAATTGTATT ACTTCCTCTG TTCGCGACTA GTTGGCTCTG AGATACTAAT 1710

AGGTGTGTGA GGCTCCGGAT GTTTCTGGAA TTGATATTGA ATGATGTGAT ACAAATTGAT 1770

AGTCAATATC AAGCAGTGAA ATATGATAAT AAAGGCATTT CAAAGTCTCA CTTTTATTGA 1830

TAAAATAAAA ATCATTCTAC TGAACAGTCC ATCTTCTTTA TACAATGACC ACATCCTGAA 1890

AAGGGTGTTG CTAAGCTGTA ACCGATATGC ACTTGAAATG ATGGTAAGTT AATTTTGATT 1950

CAGAATGTGT TATTTGTCAC AAATAAACAT AATAAAAGGA AAAAAAAAAA AAA 2003